FGF23 AND MINERAL METABOLISM, IMPLICATIONS IN CKD-MBD

PREGNANCY IN WOMEN ON CHRONIC HAEMODIALYSIS

C4D AS A DIAGNOSTIC TOOL IN MEMBRANOUS NEPHROPATHY

ELDERLY PATIENTS WITH CHRONIC KIDNEY DISEASE

SIROLIMUS IN PRIMARY STEROID-RESISTANT NEPHROTIC SYNDROME

TREATMENT OF CALCIFIC URAEMIC ARTERIOLOPATHY WITH BISPHOSPHONATES

INFLIXIMAB IN THE TREATMENT OF SECONDARY AMYLOIDOSIS
EDITORIAL
275 • FGF23 and mineral metabolism, implications in CKD-MBD
Mariano Rodríguez, Ignacio López, Juan Muñoz, Escolástico Aguilera-Tejero, Yolanda Almaden

SHORT REVIEWS
279 • Renal health and the environment: heavy metal nephrotoxicity
Ernesto Sabath, M. Ludivina Robles-Osorio
287 • Pregnancy in women on chronic dialysis: a review
Karina R. Furaz-Czerpak, Gema Fernández-Juárez, M. Ángeles Moreno-de la Higuera, Elena Corchete-Prats, Adriana Puente-García, Roberto Martín-Hernández

ORIGINALS
295 • C4d as a diagnostic tool in membranous nephropathy
Mario Espinosa-Hernández, Rosa Ortega-Salas, María López-Andreu, José M. Gómez-Carrasco, M. José Pérez-Sáez, Carlos Pérez-Seoane, Pedro Aljama-García
300 • Elderly patients with chronic kidney disease: outcomes after 5 years of follow-up
Manuel Heras, M. José Fernández-Reyes, Rosa Sánchez, M. Teresa Guerrero, Álvaro Molina, M. Astrid Rodríguez, Fernando Álvarez-Ude
306 • Optimising expanded organ donation through dual kidney transplantation: a case-control study
Miguel A. Frutos, Juan J. Mansilla, Mercedes Cabello, Jorge Soler, Pilar Ruiz, Miguel Lebron, Víctor Baena, Domingo Hernández
313 • Peripheral arterial disease and kidney failure: a frequent association
Salvador Tranche-Iparraguirre, Rafael Marín-Iranzo, Rebeca Fernández-de Sanmamed, Alba Riesgo-García, Eduardo Hevia-Rodríguez, Juan B. García-Casas
321 • Use of sirolimus in patients with primary steroid-resistant nephrotic syndrome
Miguel Liern, Verónica de Reyes, Alicia Fayad, Graciela Vallejo
329 • Successful treatment of calcific uraemic arteriolopathy with bisphosphonates
José V. Torregrosa, Carlos E. Durán, Xoana Barros, Miquel Blasco, Marta Arias, Aleix Cases, Josep M. Campistol
335 • Is there impact of mortality prior haemodialysis therapy in peritoneal dialysis patients?
Yener Koc, Abdulkadir Unsal, Taner Basturk, Tamer Sakaci, Elbis Ahbap-Dal, Ayse Sinangil-Arar, Sennur Kose-Budak, Hasan Kayabasi
343 • Erythropoietin resistance and survival in non-dialysis patients with stage 4-5 chronic kidney disease and heart disease
M. Ángeles Guerrero-Riscos, Rafael Montes-Delgado, María Seda-Guzmán, Juan M. Praena-Fernández
353 • Factors associated with early peritoneal dialysis catheter replacement in Veracruz, Mexico
Gustavo Martínez-Mier, Marisol Luna-Castillo, Jorge J. Ortiz-Enríquez, Sandro F. Ávila-Pardo, Vicente Fernández, Marco T. Méndez-López, Luis Budar-Fernández, Felipe González-Velázquez
359 • Factors determining a low dose of haemodialysis as measured by ionic dialysance in critical patients with acute kidney injury
Guillermo Rosa-Diez, Gustavo Greloni, María Cruccelegui, Mariela Bedini-Roca, Agustina Heredia-Martínez, M. Luisa Coi, Sergio Giannasi, Eduardo San-Román, Rodolfo Pizarro, César Belzitti, Salomón Algranati, Ricardo Huguilen
367 • Discrepancies among consensus documents, guidelines, clinical practice and the legal framework for the treatment of type 2 diabetes mellitus patients

REVIEW
374 • Advances in immunosuppression for kidney transplantation: new strategies for preserving kidney function and reducing cardiovascular risk
Oriol Bestard, Josep M. Campistol, José M. Morales, Ana Sánchez-Fructuoso, Mercedes Cabello, Virginia Cabello, Luis M. Pallardó, Josep M. Grinyó
CLINICAL CASE
385
- Infliximab in the treatment of amyloidosis secondary to Crohn’s disease
  Juan B. Cabezuelo, Juan P. Egea, Fernanda Ramos, Emilio Torrella, Salomé Muray, Concepción Alcázar

TECHNICAL NOTE
389
- Analysis of concordance between the bioelectrical impedance vector analysis and bioelectrical impedance spectroscopy in haemodialysis patients
  José L. Teruel-Briones, Milagros Fernández-Lucas, Gloria Ruiz-Roso, Humberto Sánchez-Ramírez, Maite Rivera-Gorrín, Antonio Gomis-Couto, Nuria Rodríguez-Mendiola, Carlos Quereda

LETTERS TO THE EDITOR
A) Comments on published articles
396
- Comment on “Haemodialysis using high cut-off dialysers for treating acute renal failure in multiple myeloma”
  Gioacchino Li Cavoli, Onofrio Schilliaci, Carmela Zagarri, Angelo Tralongo, Francesca Servillo, Silvia Passanante, Ugo Rotolo

B) Brief papers on research and clinical experiments
397
- Progression of chronic kidney disease. Prevalence of anxiety and depression in autosomal dominant polycystic kidney disease
  Tais Pérez-Domínguez, Armando Rodríguez-Pérez, Miguel A. García-Bello, Nisa Buset-Ríos, Francisco Rodríguez-Esparragón, Yanet Parodis-López, José C. Rodríguez-Pérez, HIRICARE
399
- Diabetic foot and renal failure. Theoretical and practical considerations
  Fátima Batista-García, Michele Hernández, Santiago Suría, Noemí Esparza, M. Dolores Checa
400
- Effects of suspending ACE inhibitors and ARBs in advanced chronic kidney disease
  Martha E. Díaz-Domínguez, Milagros Fernández-Lucas, Antonio Gomis-Couto, Gloria Ruiz-Roso, José L. Teruel, Carlos Quereda
401
- Microalbuminuria: another use for paricalcitol? Our experience in advanced chronic kidney disease
  Raquel Blanco-García, Juan J. Bravo-López, Mercedes Moreiras-Plaza, Walfred Nájera-de la Garza, Cynthia Cossio-Annibar, Laura Beato-Coo, Gloria Rodríguez-Goyanes
402
- Monitoring haemodialysis in the Cabueñes Hospital
  Ana Suárez-Laurés, Luis Quiñones-Ortiz, Miguel de la Torre-Fernández, Adolfo Torres-Lacalle, Montse de Pablos-Pablo, Susana Puccini, Ramón Forascepi-Roza

C) Brief case reports
403
- Topiramate-induced metabolic acidosis: a case study
  Lucía Fernández-de Orueta, Javier Esteban-Fernández, Harald Fj. Aichner, Ángel Casillas-Villamor, Sergio Rodríguez-Álvarez
404
- Giant true aneurism of the radial artery following ligation of an arteriovenous fistula for haemodialysis
  Cristina Feijoo-Cano en nombre del Grupo Servicio de Angiología y Cirugía Vascular del Hospital Clínico Universitario Miguel Servet. Zaragoza
406
- Nephrogenic ascites: a thing of the past?
  Raquel Díaz-Mancebo, Rafael Sánchez-Villanueva, Elena González-García, Marta Ossorio-González, Rafael Selgas-Gutiérrez
408
- Postpartum hemolytic uremic syndrome with multiple organ involvement in a severe case
  Guang-Yu Zhou

410
- Primary sclerosing cholangitis and interstitial nephropathy: an emerging association?
  Manuel Heras, Ana Saiz, José Fernández-Reyes, Rosa Sánchez, Álvaro Molina, Astrid Rodríguez, Fernando Álvarez-Ude
412
- Minimal-change nephropathy in systemic lupus erythematosus
  M. Dolores Redondo-Pachón, Ricardo Enríquez, Ana E. Sivento, Encarna Andrade, Isabel Millán, Francisco Amorós
414
- Minimal change disease following influenza vaccination and acute renal failure: just a coincidence?
  Silvina Gutiérrez, Beatriz Dotto, Juan P. Petiti, Ana L. De Paul, M. Elisa Dionisio de Cabalier, Alicia I. Torres, Jorge H. Mukdsi
415
- Lanthanum carbonate and peritoneal catheter dysfunction
  José R. Rodríguez-Palomares, Gabriel de Arriba, Liliana Gómez, Katia Pérez, Mariángeles Basterrechea, Beatriz Hernández, Serafín Tallón
416
- Bilateral renal infarctions
  Marta Cuberes-Izquierdo, Nerea Yanguas-Barea, Olga Martorell-Almau, Ángel Gamen-Pardo, Eduardo Parra-Moncasi, Raquel Artal-Sánchez, Rosa Coscolluela-Cabrejas
417
- Severe hypertriglyceridaemia. Treatment with plasmapheresis
  M. Jesús Izquierdo-Ortiz, Pedro Abaigar-Luquin
FGF23 and mineral metabolism, implications in CKD-MBD

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Nefrología 2012;32(3):275-8

The regulation of mineral metabolism is achieved through a complex interaction of hormonal factors and target organs. Before the discovery of FGF23 we believed that the regulation of serum calcium and phosphate was mainly the result of changes in PTH and vitamin D acting on bone, kidneys and intestine. Parathyroids and kidneys were responsible for the production of PTH and 1,25(OH)2D3 respectively. Presently we know that FGF23 is produced by bone so the bone is not longer just a target organ but an active endocrine organ that participates in the regulation of mineral metabolism by sending signals through FGF23. Nephrologists are knowledgeable about the regulation of calcium and phosphate. Otherwise, it is difficult to understand and manage the disturbances of mineral metabolism that are always present in patients with CKD. Changes in mineral metabolism in CKD are now described as chronic kidney disease-mineral and bone disorders (CKD-MBD)¹. The pathology derived from CKD-MBD includes not only bone abnormalities but cardiovascular disease with a devastating prevalence of vascular calcification. The severity of CKD-MBD is associated with increased mortality in CKD patients.

THE REGULATION OF SERUM PHOSPHATE

The regulation of calcium and phosphate was only partially understood until the discovery of FGF23. FGF23 increases phosphaturia and reduces the production of 1,25(OH)2D3 (Figure 1). Let’s think in a situation of hypocalcemia; the parathyroids respond promptly to a decrease in serum calcium, elevated PTH acts on bone to increase the exit of calcium, but the calcium release from bone is also accompanied by the release of phosphate. The PTH acts also in kidneys increasing the tubular re-absorption of calcium so the calcium released by bone is kept in the extracellular space. The PTH produces phosphaturia so the phosphate released by bone does not build up in the extracellular space. This may not be sufficient to bring the calcium up to normal, therefore the elevated PTH stimulates renal production of 1,25(OH)2D3 which in turn stimulates intestinal calcium absorption. This regulatory system appears to be adequate to control serum calcium, however 1,25(OH)2D3 not only increase gut absorption of calcium but also the absorption of phosphate. It does not seem logical that a synchronized hormonal response to correct hypocalcemia had to be concluded with an excess of phosphate. FGF23 modulates the production of 1,25(OH)2D3 and the accumulation phosphate. Both high phosphate and 1,25(OH)2D3 stimulate the production of FGF23 which feeds back on the production of 1,25(OH)2D3 and induces phosphaturia. Thus the presence of FGF23 enables the system to restore the serum calcium without the trouble of phosphate accumulation (Figure 2).

PRODUCTION AND ACTIONS OF FGF23

FGF23 is a 32-kDa (251 amino acid) protein produced by osteocytes and osteoblasts which makes the bone an endocrine organ that communicates with other organs involved in mineral homeostasis. FGF23 acts on its receptor complex, klotho-FGFR1, in the kidney to cause phosphaturia and to decrease calcitriol synthesis.²⁻⁵ FGF23 induces phosphaturia by suppressing the expression of the Na-Pi cotransporters 2a and 2c in the brush border of renal proximal tubules. FGF23 suppresses renal production of 1,25(OH)2D3 by inhibiting 1α-hydroxylase (CYP27B1) activity which produces 1,25(OH)2D3 from 25(OH)D and also by increasing 24-hydroxylase activity which inactivates the 1,25(OH)2D3.²⁻⁵ Therefore the lack of FGF23, as in the FGF23 null mouse (FGF23⁻/⁻) causes hyperphosphatemia and high levels of 1,25(OH)2D3 a situation that produces extraosseous calcification.² The endocrine action of FGF23 is dependent upon its binding and activation of the klotho-FGFR1 complex,² therefore the absence of klotho as in the klotho⁻/⁻ mouse produces a phenotype similar to the FGF23⁻/⁻ mouse, elevation of phosphate and 1,25(OH)2D3
together with calcifications. We should be aware that these FGF23-/- rodents are teaching us what has been clinically evident in uremic patients: excessive doses of Calcitriol in combination with hyperphosphatemia carries the risk of calcification.

FGF23 production by osteoblasts and osteocytes is stimulated by high dietary intake of phosphate however the mechanisms at the cellular level are unknown.8 Experiments have failed to show a direct effect of high extracellular phosphate concentration on FGF23 expression by bone cells.8 The stimulation of FGF23 production by 1,25(OH)2D3 is well defined. Liu S et al.9 showed that 1,25(OH)2D3 upregulates FGF23 expression by acting on VDR response elements of the FGF23 promoter. Interestingly Carrillo et al.10 have shown that estrogens directly stimulate the production of FGF23.

THE INTERRELATIONSHIP FGF23-PTH

Parathyroid tissue expresses a significant amount of klotho11 and FGF23 receptor. Thus it was reasonable to anticipate an effect of FGF23 on the parathyroids. FGF23 acts on the parathyroid FGF-Klotho complex12 causing activation of the MAPK pathway through ERK1/2 phosphorylation and increase in early growth response 1 mRNA levels. In vivo and in vitro experiments demonstrate that FGF23 decreased PTH mRNA and PTH secretion.13,14 FGF23 also produces upregulation of parathyroid 1 alpha hydroxilase expression.15 Canalejo et al.16 investigated the effect of FGF23 on two main parathyroid receptors that inhibit parathyroid function: the calcium sensing receptor and the vitamin D receptor. In vivo and in vitro studies demonstrated that FGF23 increased gene expression and protein levels of both calcium sensing and Vitamin D receptors. Finally the same authors showed that FGF23 decreased parathyroid cell proliferation. All these results strongly suggest that FGF23 inhibits parathyroid function in normal parathyroids. The expression of FGF23 receptor and klotho in parathyroids have been investigated. Some experiments have shown that administration of FGF23 produces upregulation of parathyroid klotho,17 other authors18 observed that FGF23 produced an increase in klotho that did not reach significance. High extracellular calcium was able to increase in both parathyroid klotho and FGF receptor expression in normal parathyroid glands.19

FGF23 IN PATIENTS WITH CHRONIC KIDNEY DISEASE. THE PATHOGENESIS OF SECONDARY HYPERPARATHYROIDISM

Several publications have illustrated the important changes in FGF23 levels in patients with CKD.15-18 Some authors have shown that in early stages of CKD serum levels of FGF23 are elevated even when PTH is not significantly increased. For many years accumulation of phosphate and vitamin D deficiency were considered the key factors in the development of secondary hyperparathyroidism.18 The increase in serum PTH in CKD not only promotes urinary excretion of phosphate but also maintains serum calcium levels and stimulate the failing kidney to produce 1,25(OH)2D3. The increased production of FGF23 in CKD patients is most likely due to the increase in body burden of phosphate (not necessarily accompanied by hyperphosphatemia). FGF23 induces phosphaturia, which may explain why serum levels of phosphate are maintained in early stages of CKD. However FGF23 decreases de production of 1,25(OH)2D3 and accelerates its metabolism by augmenting 24(OH) asa activity. Thus, the decrease in 1,25(OH)2D3 seen in early CKD may be attributed not only to the decrease in renal mass but also to the early increase in FGF23.20 There is a debate about which of the two phosphaturic hormones, PTH or FGF23 increases earlier in CKD.20-22 An study by Isakova T et al.22 showed that in a group CKD patients with an average GFR of 41 ml/min had normal serum levels of calcium, phosphate and PTH, however FGF23 were already elevated and 1,25(OH)2D3 levels significantly reduced. Progressive loss of nephrons will make both FGF23 and PTH non-operative and then serum phosphate concentration will increase.

Figure 1. Hormonal response to hypocalcemia. Ca: calcium; P: phosphate; PTH: parathyroid hormone

Figure 2. Hormonal response to hypocalcemia and the role of FGF23 to maintain phosphate balance. Ca: calcium; FGF23: fibroblast growth factor 23. P: phosphate; PTH: parathyroid hormone.
Nephrologists frequently ask whether or not it is advantageous to have elevation of FGF23. Certainly FGF23 helps to control phosphate balance but contributes to vitamin D deficiency. Furthermore recent experiments demonstrate a direct negative effect of FGF23 on the cardiovascular system. The fact that FGF23 is elevated indicates that the failing kidneys needs the "help" of a phosphaturic hormone able to handle the phosphate load. Therefore the increase in FGF23 implies inadequate phosphate control. In patients with CKD a better control of phosphate is associated with a decrease in FGF23. Another question is whether FGF23 is a clinical useful tool to assess phosphate balance in CKD patients. FGF23 levels may not reflect acute changes in dietary phosphate; however high serum level of FGF23 may reveal a long period of positive phosphate balance. Certainly, clinical studies will have to be performed to prove the usefulness of FGF23 as a marker of phosphate balance.

A considerable amount of clinical studies have shown that a high FGF23 level is an independent predictor of mortality. A considerable amount of clinical studies have shown that a usefulness of FGF23 as a marker of phosphate balance. Certainly clinical studies will have to be performed to prove the FGF23 may reveal a long period of positive phosphate balance. changes in dietary phosphate; however high serum level of FGF23 may reveal a long period of positive phosphate balance. Certainly, clinical studies will have to be performed to prove the usefulness of FGF23 as a marker of phosphate balance.

FGF23 IN ADVANCED SECONDARY HYPERPARATHYROIDISM

In dialysis patients serum FGF23 levels are markedly increased and they are positively correlated with serum PTH levels and with serum levels of phosphate. One may assume that the sustained accumulation of phosphate is the cause of a direct correlation between PTH and FGF23. Nevertheless, given the fact that FGF23 inhibits parathyroid function it is unexpected to observe a parallel increase in the serum concentrations of FGF23 and PTH.

Experimental work in uremic rats with secondary hyperparathyroidism revealed that administration of FGF23 did not reduce serum levels of FGF23 in uremic rats; and, in vitro hyperplastic parathyroid glands from uremic rats did not respond to FGF23. Further experiments showed that hyperplastic parathyroid glands presented low expression of both FGF receptors and klotho. This results suggests a resistance of hyperplastic parathyroid gland to the inhibitory action of FGF23. Similar results were obtained by other group in another rat model of renal insufficiency. In parathyroid glands obtained from patients with advanced secondary hyperparathyroidism Klotho and FGFR1c expression decreased significantly particularly in glands with nodular hyperplasia.

FGF23 AFTER RENAL TRANSPLANT

After renal transplant many patients maintain high FGF23 levels suggesting that FGF23 may be the cause of post-transplant hypophosphatemia with a relative vitamin D deficiency. Before transplantation FGF23 levels are very high and after kidney transplantation the excess of FGF23 acts to promote phosphaturia and suppress 1,25(OH)2D production. It is not clear why FGF23 secretion is maintained after transplantation despite hypophosphatemia.

Conflict of interest


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Renal health and the environment: heavy metal nephrotoxicity

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Nefrologia 2012;32(3):279-86

ABSTRACT

We currently recognise that environmental toxins such as cadmium, lead, and arsenic play a significant role in the development of chronic renal failure. Epidemiological studies have shown a strong association between exposure to these metals and the presence of chronic kidney injury. The physiopathological mechanisms behind metal-induced kidney injury are complex, and some aspects of their metabolism and damage mechanisms remain unknown. This review aims to analyse the physiopathological mechanisms of kidney injury due to cadmium, lead and arsenic.

Keywords: Cadmium. Lead. Arsenic.

INTRODUCTION

Both the incidence and prevalence of chronic renal failure have risen constantly over the last 3 decades, which is now a growing public health problem. Identifying risk factors associated with the disease is essential in order to prevent it from affecting even more patients.

Studying the toxic effects of heavy metals on the human body has become especially important in the last 50 years, given that large amounts of these products were disposed of as industrial waste and they are not biodegradable, remaining in the environment for long periods of time. For this reason, despite the fact that strict regulations enforced mainly in Europe and North America limit the disposal of heavy metals, high levels of these elements are still present in soil and sediment, resulting in chronic exposure in the general population.

Heavy metals are a poorly defined group of elements. Some are necessary for the human body, such as iron (Fe), cobalt (Co), copper (Cu), manganese (Mn), molybdenum (Mb) and zinc (Zn). It is unknown whether the other metals – lead (Pb), cadmium (Cd) and arsenic (As) – serve any purpose in the body, but they do have a direct effect on the kidneys and they are particularly nephrotoxic, even at “normal” levels. There is no clear evidence of nephrotoxicity due to other metals such as uranium and mercury.¹

The aim of this review is to analyse the epidemiology, physiopathology and clinical manifestations of nephrotoxicity associated with these metals.
**ABSORPTION AND METABOLISM OF DIVALENT METALS**

Intestinal absorption of divalent metals such as Cd and Pb is facilitated by divalent metal transporter 1 (DMT-1). DMT-1 is located in the duodenum, erythrocytes, liver and cells in the proximal convoluted tubule (PCT). This protein transports Fe and has a high affinity for other divalent metals such as Cd, Ni (nickel), Pb, Co, Mn, Zn and Cu. Decreased intake of Fe and Zn results in increased expression of DMT-1, which increases intestinal absorption of Cd and Pb and therefore toxicity by these metals. Experiments in cell lines in which DMT-1 expression has been blocked suggest that there is a different Pb transporter.

Heavy metals are metabolised in the liver, where they bind to low molecular weight proteins (<10kDa) called metallothionines (MT). These proteins are widely distributed throughout the body and contain a large quantity of the amino acid cysteine, which gives them a high affinity for reacting with and storing metals such as Zn, Cd, Hg (mercury), Cu, Pb, Ni, Co and Fe.

The main function of MT is to store essential metals such as Zn and Cu in the intracellular medium and transfer them to metalloproteins, transcription factors and enzymes. MT also play a role in the elimination of free radicals and in cellular repair and regeneration processes. Increased intracellular levels of Cd and Pb increases MT expression, and MT knockout mice are more susceptible to toxicity from these metals.

**CADMIUM NEPHROTOXICITY**

Cd is one of the most toxic elements to which humans are exposed. Environmental exposure mainly occurs by contact with tobacco smoke, water and foodstuffs such as vegetables, grains and molluscs. This metal gradually accumulates in the body and levels increase with age given its long half-life, which is more than 20 years.

**Epidemiology**

Various epidemiological studies have demonstrated that environmental exposure to Cd increases the risk of developing kidney injury. During the 1950s in Japan, doctors began to recognise an association between environmental exposure to Cd and increased numbers of women with kidney disease characterised by tubular dysfunction, chronic kidney disease, and a type of osteomalacia known as “itai-itai”. It was later found that workers suffering from industrial exposure to Cd had an increased risk of developing kidney disease. However, it was not until the publication of Bernard’s studies in Belgium that it was understood that exposure to even low Cd levels had nephrotoxic effects and that up to 7% of the exposed population suffered kidney injury.

Järup et al studied 1021 people and demonstrated that the prevalence of tubular damage marker alpha 1-microglobulin was significantly higher in subjects whose urinary excretion of Cd was within the high range of normal limits (odds ratio [OR]: 6, 95% confidence interval [CI]: 1.6-22). Noonan et al showed the same relationship between normal-to-high urinary levels of Cd and the presence of NAG (N-acetyl-beta-D-glucosaminidase) and alanine aminopeptidase tubular dysfunction markers. The literature does not currently include reports on the effects of Cd on the progression of chronic kidney injury, although a Swedish study by Hellstrom et al showed a higher incidence rate of patients on dialysis (OR: 18, 95% CI: 1.3-2.3) among people exposed to Cd than among those with no Cd exposure.

In addition to its nephrotoxic effect, Cd is also associated with increased risk of developing diabetes, cancer, and cardiovascular disease. In a sample of 13 958 adult participants in NHANES III (National Health and Nutrition Examination Survey III), Menke et al showed that high levels of Cd in urine were associated with higher overall mortality and increased risk of cancer. Exposure to Cd also increases the risk of high blood pressure and it is considered a risk factor for cardiovascular mortality and morbidity.

**Physiopathology**

Cd in food is bound to metallothionein and phytochelatin proteins, which are involved in vacuole confinement of heavy metals in vegetables. These proteins are broken down by the action of the gastric juice, releasing Cd that will be absorbed in the intestine by DMT-1 and ZIP-8 transporters.

In circulating blood, it binds to albumin and is transported to the liver, where it binds to glutathione (GSH) and metallothionein-1 (MT-1). The Cd-MT-1 complex is secreted in bile and subsequently reabsorbed into the blood by means of enterohepatic circulation. Cd-MT-1 is a low molecular weight complex (<7kDa) which is easily filtered by the glomerulus and is entirely reabsorbed in the S1 segment of the PCT by endocytosis in a process mediated by the proteins megalin and cubilin.

The ZIP-8 transporter is also located in PCT cells, and it is able to transport Cd and other divalent metals through the apical membrane of these cells; however, the role it plays in Cd toxicity is unknown.
Within the intracellular medium of PCT cells, the Cd-MT-1 complex is stored and broken down by lysosomes. Free Cd is then transported to the cytoplasm by lysosomal DMT-1. Activation of protein kinase C increases expression of DMT-1, thereby increasing tubular toxicity by Cd.

Free Cd accumulates in mitochondria, blocking the respiratory chain at complex III. This results in mitochondrial dysfunction and the formation of free radicals, which activates caspase enzymes and the apoptosis process. Free Cd also binds to protein sulfhydryl groups and affects the structure and function of the proteins. It has been demonstrated that Cd interferes with enzymatic activities of the calcium-calmodulin complex, inhibits Na+K+-ATPase activity, and stimulates activity by MAP kinases. In paracellular tight junctions, it affects the distribution of paracellular tight junction proteins and decreases transepithelial resistance.

Only 10% of filtered Cd is reabsorbed into distal ends of the nephron, and it is possible that the Cd ‘s hypercalciuric effect is the result of inhibition of calcium channel activity in the distal tubule.

Another nephrotoxicity mechanism is the one mediated by the formation of anti-MT antibodies; exposure to Cd increases MT production in the liver and kidneys, which constitutes a protective response to limit its toxicity. However, once the MT’s capacity for Cd storage has been exceeded, free Cd is able to induce the formation of antibodies against MT, which are also toxic to PCT cells.

The effect of foetal exposure to Cd is unknown. Jacquillet et al showed that an offspring of rats exposed to Cd during gestation had decreased renal function, proximal tubular damage and abnormal paracellular tight junctions in the glomeruli in adulthood, as well as PCT characterised by alterations in the expression and arrangement of claudin-2 and claudin-5.

Clinical manifestations

The main effects of chronic Cd toxicity are kidney injury, bone demineralisation, high blood pressure, pulmonary function disorders (mainly obstructive) and different types of cancer (bladder, lung, etc.)

In the kidney, Cd mainly affects PCT cells. This damage manifests clinically as low molecular weight proteinuria, aminoaciduria, bicarbonaturia, glycosuria and phosphaturia. Tubular damage markers such as alpha-1-microglobulin, beta-2-microglobulin, NAG and KIM-1 (kidney injury molecule-1) are useful in detecting early tubular damage.

People with incipient renal injury are more susceptible to the nephrotoxic effects of Cd. In patients with diabetic nephropathy, urinary excretion of CD is directly related to increased urinary excretion of beta-2-microglobulin and albuminuria.

Determining Cd levels in the bloodstream is used to diagnose acute exposure, whilst urinary excretion of Cd is used to assess Cd body burden and is useful for evaluating chronic exposure.

Prevention is the most important factor in the management of exposure to this metal, since there is no effective means of treating Cd toxicity.

LEAD NEPHROTOXICITY

The toxic effects of Pb have been known for more than 2000 years, since lead intake was a common problem among the Romans. At present, exposure to high concentrations of Pb is less common, due to better industrial management and the fact that Pb is no longer added to paint and petrol. However, Pb contamination is still a public health problem in many countries in Africa, Asia and Latin America due to domestic exposure through contaminated water and soil.

Epidemiology

The first reported case of nephrotoxicity associated with Pb was described in the 19th century. Since then, exposure to high concentrations of Pb has been considered a risk factor for developing high blood pressure and kidney injury. However, it was not until recent times that studies recognised that exposure to “normal” levels had a direct effect on kidney function and increased the risk of cardiovascular morbidity.

Based on results from the NHANES III study, Menke et al monitored a population over 12 years and demonstrated that the higher the Pb levels, the higher the mortality rates (mainly due to cardiovascular problems).

In a population of 4813 patients with high blood pressure, Muntner et al found increased risk of chronic renal failure (OR: 2.6, 95% CI: 1.5-4.45) in those with higher serum Pb levels. Follow-up studies carried out in Taiwan by Lin et al found that individuals with chronic nephritis (glomerular filtration rate [GFR]<60ml/min) and high levels of Pb in the body experienced faster deterioration of renal function, and also that chelation therapy with ethylenediaminetetraacetic acid (EDTA) decreased kidney injury progression.
Establishing the maximum non-toxic levels of Pb in blood and urine remains a matter for debate, since there is increasing evidence suggesting that levels previously considered to be non-toxic are associated with higher morbidity and mortality rates in the general population.31

**Physiopathology**

Pb is mainly absorbed by the intestine and the respiratory system and, to a lesser extent, through the skin. Intestinal absorption is mediated by DMT-1 and increases with deficient intake of Fe and Zn. The respiratory system is a highly efficient route of absorption, with an uptake rate of more than 40% of inhaled Pb; however, the molecular mechanism by which Pb is absorbed is unknown.

Once in the blood, 99% of Pb binds to proteins in the erythrocytes and it is distributed to soft tissue and bone. Bone is the main reservoir for lead in the body and Pb transport to the bloodstream increases during times with the highest bone turnover, such as adolescence and pregnancy.31 Urinary excretion is the main route of Pb elimination from the body.

Pb bound to low molecular weight proteins (<1% of the total) is filtered freely at the glomerulus and is reabsorbed by PCT cells by endocytosis. Within the cell, Pb causes mitochondrial damage, formation of free radicals, intracellular depletion of GSH and apoptosis (Figure 2).36 Pb also affects enzymatic reactions in which calcium plays a role, and the calcium-sensing receptor can also be activated by Pb, which suggests that there may be other mechanisms for lead nephrotoxicity.37,38

Pb induces activation of transcription nuclear factor kappa B, activation of the intrarenal renin-angiotensin system and attraction of macrophages, which generates an inflammatory process in the renal interstitium that may be involved in the development of tubulointerstitial damage and high blood pressure.39

In endothelial cells, it has been shown that increased formation of free radicals induced by Pb decreases nitric oxide production and the expression of the enzyme guanylate cyclase. These effects explain how high blood pressure can develop as a result of exposure to this metal.36-41 In addition, it stimulates the activity of NADP(H) oxidase by increasing production of hydrogen peroxide and hydrogen peroxide, thus affecting oxidative stress and the intracellular redox potential.42

**Figure 1.** Physiopathological mechanisms of cadmium-induced kidney injury

DMT-1: divalent metal transporter 1; MT: metallothionein
Clinical manifestations

Acute exposure to high doses of Pb can cause PCT lesions, which manifest clinically as aminoaciduria, glycosuria or hyperphosphatemia. Other clinical manifestations include haemolytic anaemia, acute attacks of gout, intense abdominal pain (“painter’s colic”) and encephalopathy.43

Diagnosing chronic nephritis due to Pb is difficult, since urinary symptoms and findings are variable and lack specificity. Diagnosis is therefore based largely on a clinical history of exposure. Chronic exposure is associated with tubulointerstitial nephritis and progressive deterioration of renal function. Urinary excretion of urates decreases due to the effect of Pb on the PCT and renal blood flow decreases as well, resulting in increased urate levels in the bloodstream.44

In bone, chronic exposure is related to the pathogenesis and progression of osteoporosis, since Pb has adverse effects on osteoblasts and osteoclasts that affect bone formation and reabsorption.45

There is no adequate treatment for decreasing high Pb levels in the blood, but EDTA chelation therapy (1g in 200ml saline at 0.9%, administered weekly during 3 months) helps decrease Pb toxicity. Preventing exposure to this metal is the best means of reducing high levels in the bloodstream.35

ARSENIC NEPHROTOXICITY

Arsenic is one of the most widespread environmental pollutants and millions of people (mostly in Asia and Latin America) suffer from exposure to As, since it is a common

In bone, chronic exposure is related to the pathogenesis and progression of osteoporosis, since Pb has adverse effects on osteoblasts and osteoclasts that affect bone formation and reabsorption.45

There is no adequate treatment for decreasing high Pb levels in the blood, but EDTA chelation therapy (1g in 200ml saline at 0.9%, administered weekly during 3 months) helps decrease Pb toxicity. Preventing exposure to this metal is the best means of reducing high levels in the bloodstream.35

Figure 2. Physiopathological mechanisms of lead-induced kidney injury

cGMP: cyclic guanosine monophosphate; NF-κβ: nuclear factor kappa B.
pollutant in drinking water. Another less common form of exposure is through medications containing As, such as arsenic trioxide used in the treatment of acute promyelocytic leukaemia, and other drugs used to treat sleeping sickness and leishmaniasis.

Epidemiology

The causal association between As and the formation of tumours in the skin, lungs, bladder, liver and kidneys has been exhaustively described. Some epidemiological studies have shown an association between exposure to high levels of As and increased risk of cardiovascular disease and diabetes mellitus. However, studies conducted in areas with low to moderate exposure have not yet demonstrated this association conclusively.

Until now, there have been few reports in the literature on the effects of As on the renal function of the general population. Hsueh et al. studied 125 people with GFR<60ml/min and 229 people with normal renal function and found a weak association between urinary levels of As and decreased renal function (r²=0.04, P≤.001). Meliker et al. showed that in patients with decreased renal function, higher As levels were associated with higher mortality rates (OR: 1.11, 95% CI: 1.09-1.13).

Physiopathology

As is absorbed by the intestine, lungs (inhalation) and, to a lesser extent, through the skin. Once it has been absorbed, it is transported to all tissues in the body. The intake of selenium and vitamin B decrease intestinal absorption of As. Arsenic is methylated in the liver in a GSH-mediated process which decreases its toxicity and facilitates its biliary and urinary excretion. Arsenic enters the intracellular medium through the aquaglyceroporins AQ3 and AQ9 and studies in cell cultures have shown that the increase in AQ3 and AQ9 cellular expression increases intracellular accumulation of As. In the liver, AQ9 is important for biliary excretion of As.

Another group of As transport proteins includes MRP-1 and 2 (ATP binding cassette-multidrug resistance protein) which were first described in the liver, where they transport As bound to GSH to the bile. The MRP-2 transporter is also located in proximal tubule cells, which favours entry of As into these cells. Arsenic toxicity in PCT cells is due to GSH depletion and an increase in oxidative activity by free radicals (Figure 3).

The literature does not currently offers sufficient information on clinical manifestations of As toxicity in the kidneys, but it is likely to manifest as data indicating tubular damage, such as low molecular weight proteinuria, aminoaciduria, glycosuria and phosphaturia, as well as progressive deterioration of renal function.

CONCLUSION

In conclusion, there is ample evidence of the renal damage associated with these heavy metals. In addition, the combination of different metals has been shown to have a cumulative nephrotoxic effect. Since these metals are commonly found in the environment and there are no treatment options that decrease their systemic effects, increased vigilance is needed in order to decrease environmental levels of Pb, Cd and As.

Conflicts of interest

The authors declare potential conflicts of interest: Grants awarded: mixed funding from the State of Querétaro (Fondos Mixtos del Estado de Querétaro). Mexican National Council for Science and Technology.

KEY CONCEPTS

1. The nephrotoxic action of metals such as Cd, Pb and As mainly affects the proximal convoluted tubule cells.
2. The initial clinical manifestations of kidney damage are subtle and include low molecular weight proteinuria, aminoaciduria, phosphaturia and glycosuria.
3. Biomarkers such as alpha 1-microglobulin, NGAL and KIM-1 are useful for detecting early renal injury.
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Pregnancy in women on chronic dialysis: a review

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Nefrologia 2012;32(3):287-94

ABSTRACT

The frequency of pregnancy in women on dialysis is extremely low, but the percentage of successful pregnancies in this context has increased over the years, with some studies placing the survival rate above 70%. These pregnancies are not exempt from both maternal and foetal complications, and so their management requires the joint efforts of nephrologists, gynaecologists, nurses, and nutritionists. Currently, we have been unable to establish consistent systematic treatment from both nephrological and gynaecological specialists in these patients. The main changes that need to be made are: increased time on dialysis, maintaining low levels of pre-dialysis urea, avoiding: maternal hypertension and hypotension, anaemia, urinary tract infections, and fluctuations in electrolytes. Adequate foetal monitoring is also necessary.

Keywords: Pregnancy. Haemodialysis. Chronic Kidney disease.

INTRODUCTION

Pregnancies in dialysis patients are uncommon and difficult to study. These pregnancies occur in widely separated dialysis units, and so the majority of nephrologists encounter one or two pregnant patients during their time in practice. Fortunately, the percentage of successful pregnancies has increased consistently, but there is still a very high maternal/foetal mortality and morbidity rate as compared to the normal population. In order to achieve a successful birth, this situation requires the joint efforts of nephrologists, gynaecologists, nephrological nurses, and nutritionists.

This article is a review of the existing medical literature regarding the management of this type of patient, the incidence of successful pregnancies, and the maternal and foetal complications involved.

FREQUENCY AND DIAGNOSIS OF PREGNANCY IN WOMEN ON DIALYSIS

Although not well documented, it is believed that the frequency of pregnancies in women on haemodialysis is on the rise, from 1% to 7%, according to the most recent publications, with different rates in different countries. Pregnancies are more common in women with preserved residual diuresis.
The majority of patients on haemodialysis have sexual dysfunction as a result of physical and/or emotional problems.\textsuperscript{2}

Fertility drops due mainly to anaemia and hyperprolactinaemia; this decrease in fertility is also associated with hypothalamic/pituitary dysfunction, which results in ovarian dysfunction and anovulatory cycles, multiple drug treatments, depression, and loss of sex drive.\textsuperscript{10,11}

However, the improved efficacy of dialysis, along with corrections to anaemia due to the standardised application of erythropoietin, has improved general health in these patients, as well as their sexual function, which involves increased fertility and normal menstrual cycles.\textsuperscript{11,12}

Pregnancy in these patients tends to be diagnosed late, since irregular cycles and abdominal pain are already common, and many doctors do not think immediately of pregnancy as a possible cause of the symptoms.\textsuperscript{13}

Further deterioration of anaemia or apparent resistance to erythropoietin as well as hypotension episodes of unknown cause in premenopausal women should arouse suspicion of a possible pregnancy.\textsuperscript{14}

Urine pregnancy tests are not very useful in these situations, even if the patient has residual diuresis. The measurement of human chorionic gonadotrophin is inexact, since this molecule is produced by somatic cells and excreted by the kidney, and so ultrasound is the only reliable method to calculate gestational age.\textsuperscript{15}

\section*{RESULTS OF PREGNANCIES IN WOMEN ON HAEMODIALYSIS}

The first pregnancy with a successful result in a patient on haemodialysis was described in 1971 by Confortini et al\textsuperscript{16}; the patient was 35 years old.

In 1980, a case series was published in the European Dialysis and Transplant Association (EDTA) register involving 1300 women of child-bearing age, reporting a 0.9\% incidence rate of pregnancies in patients on chronic haemodialysis.\textsuperscript{17}

In 1994, Hou published another case series from 206 North American dialysis units. The percentage of miscarriage was 70\% before 1990 and under 40\% in the following years.\textsuperscript{17}

The majority of case series described since 2000 reported success rates for these pregnancies over 70\%.\textsuperscript{5,18-24}

As regards maternal mortality, few such cases have been registered in the literature. The prognosis for the mother is good; especially in patients that start dialysis after conception.\textsuperscript{2,7}

\section*{MATERNAL AND FOETAL COMPLICATIONS}

Maternal complications include: miscarriage, placental detachment, anaemia, infection, premature rupture of membranes, polyhydramnios, pre-term birth, uncontrolled arterial hypertension, preeclampsia/eclampsia, haemorrhage, need for a caesarean, and maternal death.\textsuperscript{25,26}

The incidence of polyhydramnios has been estimated at 30\%–70\%. The increased production in foetal urine secondary to urea-induced osmotic diuresis is probably the cause of excess amniotic fluid.\textsuperscript{25,24} Several studies have suggested that treatment for this complication consists of increasing dialysis doses.\textsuperscript{24}

As regards preeclampsia/eclampsia, approximately 80\% of women on haemodialysis that become pregnant have arterial hypertension or require anti-hypertensive medications at some point during pregnancy.\textsuperscript{5}

Uncontrolled hypertension poses a serious risk to the mother, and must be quickly and adequately controlled, maintaining diastolic blood pressure below 80-90mm Hg.\textsuperscript{2,13,27} As in any other dialysis patient, the initial treatment consists of adjusting volume using ultrafiltration, but if the cause of hypertension is preeclampsia, fluid extraction could exacerbate hypoperfusion to the various organs.\textsuperscript{15}

Several different types of medications are used to treat hypertension in pregnant women:

- **Alpha-methyldopa** is commonly used; no adverse side effects have been observed in babies, and they are relatively few in the mother: fatigue, depression, and in a small percentage of patients, hepatitis.\textsuperscript{5}

- **Hydralazine** has been used both orally and intravenously with no problems. It is not effective as a monotherapy under oral administration, but can also be associated with first-line drugs if results are not sufficiently effective.\textsuperscript{3-28}

- **Beta-blockers** are not used due to their adverse effects on new-borns; labetalol does not produce these effects, so it is widely used.\textsuperscript{3-29}

- The experience with clonidine and prazosin is limited, and these drugs do not appear to provide any serious benefit.\textsuperscript{3-30}

- **Calcium channel blockers** that can be used include: nifedipine, nicardipine, and verapamil. These have been used in cases of severe hypertension, and do not appear to be associated with congenital defects when used...
short review

Karina R. Furaz-Czerpak et al. Pregnancy in women on dialysis

Nefrologia 2012;32(3):287-94

During the first trimester. Only limited experience has been gained using diltiazem. We must remember that combined therapy with magnesium can lead to severe episodes of hypoten
tion.\textsuperscript{15,20,31}

- **Diuretics** can be used when no other alternative exists, but must be suspended in the event of suspected preeclampsia.\textsuperscript{3} Some publications have described neonatal thrombocytopenia, haemolytic anaemia, electrolyte imbalances, and jaundice with the use of thiazides.\textsuperscript{32}

- **Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) and minoxidil** are contraindicated due to their adverse effects on the

As regards drugs used in hypertensive emergencies, labetalol and hydralazine are prescribed intravenously.\textsuperscript{1,36}

The most common foetal complications are: restricted intra-uterine growth, acute and chronic foetal suffering, pre-term birth, respiratory difficulty in the new-born, growth in neonatal intensive care units, and uterine or neonatal death.\textsuperscript{25}

Pre-term births occur in 83\% of live births; the new-borns have a low weight and the gestational age is approximately 32 weeks or even less (Table 1).\textsuperscript{3,19-24,37}

Table 2 describes the primary recommendations for managing these patients.

**INTENSIVE DIALYSIS**

It is well established that a longer duration of dialysis treatment prolongs the gestation period, resulting in babies with a higher weight at birth, improved life expectancy, and reduced long-term complications.\textsuperscript{3}

The weekly time that patients should be on dialysis varies according to study (Table 3), but regardless of the criteria followed, the prescription of haemodialysis must be sufficient to maintain stable conditions in the mother in terms of volaemia, blood pressure, and weight gain between sessions.\textsuperscript{10}

The results from the study by Hou showed that pregnant women that receive over 20 hours of dialysis per week gave birth to babies with higher weight and gestational age.\textsuperscript{3} Two studies have also shown that pregnant patients should receive the maximum possible amount of time on dialysis, at least 24 hours per week.\textsuperscript{23,38}

Nocturnal haemodialysis provides greater clearance of small and medium molecular weight molecules and improves the control of metabolic, electrolyte, phosphorous, volaemia, and blood pressure profiles.\textsuperscript{21,39-42}

**MATERNAL UREA NITROGEN**

Several retrospective studies and isolated clinical cases have reported increased new-born survival in women with blood urea nitrogen (BUN) levels ≤50mg/100ml, but Asayima et al, in a retrospective study involving 28 pregnant patients on haemodialysis, demonstrated for the first time that lower maternal BUN levels are associated with higher weight and gestational age at birth.\textsuperscript{37,39,43,44}

Predialysis BUN levels are recommended to be kept below 50mg/100ml.\textsuperscript{31}

**TECHNIQUE**

The experience with peritoneal dialysis has been limited to a very few number of patients; in fact, the incidence of

### Table 1. Parameters for pregnancy and new-borns in women on chronic haemodialysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. pregnant patients</th>
<th>Weeks pregnant</th>
<th>Weight at birth (grams)</th>
<th>% live new-borns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romao</td>
<td>1998</td>
<td>14</td>
<td>32.3±2.6</td>
<td>1400±579 (720-2650)</td>
<td>79</td>
</tr>
<tr>
<td>Bagon</td>
<td>1998</td>
<td>15</td>
<td>30.6</td>
<td>1164 (700-1600)</td>
<td>67</td>
</tr>
<tr>
<td>Toma</td>
<td>1999</td>
<td>54</td>
<td>31.9±4.5</td>
<td>1544±672 (530-2856)</td>
<td>67</td>
</tr>
<tr>
<td>Chao</td>
<td>2002</td>
<td>13</td>
<td>32</td>
<td>1542 (512-1660)</td>
<td>69</td>
</tr>
<tr>
<td>Eroglu</td>
<td>2004</td>
<td>7</td>
<td>32</td>
<td>1400 (420-2640)</td>
<td>86</td>
</tr>
<tr>
<td>Haase</td>
<td>2005</td>
<td>5</td>
<td>33</td>
<td>1765±554</td>
<td>100</td>
</tr>
<tr>
<td>Barua</td>
<td>2008</td>
<td>5</td>
<td>36.2±3</td>
<td>2417.5±657</td>
<td>86</td>
</tr>
<tr>
<td>Luders</td>
<td>2010</td>
<td>52</td>
<td>32.7±3.1</td>
<td>1554±663</td>
<td>86.5</td>
</tr>
</tbody>
</table>

pregnancies in these patients is even lower than the rates for haemodialysis patients. This could be due to the presence of hypertonic solutions in the peritoneum, previous episodes of peritonitis, or physical factors that could interfere with foetal implantation. Most of the authors do not recommend changing the dialysis technique after conception.45,46

More data are needed on the results of pregnant patients on peritoneal dialysis and the possible associated complications.46

Data from the register of pregnant patients on dialysis and several reports showed no differences in the maternal and foetal results between haemodialysis and peritoneal dialysis.27,43,47

Peritoneal dialysis has the advantage of not inducing sudden metabolic changes, and allows for a gradual control of volaemia, thus avoiding episodes of hypotension. The main disadvantage would be difficulty in maintaining proper nutrition.3

**Table 2. Recommendations for optimising the treatment of pregnant women on haemodialysis**

| 1. Coordination between gynaecology, nephrology, and nutrition departments |
| 2. Management of the pregnancy in specialised gynaecological units for high-risk pregnancies, with a neonatal intensive care unit |
| 3. Blood pressure control |
| - Avoid diuretics, ACE inhibitors, and ARB |
| - Preferred treatment: alpha methyl dopa |
| - Maintain diastolic blood pressure between 80mm Hg and 90mm Hg |
| - Avoid hypotension and volume decrease |
| 4. Prevent metabolic acidosis |
| 5. Intensify dialysis treatment |
| - Increase the frequency of dialysis sessions (5-7 per week) |
| - Maintain a predialysis urea below 45-50mg/dl |
| 6. Use the minimum possible dose of heparin |
| 7. Use biocompatible membranes and avoid sterilization with ethylene oxide |
| 8. Calcium/phosphorous metabolism |
| - Avoid hypocalcaemia and hyperphosphataemia |
| - If necessary, use calcium chelating agents. Avoid post-dialysis hypercalcaemia |
| 9. Anaemia |
| - Provide iron and folic acid supplements |
| - Adjust erythropoietin dosage |
| - Maintain haemoglobin at 10-11g/100ml and haematocrit at 30%-35% |
| 10. Nutrition |
| - Protein intake of 1-1.2g/kg pre-pregnancy weight/day +10-20g/day |
| - Calorie intake of 35kcal/kg/ pregnant weight/day +300kcal/day |
| - Supplement with water-soluble vitamins and folic acid |

ACE inhibitors: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers.
WEIGHT GAIN

Maternal dry weight and weight gain should be regularly evaluated and adjusted according to the estimated weight of the foetus. In the first trimester, the mother should gain a minimum of 1kg - 1.5kg. After this, weight should increase by 0.45kg to 1kg per week. In the third trimester, foetal weight and growth can also be directly evaluated using ultrasound.44

Maternal blood pressure and heart rate must be closely monitored before, during, and after each dialysis session.44

Ultrafiltration doses should be administered on an individual basis so as to avoid episodes of arterial hypotension, hypovolaemia, and arrhythmia; and maternal blood volume expansion and weight gain should be proportional to the gestation stage. Severe maternal weight loss due to rapid and excessive ultrafiltration can reduce the foetal-placental blood flow, which could be very harmful for the foetus. As such, these factors must be considered in ultrafiltration prescription.25

DIALYSATE

Potassium levels in the dialysate must be increased to 3-3.5mmol/l in order to avoid hypokalemia.2,3 Electrolyte levels must be checked weekly.2,3

For bicarbonate levels, Hou recommends low concentrations (25mEq/l). Based on collective experience, frequent haemodialysis can result in excessive alkali transfer to the mother, producing alkalemia.2,27,42

In order to achieve the desired haemoglobin levels of 10-11g/100ml in these women (haematocrit: 30%-35%), erythropoietin doses must be increased by 50%-100%.20-25

In addition, anaemia during pregnancy is associated with increased incidence of pre-term births, which results in greater infant mortality rates.51

Asamiya et al analysed 24 pregnant patients on haemodialysis and demonstrated a positive correlation between maternal haemoglobin and a successful pregnancy.43

The use of erythropoietin during pregnancy has proven safe, with no documented increases in blood pressure or teratogenicity.25,52

During pregnancy, the mother and foetus need 800-1000mg of iron. Oral supplements would be insufficient, so it can be administered intravenously, without adverse effects. Frequent checks of haemoglobin and ferritin values should be performed.2

Table 3. Parameters for dialysis and foetal survival

<table>
<thead>
<tr>
<th>Year</th>
<th>No. pregnancies</th>
<th>Hours per week on dialysis</th>
<th>Sessions per week</th>
<th>Kt/V</th>
<th>Predialysis urea (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>15</td>
<td>16-24</td>
<td>4-6</td>
<td>weekly Kt/V: 6-8 in 3 patients</td>
<td>-</td>
</tr>
<tr>
<td>1999</td>
<td>54</td>
<td>22</td>
<td>4.5</td>
<td>-</td>
<td>&lt;100</td>
</tr>
<tr>
<td>1998</td>
<td>14</td>
<td>12-20</td>
<td>6</td>
<td>-</td>
<td>79</td>
</tr>
<tr>
<td>2002</td>
<td>13</td>
<td>16-24</td>
<td>4-6</td>
<td>-</td>
<td>65</td>
</tr>
<tr>
<td>2004</td>
<td>7</td>
<td>16-24</td>
<td>4-6</td>
<td>No</td>
<td>&lt;65</td>
</tr>
<tr>
<td>2005</td>
<td>5</td>
<td>28.6±6.3</td>
<td>6 haemodiafiltration</td>
<td>weekly Kt/V: 7.6-11.4</td>
<td>39</td>
</tr>
<tr>
<td>2008</td>
<td>5</td>
<td>35-56</td>
<td>5-7 nocturnal</td>
<td>-</td>
<td>59.8</td>
</tr>
<tr>
<td>2010</td>
<td>52</td>
<td>15 (9-21)</td>
<td>1998 to1999:(4-6)/2000-2008:(6)</td>
<td>Std Kt/V: 3.1±0.62</td>
<td>86.4±27.4</td>
</tr>
</tbody>
</table>

Kt/V: fractional clearance of urea.

**ANTICOAGULATION**

Heparin does not cross the placenta and is not teratogenic. It must be used in order to avoid coagulation of the vascular accesses.3,53 This treatment should be administered to all patients, except for those with active bleeding.25

Coumarin is contraindicated in these patients.25

**CALCIUM AND VITAMIN D**

Physicians must take into account both the calcium provided by the dialysate and calcium intake in the form of calcium chelating agents. Daily haemodialysis with a 3.5mEq/l dialysate calcium concentration could induce hypercalcaemia, and so 2.5mEq/l concentrations are preferred, along with oral supplements of 1g-2g calcium carbonate.2

Since maternal hypercalcaemia can cause hypocalcaemia and hyperphosphataemia in the newborn and affect its skeletal development, both calcium and phosphorous levels must be monitored weekly.2,44

The placenta converts 25-OH D3 (calcidiol) into 1,25-OH2 D3 (calcitriol), and so 25-OH vitamin D must be measured every trimester, administering supplements if levels are low.1

Although primary hyperparathyroidism is known to increase the frequency of pre-term births by 10%-20%, the effects of hyperparathyroidism on the foetus are unknown. The use of 1,25-dihydroxy-vitamin D is indicated in these cases: this molecule can be used to control both hyperparathyroidism and 1,25-hydroxy-vitamin D deficiency. Calciferol does not appear to be toxic at reasonable doses. Dosage adjustments must be based on weekly calcium and phosphorous measurements.2

Sevelamer, lanthanum carbonate, aluminium hydroxide, cinacalcet, and paricalcitol have not been tested or established for use during pregnancy/lactation.34,55

**NUTRITION**

We recommend to:

- Increase calorie intake by 30-35kcal/day.3
- Consume 1-1.5g/kg of weight (haemodialysis) or 1.8g/kg of weight (peritoneal dialysis) of additional protein daily in order to ensure foetal development.2,8
- Take 1mg/day of folic acid starting from the first trimester.1
- Consume 1500mg/day of calcium.2
- Take water-soluble vitamins throughout the pregnancy, since the requirements for these molecules increase and intensive dialysis promotes their elimination.44
- Supplements for vitamins that can be dialysed (vitamin C, thiamine, riboflavin, niacin, vitamin B6).45
- Many patients also need increased potassium and phosphorous uptake in order to maintain adequate levels.3

**OBSTETRIC MANAGEMENT**

As regards tocolytic agents, intravenous magnesium must be administered with caution in these patients in order to avoid toxicity, keeping levels below 5-7mg/dl. Calcium channel blockers are also administered for this purpose.2,3,56

**KEY CONCEPTS**

1. Gestation in patients on renal replacement therapy involves a risk both to the mother and the foetus, even though new-born survival has improved in recent decades; various studies and registries report survival rates of 40%-85%.59

2. We currently have no literature reference for systematic nephrological/gynaecological treatment of these patients.30,59

3. According to the available literature on the subject, the measures to be taken in order to achieve successful pregnancies in these patients include: multidisciplinary approach, increased time on dialysis, maintain low levels of predialysis urea, prevention of pre-term birth, strict control of blood pressure and electrolyte levels, prevention of urinary infections, and adequate foetal monitoring.2,3,23,24
Indomethacin has been used successfully, especially in women with polyhydranmios. However, in women with residual renal function, this effect can be lost. Additionally, prolonged use for more than 72 hours has been correlated with severe side effects on the newborn, so it should only be used for short periods.\textsuperscript{1,2,5}

Progesterone supplements in their various presentations have not been evaluated in haemodialysis patients or women with chronic kidney disease.\textsuperscript{58}

As regards the length of the gestation period, some authors recommend inducing labour after 34-36 weeks if the baby’s lungs have developed sufficiently, but the majority prefers to prolong the gestation period to 38 weeks.\textsuperscript{3}

Caesarean sections should only be undertaken under the same indications as for women not being treated with haemodialysis.\textsuperscript{3}

Newborns should be monitored in high-risk units, since they are usually born with similar urea and creatinine levels to their mothers, and may suffer osmotic diuresis.\textsuperscript{2,3}

**Conflicts of Interest**

The authors affirm that they have no conflicts of interest related to the content of this article.

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C4d as a diagnostic tool in membranous nephropathy

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Nefrologia 2012;32(3):295-9

ABSTRACT

Introduction: Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adults. The diagnosis is based on typical findings observed using electron microscope (EM) and immunofluorescence (IF) studies. On some occasions, tissues are only available for analysis using an optical microscope (OM); in these cases, it can be difficult to differentiate between MN and minimal change disease (MCD). Recently, the use of C4d immunohistochemical staining has spread. Very little information is available regarding C4d deposits in MN. Our study consisted of analysing whether C4d staining of samples embedded in paraffin could be useful for diagnosing MN.

Material and Method: Ours was a retrospective study including all patients diagnosed with MN by renal biopsy in our unit between January 2001 and October 2008. We only included adult patients with a definitive diagnosis of MN or idiopathic MCD by OM, IF, and ME studies. In October 2008, 3µm sections of renal tissue fixed in formaldehyde were removed from paraffin and rehydrated. The samples were then stained for C4d immunohistochemical analysis using anti-human polyclonal antibodies obtained from rabbits.

Results: Our study included a final sample of 19 patients with MCD and 21 with MN. No C4d deposits were observed in any of the glomeruli in patients with MCD, and 100% of these patients were classified as negative. However, C4d deposits were detected in 100% of patients with MN, and were observable in all glomeruli with a uniform granular distribution, demarcating all capillary loops.

Conclusions: C4d immunohistochemical staining is a very useful tool for diagnosing MN.

Keywords: C4d. Complement. Membranous nephropathy.
Typical findings observed using electron microscope (EM) and immunofluorescence (IF) studies. On some occasions, tissues are only available for analysis using an optical microscope (OM); in these cases, it can be difficult and at times impossible to differentiate between MN and minimal change disease (MCD). In these cases, it would be highly useful to have a diagnostic technique that could be performed on paraffin-fixed renal tissue.

The use of immunohistochemistry to detect the C4d complement degradation product in kidney disease has sparked considerable clinical interest recently. Studies have focused on transplant biopsies as an indicator of acute humoral rejection. Very little information is available on glomerular nephropathy. We have recently demonstrated that mesangial C4d deposition can be used as a prognostic factor in IgA nephropathy.

C4d is a fragment of C4 generated during activation of the classical complement or lectin pathways. This fragment is highly stable, binds covalently to cell surfaces, and can be detected using reagents that are currently available.

MN pathogenesis is mediated by the in situ formation of immune deposits, with the resulting activation of the complement. Therefore, we can expect to find C4d deposits as a marker of complement activation in MN but not in MCD.

The aim of our study was to determine if C4d detection by immunohistochemical staining in MN patients could be a useful diagnostic tool.

**MATERIAL AND METHOD**

The study included all consecutive patients who underwent renal biopsies in our hospital between January 2001 and October 2008. The study was approved by the hospital’s Ethics and Research Committee. Patient information was processed in accordance with personal data protection regulations. Only adult patients with a diagnosis of MCN and idiopathic MN based on the histological analysis of the renal biopsy with OM, IF and EM studies were considered for inclusion in the study. For OM assessment, 2µm histological slices prepared from formaldehyde-fixed paraffin-embedded tissue were stained with hematoxylin and eosin, Schiff’s periodic acid and methenamine silver. The IF study was performed with anti-IgG, IgM, IgA, C3, C1q, Î light chain, Ï light chain antibodies, fibrinogen and albumin. The EM study was performed on glutaraldehyde-fixed renal tissue which was processed for ultrastructural analysis in line with standard laboratory protocols. The histological classification system proposed by Ehrenreich et al was used in MN. Five patients were in stage I, 15 in stage II and 1 patient in stage III.

Thirteen patients were excluded as glomeruli were not obtained for the C4d study. In the end, 19 patients with MCD and 21 patients with MN who met the criteria for inclusion were included in the study.

**C4D IMMUNOHISTOCHEMICAL STAINING IN PARAFFIN-FIXED TISSUE**

All renal biopsies were routinely processed for OM, IF and EM when they were taken, between January 2001 and October 2008. In October 2008, 3µm formaldehyde-fixed sections underwent immunohistochemical staining using anti-human C4d polyclonal antibodies from rabbits (Biomedica, Vienna, Austria).

All the patients’ histological sections were reviewed without clinical or pathology information. The details of these procedures were published previously. Patients were classified as positive when more than 75% of the glomeruli were C4d-positive and as negative when less than 25% of the glomeruli were C4d-positive.

C4d was also analysed by IF with monoclonal antibodies (Biogenesis, Vitro SA, Seville, Spain) in 2 MCD patients and 5 MN patients diagnosed after October 2008.

**RESULTS**

The Table shows the age, sex, serum creatinine and proteinuria of patients diagnosed with MCD and MN before October 2008 at the time of the biopsy. No C4d deposits were observed in any of the glomeruli in patients with MCD and 100% of these patients (n=19) were classified as negative. However, C4d was detected in 100% of patients (n=21) with MN (and in 100% of the glomeruli) (Figure 1) in the form of deposits with uniform granular distribution outlining all the capillary loops (Figure 2 and Figure 3). No mesangial deposits were found.

<table>
<thead>
<tr>
<th>Table 1. Clinical and analytical data at the time of renal biopsy</th>
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<td><strong>Minimal change n=19</strong></td>
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<tr>
<td>Age (years)</td>
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<td>Sex (male/female)</td>
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<td>Serum creatinine (mg/dl)</td>
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<td>Proteinuria (g/d)</td>
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The C4d study by IF with monoclonal antibodies was conducted on another 5 patients diagnosed with MN after October 2008. All patients tested positive for C4d (Figure 4) in both the IF study and the immunohistochemical staining.

Figure 4 shows the hematoxylin and eosin staining study (A and B), the IF studies with anti-IgG (C and D), the IF study with anti-C4d (monoclonal) (E and F), the immunohistochemical staining with anti-C4d antibodies (polyclonal) (G and H) and the EM studies in two representative patients with MCD (B, D, F, H and J) and MN (A, C, E, G and I).

DISCUSSION

Complement deposition (detected by IF, immunohistochemical staining, or EM) is a common characteristic of certain forms of glomerulonephritis (membranoproliferative, post-streptococcal, IgA nephropathy, MN, lupus nephritis and some forms of rapidly progressive glomerulonephritis), and it is generally associated with antibody deposition.\(^5\)\(^-\)\(^7\) These complement deposits often contain both C4 and C3 and are characteristics of the classical pathway of complement activation. Sometimes, they only contain C3 or lack the first components, indicative of complement activation through the alternative pathway.

C4d is the breakdown product of C4, which is activated and degrades as part of the classical pathway of component activation, which is usually mediated by antibodies. This is more useful and applicable to this disease now as the antibody responsible for more than 50%-70% of these cases has been recently identified, an antibody targeted at M-type phospholipase A2 receptor.\(^8\) C4d can also be generated when the complement system is activated through the lectin pathway. Once generated, C4d binds covalently to tissue components at the activation site and is, therefore, a biomarker of classical or lectin pathway activation. C4d deposition in the capillaries of the renal graft was first described in 1993 by Feucht et al.\(^2\) More recently, the detection of C4d in the peritubular capillaries by immunohistochemical staining has been

\[\text{Figure 1. Immunohistochemical study with anti-C4d antibodies of a patient with membranous nephropathy (x10) C4d staining was seen in all the glomeruli (arrows).}\]

\[\text{Figure 2. Immunohistochemical study with anti-C4d antibodies of a patient with membranous nephropathy (x40) C4d deposits can be seen all along the capillary loops.}\]

\[\text{Figure 3. Immunohistochemical study with anti-C4d antibodies of a patient with membranous nephropathy (x100) We can see how C4d staining shows a granular distribution that outlines all the capillary loops (arrows).}\]
Very few studies have analysed C4d deposition in glomerular diseases. Glomerular C4d deposition is expected to be found in lupus nephritis and it is believed to be the result of the immune complex mediated activation of the classical complement pathway. In IgA nephropathy, Roos et al showed that renal histology is more severe when the lectin pathway is activated (and there are C4d deposits in the mesangium). Subsequently, our group demonstrated that mesangial deposition of C4d can be used as a prognostic factor in patients with IgA nephropathy. Renal survival after 10 years stood 43.9% in C4d-positive patients compared with 90.9% in C4d-negative patients (P=.005), which suggests that a different type of complement activation (classical pathway or lectin pathway) plays an important pathogenic role. In idiopathic MN, unlike MN secondary to lupus, there is no C1q deposition. In these cases, the presence of C4d is probably an indicator that the complement is being activated through the lectin pathway.

Information on the role played by C4d in MN is limited to one study published in 1989. In this study, IF was used to test for C4d in 12 patients with idiopathic MN and was detected in 11 of these patients.

C4d immunohistochemical staining using the immunoperoxidase technique described in our study has the major advantage of being performed on paraffin-embedded tissue so that cases in which there is no tissue available for IF or EM study can be diagnosed. Suzuki et al showed that C4d immunohistochemical staining was comparable to IF detection. Our data obtained from 5 patients coincides with this idea.

The site where the C4d is deposited is also worth mentioning. In IgA nephropathy, C4d staining was mainly observed in the mesangium, indicating the probable site where the local complement was activated. In this study on MN patients, C4d deposits were located in the capillary loops of the mesangium and with a granular distribution. MN is characterised by an accumulation of immune deposits on the outer surface of the glomerular basement membrane, which causes the membrane to thicken. These immune deposits have been identified as IgG, often IgG4, and the membrane attack complex of complement C5b-9. We believe that C4d forms part of these immune deposits. Furthermore, it has been suggested that complement activation plays no role in MCD pathogenesis. Our study provides support for both of these theories. C4d deposition was observed in the glomerular basement membrane of 100% of MN patients while the results were negative in 100% of the cases with MCD.

In summary, our data suggest that C4d immunohistochemical staining is a highly useful tool for the differential diagnosis of MN and MCD in adults. This finding is particularly significant as the diagnosis can be performed even if we only have tissue for OM available.
REFERENCES

**Elderly patients with chronic kidney disease: outcomes after 5 years of follow-up**

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Nefrologia 2012;32(3):300-5

**ABSTRACT**

**Introduction:** In recent years, chronic kidney disease (CKD) has come to be considered an epidemic problem, and there is considerable interest in early diagnosis in order to slow its progression to end-stage renal disease (ESRD) and prepare patients for dialysis and transplantation programmes. Many elderly patients are labelled as having CKD based solely on having a glomerular filtration rate (GFR) of <60 ml/min. **Objectives:** Monitor renal function (RF) and outcomes associated with CKD (morbidity, mortality and progression to ESRD) in an elderly cohort. **Patients and method:** A total of 80 clinically stable patients, with a median age of 83 years (range 69–97; 69% female, 35% diabetic, 83% hypertensive) were recruited at random in our Geriatric Medicine and Nephrology Departments between January and April 2006, and monitored for 5 years. During the recruitment stage we established two groups based on baseline serum creatinine (Scr) concentration: Group 1, 38 patients with Scr <1.1 mg/dl (range 0.7-1.1) and Group 2, 42 patients with Scr >1.1 mg/dl (range 1.2–3). We determined baseline blood levels of creatinine and urea, calculated eGFR using an abbreviated Modification of Diet in Renal Disease (MDRD) formula, and repeated these measurements after 5 years. We recorded baseline comorbidity according to the Charlson comorbidity index (CCI); hospital admissions; new cardiovascular events; treatments; progression to ESRD requiring dialysis; and mortality. **Results:** In the 39 patients surviving after 5 years there were no significant differences between Groups 1 and 2 in total number of hospital admissions, episodes of heart failure and new ischaemic heart disease. Overall, the most commonly used drugs were diuretics (76.9%), while beta-blockers were used the least (10.3%). There were 41 deaths (51.3%): of these patients, 15 died due to overall decline, 8 due to infections, 4 due to stroke, 4 due to neoplasia, 3 due to cardiovascular problems, 2 due to complications from fractures and 5 due to unknown causes. Mortality was higher in Group 2 (66.7% vs 34.2%, \( P = 0.004 \)) and patient age was also higher in that group (84.73±5.69 vs 80.12±6.5, \( P = 0.001 \)). No significant differences in mortality were attributable to sex, diabetes, hypertension or CCI. Only 2 patients in Group 2 progressed to ESRD, they received conservative treatment due to comorbidity (no patients in the study have started dialysis). The evolution of RF (baseline/5 years) in all patients surviving at 5 years was as follows: Scr (mg/dl): 1.15±0.41/1.21±0.49 (not significant [NS]), urea (mg/dl) 52.21±13.0/61.21±27.0 (\( P = 0.047 \)), MDRD (ml/min/1.73m²) 57.47±15/54.86±17 (NS). There were no differences in progression between the 2 groups. In the logistic regression analysis for overall mortality (independent variables: age, sex, CCI, cardiovascular history, Scr and group), only age (relative risk [RR]: 1.12; 1.03-1.23, \( P = 0.009 \)) and group (RR: 3.06; 1.10-8.40, \( P = 0.031 \)) were independently associated with mortality. **Conclusion:** Screening for CKD using GFR only may lack clinical relevance in this population since RF slowly deteriorates in elderly patients without proteinuria. Mortality due to all causes was higher in elderly patients with a poorer baseline RF, and mortality rates were higher than rates of CKD progression to ESRD.

**Keywords:** Chronic kidney disease. Elderly. Glomerular filtration rate. Renal function. End-stage renal disease. Mortality.

**RESUMEN**

**Introducción:** En los últimos años, la enfermedad renal crónica (ERC) se ha llegado a considerar una epidemia, por lo que se ha...
INTRODUCTION AND OBJECTIVES

CKD has been considered a public health problem ever since the NKF (National Kidney Foundation) and KDIGO (Kidney Disease: Improving Global Outcomes) introduced a definition and classification method for chronic kidney disease (CKD) judged to be applicable to the entire population.1,2 For this reason, doctors now show considerable interest in early detection of CKD, in order to take actions to slow its progression to end-stage renal disease and have enough time to prepare patients for dialysis and transplant programmes where necessary.3

In general, we are taught that after the age of 30, glomerular filtration rate (GFR) decreases at a mean rate of 1 ml/min/year. The Baltimore longitudinal study of aging, which included 254 healthy volunteers, found that the mean decrease in creatinine clearance was 0.75 ml/min/year.4 At present, and as stated in KDOQI guidelines, CKD prevalence is high, particularly in the elderly. This has led to widespread debate among nephrology professionals, who disagree about whether or not decreased GFR in this population may show the physiological ageing process rather than intrinsic kidney disease.5,6

Additionally, elderly patients often present certain comorbidities associated with CKD, such as atherosclerosis, heart failure (HF), high blood pressure (HBP), diabetes mellitus (DM) and cognitive deterioration which may all affect the CKD prognosis.7,8

Objectives of this study were as follows: 1) analyse how CKD progresses from baseline renal function (RF) (rapid progression is considered to be a decrease >_4 ml/min/year); 2) analyse main outcomes associated with CKD: progression to stage 5 CKD requiring renal replacement therapy (RRT) and mortality; and 3) study associated mortality by analysing hospital admissions, the appearance of new cardiovascular events and indicated treatments.

PATIENTS AND METHODS

Patients

We studied 80 clinically stable patients with a median age of 83 years (range: 69-97 years), who were randomly recruited during scheduled outpatient check-ups with the Geriatric Medicine and Nephrology departments between January and April 2006. According to baseline serum creatinine (S_Cr) levels, we established two groups: Group 1, n=38, S_Cr ≤1.1 mg/dl (range 0.7-1.1) and Group 2, n=42, S_Cr >1.1 mg/dl (range 1.2-3). Of the total, 55 patients (69%) were male; 28 (35%) had DM and 66 (83%) had HBP. Socio-demographic characteristics, RF and baseline comorbidity for both groups are shown in Table 1.
Patient distribution by CKD stage (using the abbreviated MDRD formula) for the baseline period was as follows: stage 1: 0%; stage 2: 30%; stage 3: 60%; stage 4: 10%; stage 5: 0%.

Method

Observational analytical cohort study. The first evaluation was completed at the time of the patient’s scheduled visit during the period between January and April 2006. All of the elderly patients underwent laboratory and clinical monitoring during 5 years, and were re-evaluated during the January - April 2011 period.

Laboratory analyses were completed as a baseline measurement one week before patients came in for scheduled visits with Geriatric Medicine or Nephrology departments, and they were repeated once again after 5 years. Creatinine and urea levels were measured in venous blood according to the routine method used at Hospital General de Segovia. Systematic urine analysis was completed for all patients to screen for proteinuria; additionally, for Group 1, the protein (mg/dl) / creatinine (mg/dl) ratio was measured in a single morning void. In Group 2, the urine protein count was measured in a 24 hour sample. In the baseline period, the systematic analysis detected no proteinuria in Group 1 and the urine protein/creatinine ratio was <0.05g. In Group 2, baseline proteinuria was 0.31±0.51g/24 hours (range 0-3.0g/24 hours): 87% of Group 2 patients had proteinuria <0.5g/24 hours; 5.2% had values between 0.5g and 1g/24 hours; and 7.8%, between 2g and 3g/24 hours. GFR was estimated using the abbreviated MDRD formula.10

Baseline comorbidity was calculated using the Charlson comorbidity index (CCI) without including age.11 We also recorded hospital admissions, appearance of new cardiovascular events (HF, ischaemic heart disease, stroke) and drugs taken during the 5 year period. With regard to the CKD prognosis, we evaluated 1) changes in RF over the 5 year period in patients who remained in the study; 2) patients who progressed to ESRD and began RRT; and 3) mortality and its causes.

Statistical analysis

Statistical analysis was performed using SPSS software version 15.0. Data are expressed as percentages, means and standard deviations. Changes in RF over time were evaluated using a linear model for repeated measures. Proportions were compared using chi-square (Fisher’s test). Variables predicting mortality were analysed using logistic regression analysis. The statistical significance level was 95% (P<.05).

RESULTS

After 5 years of follow-up, 39 patients (including 10 males) with a mean age of 84.94±6 years (74-101) remained in the study. Only 2 patients (5.1%), both in Group 2, (SCr>1.1mg/dl), were taking erythropoiesis-stimulating agents (ESA); 5 (12.8%) were treated with iron salts; 10 (25.6%) with calcium salts and 12 (30.8%) with statins. Diuretics were the most commonly-used anti-hypertensive agents (76.9%) and most were loop diuretics (48.7%). Angiotensin-converting enzyme (ACE) inhibitors were prescribed for 35.9% of the patients; and angiotensin II receptor blockers (ARB) and calcium blockers for 20.5%, respectively. Beta-blockers were the least commonly-used antihypertensive agents, prescribed for 10.3% of these patients. There were no significant differences between the 2 groups with regard to prescriptions for ESA, iron salts, calcium salts, statins, diuretics, ACE inhibitors, ARB, calcium blockers or beta blockers. Systolic blood pressure

<table>
<thead>
<tr>
<th>Table 1. Socio-demographic characteristics, renal function and baseline comorbidities by group</th>
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<tbody>
<tr>
<td><strong>Group 1 (n=38)</strong></td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Sex (male/female)</td>
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<tr>
<td>Baseline SCr (mg/dl)</td>
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<tr>
<td>Baseline MDRD (ml/min)</td>
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<tr>
<td>Proteinuria (g/24h)</td>
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<tr>
<td>Hypertension (%)</td>
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<tr>
<td>Diabetes mellitus (%)</td>
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<td>Charlson comorbidity index</td>
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SCr: serum creatinine; MDRD: Modification of Diet in Renal Disease formula; ns: not significant. Group 1: SCr <1.1mg/dl; Group 2: SCr >1.1mg/dl.
(BP) recorded after 5 years was 128.83±13mm Hg (100-160); and diastolic BP 70.56±10mm Hg (50-95).

During the study period, 60% of the patients were admitted to hospital at least once. Regarding new cardiovascular events, 20.3% of the patients had an episode of HF, 7.5% suffered a stroke and 6.3% suffered IHD. If we compare new cardiovascular events between the 2 groups, we find the following: in Group 1, 13.5% of patients suffered from an HF episode and in Group 2, 26.8% suffered 1 or more episodes; ischaemic heart disease was present in 5.3% of Group 1 patients and in 7.3% of Group 2 patients; and a stroke episode occurred in 11.5% of Group 1 patients and in no patients in Group 2. These differences were not statistically significant.

Overall data regarding changes in RF (baseline/5 years) in surviving patients were as follows: SCr (mg/dl): 1.15±0.41 vs 1.21±0.49 (not significant [ns]); urea (mg/dl) 52.21±13.0 vs 61.21±27.0 (P=.047); MDRD (ml/min/1.73 m²): 57.47±15.0 vs 54.86±17.0 (ns). Changes in RF by group are shown in Table 2. Among all surviving patients, GFR decreased at a mean rate of 0.52ml/min/year. When this parameter was broken down by group, we found that in Group 1 (baseline creatinine ≤1.1) the mean decrease was 0.67ml/min/year, compared to 0.26ml/min/year in Group 2.

Only 2 patients, both in Group 2, progressed to ESRD, but neither case started RRT. Conservative treatment was administered in the first case according to the patient’s own decision, and the second patient was not included in a RRT programme due to advanced age (89 years) and high comorbidity (patient had undergone surgery for meningioma, was in a wheelchair and had a bladder neoplasm). Both patients died during the study period. Regarding overall mortality, 41 patients (51.3%) died during the 5 year follow-up period: there were 15 deaths due to general decline, 8 due to infections, 4 due to stroke, 4 due to neoplasia, 3 due to cardiovascular problems, 2 due to complications from fractures and 5 due to unknown causes. Causes of mortality broken down by group are listed below. Group 1: 4 due to general decline, 4 due to infections, 2 due to stroke, 1 due to cardiovascular problems, 1 due to neoplasia and 1, unknown. Group 2: 11 due to general decline, 4 due to infections, 2 due to stroke, 3 due to neoplasia, 2 due to cardiovascular problems, 2 due to complications from fractures and 4, unknown. A comparison of baseline comorbidities of patients who died found no significant differences between the 2 groups. Mortality was higher in Group 2 (66.7 vs 34.2%; P=.004). Patients who died were also older (84.73±5.69 vs 80.12±6.5; P=.001).

There were no statistically significant differences in mortality related to sex, presence/absence of DM or HBP or baseline CCI. Logistic regression analysis for overall mortality (independent variables: age, sex, CCI, history of cardiovascular disease, baseline SCr and group) showed that only age (relative risk [RR]: 1.12; 1.03-1.23; P=.009) and group (RR: 3.06; 1.10-8.40; P=.031) were independently associated with mortality.

**DISCUSSION**

The main findings of this study are as follows: 1) the GFR in elderly patients in this study remained stable or decreased slowly over the 5 year follow-up period, regardless of baseline GFR; 2) we did not find statistically significant differences that could be attributed to baseline GFR regarding new cardiovascular events or treatment received

### Table 2. Changes in renal function by group among patients surviving at 5 years of follow-up

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P^1</th>
<th>P^2</th>
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<tr>
<td></td>
<td>n=25</td>
<td>n=14</td>
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<tr>
<td>Baseline SCr</td>
<td>0.93±0.1</td>
<td>1.53±0.5</td>
<td>ns</td>
<td>ns</td>
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<tr>
<td>SCr at 5 years</td>
<td>0.99±0.1</td>
<td>1.60±0.6</td>
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<tr>
<td>(mg/dl)</td>
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<td></td>
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<tr>
<td>Baseline urea</td>
<td>43.66±8</td>
<td>59.90±12</td>
<td>0.046</td>
<td>ns</td>
</tr>
<tr>
<td>Urea at 5 years</td>
<td>45.33±12</td>
<td>75.50±30</td>
<td></td>
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<tr>
<td>(mg/dl)</td>
<td></td>
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<tr>
<td>Baseline eGFR (MDRD)</td>
<td>65.19±10</td>
<td>43.82±10</td>
<td>ns</td>
<td>ns</td>
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<tr>
<td>eGFR at 5 years</td>
<td>61.84±14</td>
<td>42.51±15</td>
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<td>(ml/min/1.73m²)</td>
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^1 Differences between the groups are present in the baseline period (P=.000); P^1: changes during follow-up; P^2: changes are different between the 2 groups.

SCr: serum creatinine; eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease formula; ns: not significant.
during the 5 year follow-up; 3) almost no patients progressed to stage 5 CKD; 4) mortality was significantly higher among Group 2 patients (SCR >1.1mg/dl). It was associated with older patients, and seemed to be independent from all other comorbidities.

In our follow-up reports for these patients at 24 months and 36 months, we stated that RF remained stable or decreased slowly over time. Our follow-up report at 5 years confirms prior conclusions: RF decreases slowly in elderly patients, and most die before progressing to RRT-dependent ESKD.

Overall, the mean decrease in GFR was 2.61ml/min over the 5 years of follow-up covered by our study. In the analysis broken down by group, we find a slight, non-significant decrease in GFR over time, but there is an interesting paradox: Group 1 patients (those with SCR levels within the normal range) showed a greater decrease in GFR (ml/min/year) than Group 2 patients, who had a poorer baseline GFR. A possible explanation is that the decline in Group 1 simply represents the physiological phenomenon of GFR decreasing with age, while rates in Group 2 remained almost constant since patients whose GFR declined sharply died and patients whose GFR was more stable survived.

In recent years, increased demand for RRT (dialysis or transplant) has sparked interest in the early detection of CKD. In fact, one of the goals of early detection is to initiate preliminary treatments to slow the rate of CKD progression to stage 5, and prepare patients for RRT where appropriate. Nevertheless, these objectives seem less clear for the elderly population, as the vast majority are not going to receive specific preparation for RRT. This may be due to the patient’s own decisions, doctors’ decisions based on the comorbidities associated with RRT that may contraindicate such treatment (neoplasia, cognitive deterioration, etc.), or death. Some preliminary studies have shown that risk of death is higher than the risk of reaching ESRD: for example, the study by Eriksen and Ingebretsen reported a 31% mortality rate, while only 2% of their patients started RRT. In our elderly population, we also recorded high mortality rates (more than 50% at 5 years) and noted that patients died before reaching ESRD and/or requiring RRT (only 2 patients reached ESRD and neither one was included in the RRT programme).

Patients with a poorer baseline RF (Group 2) had significantly higher mortality rates in our study. A possible explanation is that these patients, in addition to having poor baseline RF, were significantly older. In fact, logistic regression analysis found an association between age and mortality that was independent from the group; progressive decline was the leading cause of death in this cohort, and not cardiovascular disease (which is the primary cause of death in CKD patients in general). For this reason, the high mortality rates recorded among elderly patients with poor GFR support the need to provide overall patients with poor GFR support the need to provide overall treatment, even if kidney function is not the key factor on which their survival depends.

Regarding morbidity, 60% of the total patients were hospitalised at least once. HF was the main cardiovascular event (followed by ischaemic cardiopathy and stroke). Although differences were not statistically significant (either due to the low number of patients evaluated or the period of time in question), Group 2 patients experienced more HF episodes during follow-up.

Diuretics are drugs that aid in BP control and have the added benefit of preventing HF episodes. In our study population, diuretics were the main anti-hypertensive agents prescribed (76.9%); however, 20% of patients presented 1 or more HF episodes. In addition to preventing HF, use of diuretics may increase SCR values due to the volume depletion associated with use of such drugs, as we reported in a previous study. Treatment with diuretics is therefore a factor that must be considered when evaluating CKD in elderly patients: the same patient may be categorised in different stages of CKD depending on whether he or she was taking diuretics when SCR and GFR (MDRD) were measured.

Proteinuria is the main sign of kidney injury. In our study, Group 1 patients had no proteinuria at the time of the baseline measurement, and more than 80% of Group 2 patients had proteinuria levels below 0.5g/24h. Only 14 patients in Group 2 were still in the study 5 years later, and this number is too low to allow us to reach any conclusions regarding the prognostic value of proteinuria. In fact, we believe that our assessment at 36 months was more reliable. At that time, we showed that patients with proteinuria were the ones whose renal function deteriorated the most over time, and that proteinuria and age were the main variables associated with mortality.

In conclusion, CKD screening based solely on GFR may have no clinical relevance in these patients since GFR decreases slowly over time in elderly patients without proteinuria. Patients with poorer baseline GFR do not present an increased risk of new cardiovascular morbidity and mortality, although their overall mortality rate is higher, particularly in the very old ones. The risk of mortality is higher than the risk of progressing from CKD to ESRD. Based on these findings, we recommend caution when applying current guidelines to elderly patients.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.
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Optimising expanded donor organs through dual kidney transplantation: a case-control study

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Nefrologia 2012;32(3):306-12

ABSTRACT

Introduction: In order to take full advantage of ECD kidneys, which may not provide sufficient renal mass if used individually, it has been suggested that such organs be used in dual or bilateral kidney transplantation (DTx). Patients and method: We analysed the experience in a single hospital between May 2007 and March 2011 in a case-control study. Criteria for determining whether to perform single or dual Tx were defined in a protocol in which the biopsy score was important, but not the only factor. Donor’s age, medical history, kidney size and creatinine clearance were also considered. During this time period, 80 kidneys from donors over age 65 were transplanted. Single transplants (STx) accounted for 40 of the organs, and another 40 were used in DTx. Results: Mean donor age for STx was 68.7±3.0 years; for DTx, it was 74.2±4.3 years (P<.001), with more female donors for DTx (75%) than for STx (40%) (P<.001). There were no differences between groups with regard to glomerular filtration rate or proteinuria. Kidneys assigned to DTx received higher biopsy scores than those assigned to STx (2.95±1.01 vs 1.8±1.04; P<0.01). DTx recipients were older than STx recipients. There were no differences between the groups regarding cold ischaemia time, delayed graft function, haemorrhagic complications or re-surgeries. However, DTx recipients achieved better creatinine clearance at 1, 3, 6 and 12 months, although the difference was only statistically significant at 6 months (53.4±19.5ml/min vs 44.5±15.6ml/min; P<0.05). Renal artery thrombosis appeared in 2 STx patients and in both kidneys of 1 DTx patient. Another 2 patients in the DTx group each lost 1 kidney due to thrombosis and ureteral necrosis respectively, but were able to remain dialysis-free.

Graft survival at 3 years was 90% for both groups. During the study period 3 patients died (2 in the STx group and 1 in the DTx group). Conclusions: Our preliminary experience indicates that DTx provides good results in terms of survival and renal function data, despite surgery being more complicated and the organs having characteristics that probably make them unsuitable for STx. The decision to perform DTx makes using ECD kidneys easier, and it should be based on a combination of pre-transplant histological criteria and the donor’s clinical characteristics.

Keywords: Dual kidney transplant.

Optimización de donantes expandidos con el trasplante birrenal: estudio caso-control

RESUMEN

Antecedentes: El perfil clínico de los donantes fallecidos se está transformando velozmente hacia un incremento de donantes con criterios expandidos (DCE), por lo que el número de riñones descartados para trasplante está creciendo. Con la finalidad de optimizar el aprovechamiento de riñones de DCE que individualmente podrían aportar una masa renal insuficiente, se ha sugerido su utilización en sinergia con riñones de donantes con criterios normales (CNE), con el fin de aprovechar el riñón ilícito de los DCE. Pacientes y métodos: Se analizó la experiencia en un hospital entre mayo de 2007 y marzo de 2011. Se excluyeron casos en los que se mantuvo el riñón ilícito del DCE en el grupo de recubiertos. Se seleccionaron 20 pacientes para el grupo de recubiertos de ECD y 20 pacientes para el grupo de recubiertos de CNE. Resultados: No hubo diferencias significativas en el tiempo de coagulación, la función renal crónica o la función renal aguda. En el grupo de recubiertos de ECD hubo una mejor función renal a los 3 meses, aunque la diferencia fue únicamente estadísticamente significativa. En el estudio se observó una mejor función renal a los 6 meses para el grupo de recubiertos de CNE. Conclusiones: La combinación de riñones de ECD y riñones de CNE puede mejorar la función renal a largo plazo.

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INTRODUCTION

Changes in the organ donor profile in Spain have resulted in a gradual increase in numbers of donors who are elderly, have co-morbidities and who die due to cerebral vascular accidents. These factors affect renal function and allograft survival in transplant recipients.

Meanwhile, mean ages of kidney transplants (Tx) recipients have increased; today it would be quite uncommon for a patient on the Tx waiting list to be excluded based on age alone. This practice is supported by studies that show that for all age groups, including septuagenarians, kidney transplant recipients live longer than patients of similar ages who remain on the waiting list and never receive transplants. The current situation therefore includes growing numbers of both elderly recipients and elderly donors.

Unfortunately, given a scenario with numerous expanded criteria donors (ECD), a significant number of harvested kidneys are discarded in the end due to uncertainty about their being able to function acceptably as grafts. This is currently the leading cause of kidneys being declared unacceptable for transplantation, both in Spain and abroad. For example, according to the UNOS database for 2009, 2,762 kidneys harvested in different transplant centres in the United States (19% of the total) were discarded, and this figure increases year after year. In our own region of Andalusia, according to Andalusian Transplant Coordination Authority data (currently unpublished), a total of 149 kidneys (32.1% of the total) were discarded in 2010. This figure is slightly higher than the mean in Spain.

Nevertheless, some of these organs may have been viable for transplants. The decision to discard them is taken based on an urgent evaluation following harvest which considers donor history, macroscopic appearance and results from a kidney biopsy, even though the biopsy findings may have poor predictive value beyond previously known information. Although scientific evidence is quite limited, biopsy results are being used to determine whether a kidney will be accepted for transplant or discarded.

Several years ago, in order to optimise ECD kidney use, doctors suggested that these organs could be accepted as long as they were used in paired or dual kidney transplants (DTx). Medium- and long-term results from DTx procedures were published by OPTN/UNOS in the United States and by numerous authors. This led to a growing trend in ECD kidney use in hospitals that had previously discarded them for not meeting the quality standards established for single Tx. Experiences with DTx have also been reported by different Spanish hospitals, with acceptable results. However, despite the fact that DTx has proven itself useful, it is not widely performed in Spain; fewer than 30 DTx are performed yearly, well below the averages recorded in Europe and the United States.

We must keep in mind that the goal is to match possibilities with needs by considering each recipient’s biological data (advanced age, lower rejection rate, shorter life expectancy, etc.). This encourages use of DTx as a valid option for transplanting pairs of certain types of kidneys in selected recipients.

Lastly, the aim of our study was to analyse results of DTx procedures performed in the Hospital Regional Universitario Carlos Haya, which has been the centre of reference for DTx in Andalusia since 2007.

PATIENTS AND METHODS

We analysed kidney donation and transplantation activity in the Malaga province between May 2007 and March 2011. During these 47 months, 333 donors were recorded by different hospitals within the Malaga province. Of these...
donors, 219 were younger than 65 (65.7%) and 114 older than 65 (34.2%). A total of 96 kidneys from the first group were not transplanted (53 due to macroscopic or microscopic defects; 28 due to prior disease; 15 due to lack of matched recipient). For the donors older than 65, 140 kidneys were discarded (63 due to prior disease and 77 due to macroscopic or microscopic lesions).

The inter-group analysis was designed as a case-control study. Cases were the 40 kidneys approved for DTx in 20 patients. Thirty-two kidneys were harvested in hospitals within the Malaga province, while 8 came from hospitals in other Andalusian provinces (Granada 4; Huelva 2; Córdoba 2). Controls consisted of single transplants (STx) performed in 40 patients in Hospital Carlos Haya during the same time period (2007-2011), where donors were older than 65 years with no other selection criteria.

The decision to accept or reject ECD grafts was made based on results from the pre-transplant biopsy. Biopsy samples, taken once the harvest team had finished the harvesting process, consisted of wedges of renal tissue measuring 10mm by 5mm by 5mm from a representative part of the renal parenchyma that were large enough to permit study of 25 or more glomeruli and two small-calibre arteries in each kidney. The study was carried out using cryostat sections stained with haematoxylin-eosin and methylene blue. The evaluation screened for four types of lesions: sclerotic glomeruli, myointimal hyperplasia, tubular atrophy, and interstitial fibrosis. Each lesion type was given a score between 0 and 3 points, ranging from no lesions to mild, moderate, or severe damage. All kidney biopsies were interpreted by the same 2 pathologists at Hospital Carlos Haya.

Criteria for deciding whether to perform single or dual TX were defined in a protocol in which the biopsy score was important, but not the only factor. Donor’s age, medical history, kidney size and creatinine clearance were also considered. DTx recipients were informed about this option by the nephrologist on duty, and they signed the appropriate consent forms. Figure 1 shows the algorithm used in decision-making.

Dual kidney transplantation was performed through 2 independent incisions in each of the recipient’s iliac fossae. Cold ischaemia time was defined as the arithmetic mean of the time to unclamping for each of the two kidneys.

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**Figure 1.** Algorithm for the decision to choose single or dual kidney transplantation according to the type of kidney donor.

There were no differences in immunosuppressant regimens between the STx and DTx groups. The treatment basically consisted of induction with anti-CD25 antibodies (basiliximab), steroids, tacrolimus introduced on the 3rd or 4th post-operative day to maintain levels of 8-12ng/ml during the first 90 days, and mycophenolate mofetil. There were no differences in follow-up after admission to the Tx unit between single or dual kidney recipients.

**Statistical analysis**

Numerical data are expressed as percentages, mean ± standard deviation or median with interquartile ranges, as appropriate. Quantitative variables were compared using Student’s t-test or the Mann-Whitney U test if they did not follow a normal distribution, which was determined using the Shapiro-Wilk test. Either the chi-squared test or Fisher’s exact test were used for qualitative parameters, as appropriate. Graft survival rates in both groups were calculated using Kaplan-Meier curves and the log-rank test. Patients in the DTx group who maintained function in one of the two graft kidneys were considered dialysis-free for purposes of measuring graft survival. Values of P<0.05 were considered statistically significant. Data analysis was performed using SPSS statistical software, version 15.0 (SPSS Inc, Chicago, IL).

**RESULTS**

During the study period, 396 cadaver-donor kidneys were transplanted in our hospital. Of these organs, 80 came from donors older than 65 years.

Table 1 summarises the main characteristics of the donors in each of the 2 study groups. Donors of kidneys that were transplanted as DTx were older and mainly female. There were no differences between the 2 study groups with regard to renal function, proteinuria, hypertension, diabetes, or cause of death. All kidneys were biopsied, and those with a score of more than 6 were ruled out for transplant. Mean biopsy scores for the STx group were 1.80±1.04 vs 2.95±1.01 for the DTx group (P<0.001).

Table 2 lists the most relevant characteristics of recipients in the 2 study groups. Mean age was higher in the DTx group. There were no differences with regard to moderate-to-severe atherosclerosis, which was present in 15 (42.8%) STx recipients and in 7 (41.2%) DTx recipients. Cold ischaemia times were similar for both groups, as were the percentages of grafts with delayed function. Creatinine clearance (CrCl) estimated by the MDRD method (Modification of Diet in Renal Disease Study Group) was slightly higher in the DTx group than in the STx group, but this difference was only statistically significant 6 months after Tx (P<0.05).

Most complications occurred immediately after transplantation. Table 3 shows the main complications in both groups. There were 2 cases of vascular thrombosis in the STx group that resulted in nephrectomy and return to dialysis. In the DTx group, 1 kidney was lost due to ureteral necrosis and the patient maintained a Cr level of 2.9mg/dl with a CrCl rate of 20ml/min. Additionally, 2 patients experienced arterial thrombosis, which was bilateral in one case and unilateral in the other. The latter case remained dialysis-free with serum creatinine levels at 1.9mg/dl and a CrCl rate of 36ml/min.

Figure 2 shows overall survival rates for kidney graft in each of the study groups (not death-censored). The median follow-up period was 410 days for the STx group and 284 days for the DTx group; the dialysis-free graft survival rate was 90% at 3 years (P=NS).

One patient with DTx died in the third month due to bilateral pneumonia. Two patients in the STx group died due to sepsis and neoplasia at 14 and 44 months, respectively.

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**Table 1. Donor characteristics analysed for both patient groups**

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Sex F (%)</th>
<th>CVA (%)</th>
<th>CrCl 1 (ml/min)</th>
<th>CrCl 2 (ml/min)</th>
<th>Prot-U (mg/l)</th>
<th>HBP (%)</th>
<th>DM (%)</th>
<th>BR (score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STx</td>
<td>68.7±3.0</td>
<td>40</td>
<td>77.5</td>
<td>92.2±22</td>
<td>84.0±18</td>
<td>14.8±2.3</td>
<td>60</td>
<td>20</td>
<td>1.8±1.04</td>
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<td>(n=40)</td>
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</tr>
<tr>
<td>DTx</td>
<td>74.2±4.3</td>
<td>75</td>
<td>90</td>
<td>84.0±24</td>
<td>75.8±18</td>
<td>7.8±1.6</td>
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<td>30</td>
<td>2.95±1.01</td>
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<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

RB: renal biopsy; CrCl 1: creatinine clearance estimated by MDRD (Modification of Diet in Renal Disease); CrCl 2: creatinine clearance estimated by Cockcroft; DM: diabetes mellitus; F: Female; HBP: high blood pressure; NS: not significant; Prot-U: proteinuria; DTx: dual kidney transplantation; STx: single kidney transplantation.
DISCUSSION

Although DTx make up a small percentage of the total cadaver-donor transplants performed in our hospital (5.6%), they present yet another option for optimising the use of kidneys from donors older than 65 years, as shown by our study.

The question of what to measure in expanded criteria donors, and how to measure it, remains controversial. An ideal method would be objective, reproducible and more reliable in identifying high-risk donors, kidneys that are acceptable or unacceptable for Tx, and kidneys that would provide reduced renal function as grafts.16 Using intuition in addition to transplantation records and data from large cohorts, we can point out certain donor characteristics that are associated with poorer functional stages and lower graft survival rates.17,18 Several nomograms have been proposed for evaluating ECD, generally defined as donors 60 years of age or older or donors aged 50-60 with at least two of the following conditions: history of high blood pressure, cerebrovascular accident as cause of death and serum creatinine levels higher than 1.5mg/dl.2 The KDRI (*Kidney Donor Risk Index*) was introduced in 2009; this index includes conditions in both the donor and the recipient which can lead to allograft failure or significant dysfunction.19 Its webpage lets us calculate the risk of delayed graft function according to variables present in the donor and in the recipient.20

Some groups consider that measuring kidney function using estimated glomerular filtration rate formulas is sufficient for accepting kidneys as long as harvesting reveals no major macroscopic abnormalities.21,22 Others, however, feel that strict acceptability testing is necessary for kidneys from elderly donors, and that histological studies of the graft should always be completed prior to transplantation. Although some authors feel that the percentage of glomerulosclerosis may be a sufficient measure,23 other studies24 and consensus documents support individualised, precise measurements of the abnormalities present in different kidney structures (glomeruli, interstitium and blood vessels) prior to Tx.25

Unfortunately, urgent biopsies that are evaluated based on emergency criteria entail some drawbacks. Some of these weaknesses have to do with the methodology; use of quick cryostat sections and less staining does not enable perfect

| Table 2. Recipient characteristics and kidney transplant outcomes |
|------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age (years) | Sex F (%) | Atherosc. (%) | CIT (h) | DGF (%) | CrCl 1m (ml/min) | CrCl 3m (ml/min) | CrCl 6m (ml/min) | CrCl 12m (ml/min) |
| STx (n=40) | 65.5±6.0 | 35 | 15 (42.8) | 15.3±3.7 | 35 | 44.1±14.2 | 45.5±15.6 | 44.4±16.9 | 51.3±6.2 |
| DTx (n=20) | 69.2±4.7 | 45 | 7 (41.2) | 15.8±3.7 | 30 | 48.4±18.7 | 53.4±19.5 | 59.0±18 | 55.0±18.5 |
| P | <0.02 | NS | NS | NS | NS | NS | NS | NS | <0.05 | NS |

Atherosc.: moderate/severe atherosclerosis; CrCl: creatinine clearance estimated by MDRD (*Modification of Diet in Renal Disease*) at 1, 3, 6 and 12 months; DGF: delayed graft function; CIT: cold ischaemia time; NS: not significant; DTx: dual kidney transplantation; STx: single kidney transplantation.

| Table 3. Post-operative complications in transplant patients |
|------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Haemorrhage no. (%) | Linfocele/uropatía no. (%) | Re-surgery no. (%) | Arterial thrombosis no. (%) | Return to dialysis no. (%) | Death no. (%) |
| STx (n=40) | 10 (25.0) | 2 (5.0) | 1 (2.5) | 2 (5.0) | 2 (5.0) |
| DTx (n=20) | 8 (40.0) | 3 (15.0) | 1 (5.0) | 2 (10.0) | 1 (5.0) | 1 (5.0) |
| P | NS | NS | NS | NS | NS | NS |

NS: not significant; DTx: dual kidney transplantation; STx: single kidney transplantation.
visualisation of abnormalities involving vascular damage, especially hyaline arteriopathy (usually underestimated) and the degree of glomerulosclerosis (usually overestimated). Our hospital opted for a pathology study with quick cryosection and haematoxylin-eosin and methylene blue staining; biopsies were evaluated by the same 2 pathologists. Reading quick-section biopsies has its limitations and does not allow for evaluation of hyaline arteriopathy, our hospital decided to continue using the technique after reading a preliminary analysis of 180 ECD kidney biopsies (currently unpublished). In this study, retrospective evaluation of biopsies from kidneys accepted for Tx based on frozen section biopsies resulted in scores of 3 (which would have ruled out transplant use) in 1.1% due to glomerulosclerosis and 5.6% due to hyaline arteriopathy. This obviously allowed us to continue using the simplified method, which provides reports in less time. The Spanish Society of Nephrology recently issued a consensus statement on assessing histological damage in order to decide whether or not a kidney is viable after a certain score threshold.

At the same time, we decided to begin DTx procedures using ECD grafts that could theoretically be discarded due to the histological score being too high (>6). This was in line with Spanish National Transplant Organisation and Andalusian Transplant Coordination Authority directives. This step called for specific selection criteria for the recipients of such grafts: older than 60, absence of cytotoxic antibodies, first-time grafts and no human leukocyte antigen (HLA) match required.

Our team made the technical decision to perform separate implants, placing 1 kidney in each of the iliac fossae using 2 independent approaches. This was considered to lower the risk of complications regarding ureteral integrity and preserving the arterial flow to the lower limbs in patients with differing degrees of atherosclerosis. Other alternatives, such as placing both kidneys in the same iliac fossa so as to preserve the other one for future Tx procedures, have been shown to be useful.

We understand that despite having defined protocols and algorithms, it is sometimes difficult to accept or discard a pair of ECD kidneys that exceed the normal expanded criteria score; we might refer to such organs as “expanded plus”. In these cases, the biopsy score constitutes an objective evaluation and it helps the on-duty nephrologist make the final decision by offering a certain guarantee of good results, at least for the short- and medium-term. The fact that survival rates and renal function data were similar in both of our study groups supports this hypothesis. In any case, we must remember that important factors such as experience and intuition, supported by the donor’s clinical and analytical data, are also involved in the evaluation process.

Lastly, some might argue that some of the kidneys used in DTx could have been transplanted separately, thereby benefiting two different patients on chronic dialysis. Little is known about this matter; there have been no studies specifically designed to determine the precise threshold of viability for STx or to determine when organs should be used in DTx or be discarded. The 2 patients in the DTx group who remain dialysis-free with 1 functioning kidney have slightly higher serum creatinine levels than those in the STx group, and this coincides with data from other studies.

In conclusion, this preliminary study suggests that DTx offers good results as shown by survival rate and renal function data, despite surgeries being more complex. Decisions to perform DTx in experienced Tx centres should be based on the combination of pre-Tx histological criteria and the donors’ clinical characteristics.

Acknowledgements

The authors would like to thank all of the kidney coordination, harvest and transplant teams in Andalusia, as well as the Andalusian Transplant Coordination Authority. This study was financed in part by the Andalusian Regional Ministry of Health (PI-0499/2009) and by the Spanish Ministry of Science and Innovation (Instituto de Salud Carlos III, FIS PI10/01020).

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.
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Peripheral arterial disease and kidney failure: a frequent association

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Nefrologia 2012;32(3):313-20

ABSTRACT

Objectives: To determine the prevalence of kidney disease in people older than 49 years old with peripheral arterial disease and to analyse its relationship with risk factors and cardiovascular disease. Material and method: Prospective epidemiological study 3 years in duration with selection by simple random sampling in the general population aged over 49 years. Data on demographic, clinical, prevalence of risk factors and cardiovascular disease were registered. We defined peripheral arterial disease (PAD) by ankle-brachial index (ABI) < 0.9 and chronic kidney disease (CKD) according to estimated glomerular filtration rates by the MDRD < 60 ml/min/1.73m2. Baseline data are presented. Results: 511 people were included. The mean age was 66.6 (9.7) years (SD), 37% were men. The prevalence of PAD was 12.4% (N=63) of the sample, average age 72.6 years, 46% men. The presence of CKD stages 3-5 was 39.7%. Patients with PAD and CKD compared with those with normal renal function were older (75.6 vs. 70.6, p=0.08), predominantly women (64% vs 47.4%, p=ns), and showed higher values for systolic and diastolic blood pressure (159.2 vs 146.1, p=0.08), CRP (1.23 vs 0.38 mg/dl, p=0.05), and albumin creatinine ratio (90.2 vs 26.4 mg/g, p=ns). In this group, the prevalence of cardiovascular risk factors and associated cardiovascular disease, were significantly higher without reaching statistical significance. Conclusions: Kidney failure is present in 39.7% of patients with PAD and it defines a subgroup of patients with high cardiovascular risk.

Key Words: Peripheral arterial disease. Chronic kidney disease. Primary Care.
defined as being caused by stenosis or thrombosis of leg arteries, and one manifestation of systemic atherosclerosis.1

Although the presence of intermittent claudication has traditionally been used as a PAD marker to give an approximate calculation of its prevalence in the general population, the ankle-brachial index (ABI) is currently considered to have more diagnostic precision, and it is recommended for both individual diagnoses and epidemiological studies.1,2 An ABI below 0.9 is 95% sensitive and 100% specific for the presence of stenosis in the vascular array of the lower limbs, which is indicative of atherosclerosis in that region.3,4 ABI is also recognised as a marker of cardiovascular risk, and it has an excellent correlation with the development of coronary artery complications, the incidence rate of strokes and death by cardiovascular or other causes in the general population, particularly in the geriatric population.5,6

It is well understood that the presence of end-stage kidney failure in patients with kidney replacement therapy and PAD is accompanied by increases in lower limb amputations, hospitalisation, and total cardiovascular mortality.7-9 There is a growing interest in examining the correlation between kidney function and PAD, not only during end-stage kidney failure, but also throughout all stages of kidney disease. The NHANES 1999-2000 epidemiological study analysed the prevalence of PAD in patients with kidney disease, defined as those having an estimated glomerular filtration rate (eGFR) measured with the Cockcroft-Gault formula below 60ml/min/1.73 m². Prevalence in this population was 24% compared with 3.7% in the population whose eGFR was higher than 60ml/min/1.73 m² (odds ratio [OR]: 9.7, 95% confidence interval [CI]: 5.6-16.7), P<.001. This correlation was independent from other variables such as age, diabetes, hypertension, hypercholesterolaemia, coronary artery disease and ictus (OR: 2.5, 95% CI: 1.2-5.1, P<.011).10 Very similar results were obtained in NHANES 1999-2004.11 Longitudinal follow-up studies have also shown increased risk of developing PAD in patients with an eGFR below 60ml/min compared to those with a higher glomerular filtration rate (GFR).12,13

Chronic kidney disease (CKD) and PAD have more than just atherosclerosis as a common underlying factor in their anatomical pathology. They also share risk factors such as diabetes, arterial hypertension and smoking, and it is possible that gaining control over these risk factors would reduce or slow the progression of both diseases. This would explain the reciprocal relationship between both entities; that is, patients with reduced kidney function will have higher incidence and prevalence rates for arterial disease, and in turn, kidney failure will be more common in patients with chronic ischaemia of the lower limbs. However, this last postulate has not received much study.

OBJECTIVES

Main objective

Determine the prevalence of chronic kidney disease (CKD) defined as an eGFR <60 ml/min/1.73 m² in a population aged 49 years and older with PAD.

Secondary objective

Analyse the relationship between patients with PAD and kidney failure and classic cardiovascular risk factors and vascular disease at other levels.

MATERIAL AND METHOD

Population and sample

The study population includes all individuals 49 years old or older (n=76 660) residing in Oviedo, Asturias, Spain, identified in the database containing individual health card data. For the purpose of calculating PAD prevalence, 1000 individuals were selected from the initial population through simple random sampling. This number was established based on the following suppositions: estimated prevalence of 0.10 based on other studies, with a Type I error of 0.05 and desired precision 0.03, giving us a sample size (453) that was increased according to an estimate of 60% drop-outs and non-responses. The final sample size was 996 individuals. Terminal and immobilised patients were excluded. Deceased patients, those who moved their residence and those who declined to participate in the study were considered lost and they were not substituted. The study was approved by the Clinical Research Ethics Committee of Asturias.

The main objective of this study is to verify the relationship between PAD and cardiovascular disease in a population 49 years or older during a 3 year follow-up period. This project is a sub-study to determine whether patients with both PAD and chronic kidney disease (CKD) show a more unfavourable risk profile, both at baseline and during disease evolution. Initial data are shown here.

Data registry

We elaborated a protocol for collecting demographic data (age and sex), clinical data (weight, height, body mass index), systolic blood pressure (SBP), diastolic blood pressure (DBP), presence of cardiovascular risk factors (smoking, dyslipidaemia, hypertension, diabetes, obesity), cardiovascular disease (ischaemic heart disease, heart failure, cerebrovascular accident, peripheral arterial disease), in addition to data corresponding to hypertension,
dyslipidaemia, diabetes and anti-platelet drugs. All patients underwent an electrocardiogram and a general biochemical study that included serum concentrations of glucose, uric acid, creatinine, total cholesterol, HDL cholesterol, triglycerides, fibrinogen, C-reactive protein and lipoprotein(a).

Hypertension was diagnosed in the presence of SBP figures $\geq 140\text{mmHg}$ and/or DBP $\geq 90\text{mmHg}$ on 3 separate visits, or in individuals who were already receiving dietary or pharmacological antihypertensive treatment. Arterial blood pressure figures represent average readings from three measurements taken 2 minutes apart.

All subjects who had consumed tobacco during the past month were considered smokers; those who had been smokers but who had not smoked in the past year were considered former smokers.

Subjects with baseline glycaemia figures $\geq 126\text{mg/dl}$ on 2 occasions, or with an oral glucose tolerance test reading above $200\text{mg/dl}$ at 2 hours were considered diabetic, along with subjects already receiving anti-diabetic treatment, whether in the form of insulin or oral anti-diabetic drugs.

Hypercholesterolaemia was declared for total cholesterol scores above $240\text{mg/dl}$ on 2 occasions at least 3 weeks apart, and high triglyceride levels were declared for levels above $200\text{mg/dl}$ on 2 occasions or for subjects already receiving lipid lowering treatment.

Subjects were considered obese if their body mass index (weight in kilograms divided by height in metres squared) was greater than or equal to $30\text{kg/m}^2$.

Presence of cardiovascular disease was considered for ischaemic heart disease, heart failure, cerebrovascular accident and abdominal aortic aneurysm if events were documented by either hospital admission or by a specialist study. There was no active search for subclinical cardiovascular disease (lacunar stroke, silent ischaemic heart disease, etc.).

To determine ABI, each subject remained in dorsal decubitus during 5 minutes, and the ratio of the systolic pressure at the ankle (posterior tibial artery) to that at the dominant arm (humeral artery) was calculated separately for each of the limbs. We used a pocket non-directional Doppler ultrasound (Mini/Audio/Aqua/Dopplex$^\text{®}$) with an 8MHz VP8 transducer. PAD was considered to be present if the index was less than or equal to 0.90.

The abbreviated or modified Modification of Diet in Renal Disease formula (MDRD) was used to estimate GFR, and a rate of less than $60\text{ml/min/1.73m}^2$ was considered indicative of kidney failure.$^{14,15}$ CKD stages are those described in K/DOQI guidelines, and they included the modifications recently suggested by Levey et al. and Tonelli et al.$^{16,17}$

Albuminuria was measured as the albumin-creatinine ratio (mg/g) in a sample collected during morning hours. It was classified as optimal for values $<10\text{mg/g}$; normal-high, $10-29.9\text{mg/g}$; high, $30-299\text{mg/g}$; very high, $300-1999\text{mg/g}$; and nephrotic for values $>2000\text{mg/g}$.

Quantitative variables are given as a mean and 95% CI. Qualitative variables are given with their frequency distributions. Association between variables was assessed using $\chi^2$ or Fisher’s exact test for qualitative variables, and Student’s t-test for quantitative variables. In all cases, values of $P<0.05$ were considered statistically significant. Statistical analysis was performed using the software suite SPSS 15.0.

RESULTS

There were 511 subjects at the start of the study (exclusion criteria are listed in Figure 1); 37.4% were male and the mean age was 66.6 years. From their medical histories, we concluded that the prevalence of hypertension was 31.2%.

The abbreviated or modified MDRD formula:

$$
\text{GFR (ml/min/1.73 m}^2\text{) = 186 x [serum creatinine (mg/dl)]} -1.154 \times \text{age} -0.203 \times (0.742 \text{ if female}) \times (1.212 \text{ if black})
$$

**Figure 1.** Study population flow.
16.6% were smokers, 7.8% had diabetes and 26.7% had a lipid metabolism disorder. General data are described in Table 1.

In total, 63 cases (12.4%) in the sample had PAD as defined by an ABI<0.9. The PAD patient group was 46% male with a mean age of 72.6 years. This group presented slightly elevated SBP (150.3mmHg), baseline glycaemia (113.8mg/dl) and microalbuminuria (51.46mg/g). Their cardiovascular risk factors included hypertension (40.3%), dyslipidaemia (24.2%), microalbuminuria (22.9%), smoking (19.4%) and diabetes mellitus (12.9%). The microalbuminuria section also includes 1 patient with urinary albumin values above 300mg/g (Table 2).

A total of 25 (39.7%) PAD patients had an eGFR<60ml/min/1.73 m$^2$. Table 3 shows distribution by different CKD stages according to eGFR and urinary excretion of albumin for both the general sample and for patients with PAD. Patients with both PAD and kidney failure were older, with higher values for SBP and DBP, baseline glycaemia, C-reactive protein and urinary albumin excretion, although there were no cases in which differences were significant (Table 4). The group with CKD had a higher prevalence of abdominal aortic aneurysm and a tendency towards a higher presence of coronary artery disease, heart failure and global cardiovascular disease, but this was not statistically significant (Table 5).

### DISCUSSION

This is the first study in our country to analyse the prevalence of CKD in the population with PAD. In PAD patients aged ≥50 years, the prevalence of CKD (defined by eGFR, MDRD formula, <60ml/min/1.73 m$^2$) was 39.7%.

The prevalence of PAD in our population (12.4%) corresponds to that reported in other population studies that used ABI<0.9 as a criterion. According to the National Health and Nutrition Examination Survey (NHANES 1999-2004), prevalence in the population aged 60 years and older was 12.2%; it was 19.1% in an epidemiological study in the Netherlands, but this was in a general population aged 55 years and older. However, a recent Spanish study of a

---

**Table 1. General sample data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (people)</td>
<td>511</td>
</tr>
<tr>
<td>% males</td>
<td>37.4</td>
</tr>
<tr>
<td>Age in years</td>
<td>66.66 (9.7)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>141.4 (21.5)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.9 (10)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>28.08 (4.6)</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>102.8 (29.6)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.01 (0.19)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>222.7 (38)</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>138.2 (33.69)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>62.1 (16.04)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>113.8 (68.4)</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.4 (0.2)</td>
</tr>
<tr>
<td>Albumin-creatinine ratio (mg/g)</td>
<td>16.43 (66.4)</td>
</tr>
<tr>
<td>Microalbuminuria (%)</td>
<td>9</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6.1</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>2.5</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>1.2</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm (%)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**Table 2. Characteristics of patients with peripheral arterial disease**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>63</td>
</tr>
<tr>
<td>Men (%)</td>
<td>29(46)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.67(10.8)</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>150.37(30.4)</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>82.16(12.7)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>28.01(4.6)</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>113.8(54.1)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.08(0.3)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>215.81(38.6)</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>129.4(35.3)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>61.71(17.1)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>116.52(55.4)</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.72(1.7)</td>
</tr>
<tr>
<td>Albumin-creatinine ratio (mg/g)</td>
<td>51.5 (170.9)</td>
</tr>
<tr>
<td>Microalbuminuria (%)</td>
<td>22.9</td>
</tr>
<tr>
<td>Coronary disease (%)</td>
<td>16.1</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>3.2</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>6.5</td>
</tr>
<tr>
<td>Kidney failure (%)</td>
<td>39.7</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm (%)</td>
<td>6.3</td>
</tr>
<tr>
<td>Overall cardiovascular disease (%)</td>
<td>17.5</td>
</tr>
</tbody>
</table>

SD: standard deviation; BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; CRP: C-reactive protein.
population aged 49 years and older in 28 different health centres describes a prevalence of 7.6% for PAD. This is justified when we recall that Spain has low figures for cardiovascular risk according to international risk tables. Explaining this difference in prevalence is difficult, because when we compare both populations, we observe that age (72.67 vs 70.7 years), hypertension prevalence (40.3% vs 11.9%), smoking (19.4% vs 11.9%) and hypercholesterolaemia (24.2 vs 10.2%) are much higher in our study. The opposite is true for diabetes (12.9% vs 17%), obesity (1.6 vs 8.2%) and cardiovascular disease, especially myocardial infarction (6.1% vs 29%) and ictus (3.2% vs 24%), which were higher in the other study.

Nearly 40% of the patients with PAD suffered from CKD, which was higher than the 29.7% given by the EROCAP study and the 35% given by the YP Liew study which contained more than 1000 patients. The association of the two diseases is very common. O’Hare analysed the prevalence of PAD in 2229 subjects aged 40 years and older and established 2 groups according to eGFR (greater or less than 60ml/min/1.73 m²). PAD prevalence in the group with normal kidney function was 3.7%, and reached 24% of subjects with a low eGFR. The OR was 3.0 (95% CI [1.7-5.3], \( P < .001 \)), and 2.5 (95% CI [1.2-5.1], \( P = .011 \)), after adjusting for risk factors such as cholesterol, age, ATH and coronary artery disease. The same tendency can be found in

<table>
<thead>
<tr>
<th>Stage eGFR (ml/min/1.73m²)</th>
<th>General sample N (%)</th>
<th>Population with PAD N (%)</th>
<th>Microalbuminuria mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>General sample N (%)</td>
<td>Population with PAD N (%)</td>
<td>Microalbuminuria mg/g</td>
</tr>
<tr>
<td>1 (&gt;90)</td>
<td>24 (4.7)</td>
<td>3 (4.8)</td>
<td>3</td>
</tr>
<tr>
<td>2 (60-89)</td>
<td>347 (68.2)</td>
<td>35 (55.5)</td>
<td>0</td>
</tr>
<tr>
<td>3 (30-59)</td>
<td>133 (26.2)</td>
<td>24 (38.1)</td>
<td>11</td>
</tr>
<tr>
<td>4 (15-29)</td>
<td>3 (0.6)</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>5 (&lt;15)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

PAD: peripheral artery disease; eGFR: estimated glomerular filtration rate.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PAD with CKD Value (SD)</th>
<th>PAD without CKD Value (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males [n(%)]</td>
<td>9 (36)</td>
<td>20 (52.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>75.6(9.5)</td>
<td>70.6(11.4)</td>
<td>.08</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>159.2(34.4)</td>
<td>146.1(25.1)</td>
<td>ns</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>85.7(15)</td>
<td>80.3(10.1)</td>
<td>.09</td>
</tr>
<tr>
<td>BM1 (kg/m²)</td>
<td>29.4(4.1)</td>
<td>27.2 (4.7)</td>
<td>.07</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>118.3(57.7)</td>
<td>110.7(52.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.30(0.28)</td>
<td>0.95(0.13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>205.9(36.8)</td>
<td>222.5(38.9)</td>
<td>ns</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>121.1(32.3)</td>
<td>135.1 (36.5)</td>
<td>ns</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>60.8(18.1)</td>
<td>62.3(16.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>120.7(59.4)</td>
<td>113.7(53.3)</td>
<td>ns</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>1.2(2.6)</td>
<td>0.38(0.4)</td>
<td>.05</td>
</tr>
<tr>
<td>Albumin-creatinine ratio (mg/g)</td>
<td>90.2(261.9)</td>
<td>26.4(56.5)</td>
<td>ns</td>
</tr>
</tbody>
</table>

SD: standard deviation; PAD: peripheral artery disease; HDL: high-density lipoproteins; BMI: body mass index; CKD: chronic kidney disease; LDL: low-density lipoproteins; ns: not significant; DBP: diastolic blood pressure; SBP: systolic blood pressure; CRP: C-reactive protein
a sub-analysis of the ARIC study in which the relative risk of developing PAD, comparing patients with eGFR $>$90ml/min/1.73 m$^2$ and eGFR $\leq$60ml/min/1.73 m$^2$, was 1.04 (95% CI, 0.91-1.18) and 1.82 (95% CI, 1.13-2.14) respectively.12

Analysing known risk factors that are shared by both diseases shows that the group with PAD and CKD was made up of older subjects, predominantly women (64%), and for all variables except the lipid profile, values were higher than in patients with a normal kidney function. The only parameters for which there were statistically significant differences were plasma creatinine and C-reactive protein. Various studies undertaken in patients with stage III, IV or V kidney failure presented results similar to our own with regard to the prevalence of cardiovascular risk factors.23,24

The differences in serum creatinine are logical due to the correlation between creatinine and kidney function, and this is consistent with findings from other studies in which increased serum creatinine is accompanied by increase in the PAD incidence rate.21,25

Differences in the lipid profile may be explained by the possibility of pharmacological treatment currently being used, given that the prevalence of dyslipidaemia is higher in patients with renal conditions.

Urinary excretion of albumin is higher in the group of subjects with kidney disease [90.16 (261.9) vs 26.36 (56.53)], although the difference is not statistically significant. CKD is not defined solely on the basis of decreased GFR; it also entails the presence of persistent kidney injury during at least 3 months, demonstrated by direct methods (kidney biopsy) or indirectly by the presence of albuminuria or proteinuria or abnormalities in imaging tests or in urine sediment.14 Baber states that the association between decreased GFR and decreased microalbuminuria has to do with a high prevalence of PAD, and this could be useful for identifying a subgroup with vascular disease, although this could not be verified in our study.11

In the present study, the prevalence rates of ischaemic heart disease, ictus and heart failure were all listed separately; all of these entities were far more prevalent in the group with concomitant kidney and vascular disease, although prevalence figures were considerably lower than those published in other studies.26,27

We have not found literature analysing the association of abdominal aortic aneurysms (AAA) in the population with PAD and kidney failure. Our results may be consistent with the findings of Nakamura et al. in a small study that observed poorer kidney function in patients with AAA than in the hypertensive population, and with those of Barba et al. documenting a much higher prevalence of AAA in the PAD population than in the general population. Chue postulates that CKD, in addition to being related to atherosclerosis, might increase arterial rigidity through a series of complex processes related to uraemia. In conjunction with other risk factors, especially hypertension, this could be associated with an increased risk of aneurysm. However, the incidence and prevalence rates of AAA in CKD patients are unknown.28-31

The presence of PAD is a sign of generalised atherosclerosis, and it is associated with higher cardiovascular morbidity and mortality rates. Several population studies corroborate this

### Table 5. Prevalence of cardiovascular risk factors in patients with peripheral arterial disease with and without associated chronic kidney disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>PAD with CKD</th>
<th>PAD without CKD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypertension</td>
<td>40</td>
<td>35.1</td>
<td>ns</td>
</tr>
<tr>
<td>Smoking</td>
<td>16</td>
<td>21.6</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12</td>
<td>13.5</td>
<td>ns</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>80</td>
<td>73</td>
<td>ns</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>28</td>
<td>21.6</td>
<td>ns</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>16</td>
<td>8.1</td>
<td>.08</td>
</tr>
<tr>
<td>Stroke</td>
<td>4</td>
<td>2.7</td>
<td>ns</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8</td>
<td>5.4</td>
<td>ns</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>16</td>
<td>0</td>
<td>.012</td>
</tr>
<tr>
<td>Overall cardiovascular disease</td>
<td>24</td>
<td>10.8</td>
<td>ns</td>
</tr>
</tbody>
</table>

**PAD**: peripheral artery disease; **CKD**: chronic kidney disease; **ns**: not significant.
finding; some well-designed studies with long follow-up periods show a close relationship between decreased kidney function (identified by serum creatinine levels or eGFR), and total/cardiovascular morbidity and mortality. 26,27 It would therefore seem that this group is a target population for treatment to prevent cardiovascular events, and a detection strategy must therefore be implemented in order to identify the at-risk population.

Unfortunately, the exact mechanisms contributing to the high prevalence of CKD among patients with peripheral arterial disease are still unknown. Classic cardiovascular risk factors, which are very prevalent in CKD patients, may contribute aetiologically to PAD development, but they only explain a small part of this association. Atheromatous lesions are not restricted to a single area; rather, they become more widespread and severe, and therefore PAD patients frequently suffer from renal artery stenosis, as described in the prospective study by Marin et al. which monitored 418 patients admitted to hospital with severe PAD. An unsuspected stenosis was discovered in the renal artery in 27% of the cases, together with decreased kidney function and increased prevalence of ischaemic heart disease. Since they share aetiology and differentiation, differing stages of ischaemic nephropathy and nephroangiosclerosis might coexist, which would explain the decrease in GFR.33 The role which alterations in the calcium-phosphorus metabolism may play in causing increased vascular calcification and therefore increased PAD and/or kidney disease, especially in the subgroup of patients with both CKD and PAD, is beyond the scope of this study.

A number of authors cite other, less traditional and less commonly-studied risk factors, such as inflammatory markers, increase in lipoprotein(a), oxidative stress, endothelial dysfunction and hyperhomocysteinaemia as factors that could contribute to atherosclerosis development in these patients.32 We found high lipoprotein(a) and C-reactive protein values in the first group, which supports this theory.

Our study has certain limitations. Firstly, the sample size could be called small; it was appropriate for estimating PAD prevalence, but probably insufficient for finding statistically significant differences between the two groups with regard to the risk factor and cardiovascular disease distributions. Secondly, its objective was to measure CKD prevalence in patients with PAD, and not vice versa (prevalence of PAD in CKD patients). This made it difficult to compare it with major studies that did not have the same design. Limitations include the cross-sectional design; since associations are not prospective, we cannot establish a causal relationship between PAD and kidney failure in either direction. Due to these limitations, and particularly the sample size, we may only venture the hypothesis that CKD in the population with vascular disease poses a larger cardiovascular risk. We may be able to confirm this with follow-up data from the study.

CKD is present in nearly 40% of patients with PAD. The presence of decreased kidney function must be taken into account not only for proper adjustment and use of a number of drugs, but also because the copresence of the two conditions is likely to delimit a patient subgroup with a high risk of cardiovascular events. This group may benefit from early diagnosis and treatment, and studies providing an in-depth analysis of the relationship between both conditions are therefore necessary.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

Acknowledgments

The study was made possible by a grant from the Spanish Society of Family and Community Medicine (semFYC).

REFERENCES


Use of sirolimus in patients with primary steroid-resistant nephrotic syndrome

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Nefrologia 2012;32(3):321-8


ABSTRACT

Persistent nephrotic syndrome that does not respond to treatment may cause progression to kidney failure. We designed a therapeutic protocol with sirolimus for this group of patients. We conducted a prospective, interventional, time series, cohort study lasting 20 months. Thirteen patients were enrolled, with a mean age of 10 years (range: 8-18 years old) with steroid-resistant primary nephrotic syndrome and a histological diagnosis of focal and segmental glomerulosclerosis. We administered sirolimus 3.6mg/m²/day. The duration of this regimen was 12 months in responsive patients. The protocol’s efficacy was assessed according to reduction of proteinuria (3 response levels: total, partial, or no response). Severity of histological renal damage and mean time from clinical diagnosis to protocol initiation were also assessed. Nine of 13 patients responded to the treatment with sirolimus, and mean progression time and the severity of histological renal damage influenced response to therapy. We believe that sirolimus is a valid treatment option in patients with steroid-resistant nephrotic syndrome, even though this regimen probably requires an earlier treatment.

Keywords: Steroid-resistant nephrotic syndrome. Sirolimus. Focal and segmental glomerulosclerosis.

INTRODUCTION

Steroid-resistant nephrotic syndrome (SRNS) can lead to chronic renal failure. Proteinuria values in the nephrotic range provide a good marker for renal damage, and reducing these values is correlated with preserved glomerular filtration rate. The massive flow of proteins to the mesangium causes cell proliferation and the activation of chemotactic factors, with a consequent progression towards extrinsic compression of the glomerular vessels, finally leading to global and diffuse glomerulosclerosis. In order to avoid this progression, several different therapeutic options have been employed (cyclophosphamide [CPM], sodium mycophenolate, cyclosporine [CsA], levamisole, tacrolimus, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARB], etc.), in some cases with fairly unsatisfactory results and severe toxic effects.
We designed a treatment protocol for sirolimus (mTOR inhibitor with antiproliferative effects) for primary nephrotic patients with focal segmental glomerulosclerosis (FSGS) that are unresponsive to normal treatment.

**OBJECTIVES**

The primary objective was to evaluate the reduction of proteinuria in patients with primary SRNS treated with sirolimus.

Secondary objectives included: 1) evaluate the correlation between response to treatment and time elapsed from the clinical diagnosis of nephrotic syndrome to treatment with sirolimus; 2) evaluate the relationship between histological damage at the start of treatment and the type of response to treatment.

**MATERIAL AND METHOD**

We performed a prospective, interventional, non-randomised intra-subject study, using a cohort series of 13 patients with a mean age of 10 years (range: 8-18 years) who had primary SRNS resistant to calcineurin inhibitors (CsA, tacrolimus), and cyclophosphamide. They did not respond to enalapril (EN) or losartan (LO) treatment either.

We defined nephrotic syndrome as proteinuria >40mg/m 2/hour, hypoalbuminaemia <2.5g%, and frequent hypercholesterolemia above the 95th percentile for the patient’s sex and age group.12 We defined SRNS as persistent nephrotic syndrome after having completed 4 weeks of treatment with meprednisone at 48mg/m2/day (steroid dose equivalent to 60mg/m 2/day of prednisone), followed by 3 consecutive pulses of 16-beta-methylprednisolone at 15mg/kg/dose.13,14

Patients were biopsied before starting treatment with CsA, and the pathological diagnosis of FSGS was defined as at least one glomerulus with a segmental lesion, which in turn was defined as the existence of at least one lobule with capillary scarring in the glomerulus examined. The diagnosis was considered to be primary in the absence of immunopathological or ultrastructural evidence of other coexisting glomerular diseases, or in the absence of a systemic disease associated with FSGS. It was not possible to perform genetic analyses of any of the patients studied.

Inclusion criteria were: nephrotic syndrome with primary FSGS, negative pregnancy test, and approved medical consent. The exclusion criteria were: creatinine clearance (CCr) <60ml/min/1.73m 2, gastric or duodenal ulcers, active tumours and/or infections with or without specific treatment, diabetes, morbid obesity, vesicoureteral reflux, single kidney, or intravenous drug abuse. Finally, the criteria for interrupting treatment were a reduction in CCr>30% from initial levels for a period >3 months, leukopenia (leukocyte count <3000/mm³), refractory anaemia, active infection, persistent gastrointestinal intolerance, or lack of response in proteinuria reduction, <50% from initial values, after 6 months of treatment.

The variables evaluated included: nephrotic proteinuria, severity of the initial histological lesion, adverse events related to treatment with sirolimus, and time elapsed between establishing the clinical diagnosis and starting treatment with sirolimus.

In order to evaluate the efficacy of treatment, we established three different levels of therapeutic response: 1) total response: reduction in proteinuria <4mg/m 2/hour; partial response: reduction in proteinuria of 4-40mg/m 2/hour; and no response: persistent nephrotic proteinuria >40mg/m 2/hour.

All histological lesions were classified by the same pathologist, who established the severity of histological renal damage according to medical literature values15 and personal experience, establishing a scale of 0-3 (absent, mild, moderate, and severe) for glomerular sclerosis, interstitial fibrosis, and vascular atrophy, respectively. Based on the level of sensitivity and specificity for each histological variable measured, a score >6 was considered to be indicative of high risk. We also evaluated the time elapsed between the clinical diagnosis of nephrotic syndrome and the start of treatment with sirolimus.

The 13 patients were receiving EN at the start of the study, with a dosage range of 0.1-0.3mg/kg/day, and LO at a dose of 0.8-1.5mg/kg/day. Sirolimus was administered at 1-5mg/m 2/day (maximum dose of 5mg/day) once a day, maintaining a whole blood concentration of 7-10ng/ml.

We took monthly blood samples and tested for: creatinine (calculating CCr using the Schwartz method) uraemia, complete haemogram, cholesterolemia, triglyceridemia, LDL cholesterol (low-density lipoprotein), HDL cholesterol (high-density lipoprotein), protein electrophoresis, serum amylase, blood uric acid, serum lipase, hepatogram, serum electrolytes, and sirolimus levels in whole blood samples. We also measured urine electrolytes, proteinuria/day, and urine urea in urine samples.

If adverse events occurred related to the treatment provided, the following measures were taken:

- 25% reduction of the initial sirolimus dose
- Treatment of symptoms,
Miguel Liern et al. Treatment of nephrotic syndrome with sirolimus

Nefrologia 2012;32(3):321-8

- Return to initial drug dose once symptoms disappeared.

The statistical methods used for analysing the data were:

- Wilcoxon test for evaluating the probability of response based on the type of therapy employed and variation in proteinuria,

- Multiple regression analysis to evaluate the relationship between each variable evaluated (tubular atrophy, interstitial fibrosis, glomerular sclerosis, time elapsed between the clinical diagnosis of nephrotic syndrome and the start of therapy, and proteinuria prior to treatment) and variation in proteinuria during the study.

A \( P \)-value <0.05 was considered to be statistically significant. Results were expressed as mean ± SD. We used SPSS statistical software, version 13.0, for all analyses.

We obtained informed consent from all patients prior to inclusion in the study, and all steps of the treatment protocol were evaluated and approved by the ethics and research committee at our hospital. There were no conflicts of interest.

Treatment lasted a total of 12 months, and the last check-up was performed 26 months after treatment had commenced.

RESULTS

Upon completing the study, 9/13 patients had responded to treatment; of them, 5 had complete remission of disease and 4 had a partial response. The Wilcoxon test showed very significant results (\( P \)=.0002). The mean pre-treatment value for proteinuria in the 9 patients that responded was 212mg/m²/hour (SD: 20), and the mean post-treatment value in the 4 patients with a partial response was 18mg/m²/hour (SD: 3), with a 92% reduction in proteinuria. The 5 patients with a complete response had a mean post-treatment proteinuria value of 3mg/m²/hour (SD: 1), a 99% reduction in proteinuria (Figure 1). The mean pre-treatment proteinuria value in the 4 unresponsive patients was 226mg/m²/hour (SD: 22) and the post-treatment value was 79mg/m²/hour (SD: 27). This corresponded to a 65% reduction.

During the 12 months of treatment, 2 of the patients with a partial response suffered recurrences. Both reached a partial response again after receiving traditional steroid treatment, with no changes at 1 year.

Of all the variables evaluated, the time at which sirolimus was started (a mean 21.2 months for total response patients, 25 months for partial response, and 31.5 months for no response; R2: 0.70) and tubular atrophy (R2: 0.72) had a strong correlation with variation in proteinuria for all three response types (Table 1).

On the other hand, only mild correlations were observed for interstitial fibrosis (R2: 0.52) and glomerular sclerosis (R2: 0.52), and low correlations were observed for pre-treatment proteinuria levels (R2: 0.38) (\( P \)=.01) (Table 2).

The mean dose of sirolimus was 3.6mg/m²/day (3.1mg/m²/day for total response patients, 3.5mg/m²/day for partial response patients, and 5.8mg/m²/day for unresponsive patients).

The mean EN dose was 0.18mg/kg/day (0.18mg/kg/day for total response, 0.16mg/kg/day for partial response, and 0.20mg/kg/day for no response). The mean dose of LO was 1.1mg/kg/day (1.1mg/kg/day for total response, 1.2mg/kg/day for partial response, and 1.2mg/kg/day for no response).

The mean whole blood concentration of sirolimus was 8.4ng/ml (7.7ng/ml for total response, 8.5ng/ml for partial response, and 9ng/ml for no response) (Table 3).

The following is a description of the adverse events:

- Anaemia: Three patients. Two patients had low ferritin levels and responded well to treatment with ferrous sulphate, and the others had normal ferritin levels but...
inadequate transferrin saturation levels. This patient improved after receiving ferrous sulphate at 7mg/kg/day and 5mg/day of folic acid.

- Acute diarrhoea: Two patients responded well to a temporary dosage reduction of sirolimus and a diet low in fermented foods.

- Mouth ulcers: Three patients went into remission following oral rinses with sucralfate and did not require suspension of sirolimus treatment (Figure 2).

No significant differences were observed in the doses or whole blood levels of sirolimus between patients with and without adverse effects. No other adverse effects occurred that could have been correlated with treatment.

Throughout the study period, 13 patients had the following mean blood pressure values: 77±5mm Hg for total response, 74±5mm Hg for partial response, and 77±5mm Hg for no response. Serum creatinine values were: 0.8±0.1mg/dl for total response, 0.9±0.2mg/dl for partial response, and 0.8±0.1mg/dl for no response.

The 13 patients completed the 12 month treatment protocol, including the 4 that remained within the nephrotic range, since they still underwent a reduction in proteinuria >50% as compared to initial values. Of the 9 patients that responded to treatment, 8 had varying values of proteinuria, but had no relapses by the last check-up performed after 26 months. The 4 unresponsive patients remain within the nephrotic syndrome and have normal glomerular filtration rates (Table 4).

By the time the last control check-up was performed, none of the 13 patients had undergone another biopsy.

**DISCUSSION**

In our study, proteinuria values decreased by more than 90% in 9 of 13 patients. With this substantial decrease, the nephrotic syndrome went into remission in 5 patients, and the other 4 continued with significant proteinuria; even the 4 children that continued to have massive proteinuria experienced a decrease >50% from initial values. Similar results were described in a study by Tumlin,16 after 6 months of treatment with sirolimus.

The management of SRNS is a challenging health situation. Approximately 80% of patients with primary nephrotic syndrome respond to steroid treatment, and the combined use of cytotoxic drugs generally improves the rate of remission15; however, the remaining 20% may require other treatment regimens. This can result in very
Miguel Liern et al. Treatment of nephrotic syndrome with sirolimus

Nefrologia 2012;32(3):321-8

high rates of adverse effects, 4,5 motivating the search for other treatment alternatives that can reduce proteinuria, even if complete recovery from renal damage is not an option. Several different alternative methods have been tested (steroids, CPM, CsA, tacrolimus, ACE inhibitors, ARB, etc.) in monotherapy and combined therapy, although results are often less than satisfactory. 16,17 The use of CsA and tacrolimus-based treatment can result in14,18,19 remission rates as high as 70%, although many of the

### Table 2. Relationship between histological damage and time elapsed to use of sirolimus and variation in proteinuria

<table>
<thead>
<tr>
<th>Partial remission</th>
<th>Complete remission</th>
<th>No remission</th>
<th>Multiple correlation coefficient between each variable of histological damage and change in proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td>de atrofia tubular</td>
<td>de fibrosis intersticial</td>
<td>de glomerular sclerosis</td>
<td>time from the start of sirolimus treatment (months)</td>
</tr>
<tr>
<td>1.5</td>
<td>1</td>
<td>2.2</td>
<td>20.6</td>
</tr>
<tr>
<td>1.2</td>
<td>0.6</td>
<td>1.8</td>
<td>19.8</td>
</tr>
<tr>
<td>2.5</td>
<td>1.7</td>
<td>3</td>
<td>30.7</td>
</tr>
<tr>
<td>0.7202</td>
<td>0.5298</td>
<td>0.5295</td>
<td>0.7048</td>
</tr>
</tbody>
</table>

Multiple correlation coefficient between the mean values for the variables under consideration and changes in proteinuria during treatment with sirolimus; P=.0121.

### Table 3. Final proteinuria values, dosage, and whole blood levels of sirolimus

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pr (mg/m²/hour)</th>
<th>Sirolimus dose (mg/m²/day)</th>
<th>Blood level of sirolimus (ng/ml)</th>
<th>Type of response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>118</td>
<td>5</td>
<td>9.1</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>5</td>
<td>9.7</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>4.5</td>
<td>8.4</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>4</td>
<td>8.8</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>4</td>
<td>9.1</td>
<td>PR</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>3</td>
<td>9.5</td>
<td>PR</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>4</td>
<td>8.8</td>
<td>PR</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>3</td>
<td>6.8</td>
<td>PR</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>4</td>
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<td>TR</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>4.5</td>
<td>7.4</td>
<td>TR</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>2</td>
<td>7.5</td>
<td>TR</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>2</td>
<td>8.1</td>
<td>TR</td>
</tr>
<tr>
<td>13</td>
<td>3</td>
<td>3</td>
<td>7.9</td>
<td>TR</td>
</tr>
</tbody>
</table>

Pr: proteinuria; NR: no response; PR: partial response; TR: total response. Final proteinuria in each patient treated, with corresponding mean doses and mean whole blood levels of sirolimus.
patients treated with these drugs then suffer relapses within 6 months after completing the treatment regimen. In order to avoid this large number of recurrences, treatment periods have been extended, which involves an increased risk of nephrotoxicity.18

Sirolimus is a new immunosuppressant that blocks T-cell proliferation and has a similar structure to tacrolimus, binding to the same immunomodulators without affecting the activity of calcineurin. At therapeutic doses, sirolimus blocks the proliferation of T-cells in the G1-S phase. This mechanism probably reduces structural alteration of podocytes in FSGS.19,20

Few studies have been published on the mechanism of action of rapamycin in these glomerulopathies, and the main objections are its potential long-term toxic effects.21,22 One of the most commonly mentioned side effects is anaemia, with reduced haematocrit in 50% of the treated population. This type of anaemia can be caused by several different mechanisms, such as the drug interfering with the proliferation of primitive erythroid cells.23,24 Three of our patients developed iron-deficiency anaemia, which was effectively treated with ferrous sulphate and folic acid; we did not need to administer erythropoietin to any of our patients.

A causative relationship has been described between sirolimus and hyperlipidaemia, characterised by increased total and LDL cholesterol, apo-B100, apo-C-III, free fatty acids, and triglycerides.23,26 In our study sample, hyperlipidaemia was present prior to starting the treatment protocol, which is frequently observed in nephrotic syndrome. However, considering the reduction in lipid levels observed in the group that went into remission, we were unable to establish a causative relationship between the use of sirolimus and hyperlipidaemia.

With regard to the eventual development of pathological proteinuria and renal failure due to a hyperfiltration mechanism caused by the use of sirolimus, whether in the form of haemodynamic changes (increased renal blood flow and intraglomerular pressure)27 or an unknown mechanism of nephrotoxicity, Fervenza21 reported worsening renal failure (from a pre-existing condition) in 6 of 11 patients diagnosed with FSGS, IgA nephropathy, and primary membranous glomerulonephritis, all treated with sirolimus. Letavernier described adult recipients that developed FSGS with consequent nephrotic syndrome after receiving high doses of sirolimus.28 In a study by Cho,29 0 out of 5 adult patients treated with sirolimus had a total or partial remission of nephrotic syndrome, and treatment had to be suspended due to the appearance of adverse effects (decreased glomerular filtration rate and hyperlipidaemia). In contrast, none of our patients suffered renal function deterioration (the fact that they started the treatment regimen with normal glomerular filtration rates was probably an important factor for patient evolution). Furthermore, proteinuria decreased in all of them, although not always to the same extent.

Diarrhoea is another potential adverse effect.30 In our study, three children suffered acute diarrhoea, abdominal pain, nausea, and vomiting during the treatment period, but responded rapidly to a temporary reduction in the dose of sirolimus and proper diet. The eventual appearance of mouth lesions (ulcers, glossitis, gingivitis, etc.) can occur in patients receiving sirolimus (apparently depending on the dosage). The majority of these diagnoses were made according to clinical criteria (not microbiological), and it has been proven that a reduced dose or temporary suspension of treatment can be used to minimise these effects. In addition, symptomatic treatment appears to improve the symptoms.31 Three of our patients developed mouth ulcers, which disappeared after administering oral rinses with sucralfate and did not require reducing the dose of sirolimus.

The available medical literature highlight the moment of diagnosis and an early start of treatment as factors influencing the failure of SRNS treatment.32-34 In agreement with other results, we observed that the time elapsed before administering sirolimus and the severity of histological lesions prior to treatment had an impact...
on the response to treatment. However, we must admit that our inability to perform genetic tests for nephrotic syndrome impeded the analysis of this important variable. We believe that the two factors are inter-related, possibly promoting the progressive development of non-immunological proteinuria, which is present in the process of hyperfiltration that damages the remaining nephrons. As such, we maintained EN and LO in combination throughout the treatment regimen. The addition of this combined therapy to sirolimus is justified in the haemodynamic and molecular mechanisms of ACE inhibitors and ARB, resulting in a decrease in the diffusion gradients and, eventually, reduced proteinuria.35,36

**CONCLUSION**

We believe that sirolimus is a valid treatment option for patients with SRNS, although an earlier start to treatment is probably necessary. Future studies could contribute to clarifying this issue.

**Conflicts of interest**

The authors affirm that they have no conflicts of interest related to the content of this article.

**REFERENCES**


Successful treatment of calcific uraemic arteriolopathy with bisphosphonates

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Nefrología 2012;32(3):329-34

ABSTRACT

Background and objectives: Calcific uraemic arteriolopathy (CUA), also known as calciphylaxis, is a rare but life-threatening condition that almost exclusively affects patients with chronic kidney disease. Several therapies have been employed to treat this disease but with irregular results. We report a prospective case series of eight patients diagnosed with CUA in our unit between 2002 and 2010.

Material and method: The series consisted of eight patients with CUA (including 4 men, 5 dialysis patients and 3 with functioning allografts) who were treated with bisphosphonates. The diagnosis was by clinical suspicion and a confirmatory biopsy. Five patients had a previous history of high calcium-phosphorus product, 6 had a history of high parathyroid hormone levels (>800pg/ml), 4 had undergone parathyroidectomy, 5 had a history of high cumulative doses of steroids, and 6 patients were under dicumarin treatment. None of the patients were obese or had diabetes mellitus.

Results: In all patients, progression of skin lesions stopped between 2 to 4 weeks after starting bisphosphonate therapy, with no changes in blood levels of calcium and phosphate. Improvement in pain and lesions was faster in patients receiving intravenous ibandronate. All of these patients remained on bisphosphonate treatment for at least 6 months until the wounds healed completely. No recurrences have been observed after follow-up periods between 1 and 9 years. Renal function remained stable in transplant recipients. The treatment was well tolerated and no adverse effects were observed.

Conclusions: Bisphosphonates could be a new and attractive alternative to treat CUA.


INTRODUCTION

Calcific uraemic arteriolopathy (CUA), also known as calciphylaxis, is a rare but potentially life-threatening...
condition that almost exclusively affects patients with chronic kidney disease (CKD). The incidence of CUA among dialysis patients has been estimated at 1% annually, with a prevalence rate as high as 4%. CUA is a crippling disease with a mortality rate of 60%-80%; the main cause of death is sepsis.\textsuperscript{1,2} Despite the fact that medial calcification in large vessels is very common in CKD patients, small vessel calcification is rare. The skin’s vulnerability to CUA is probably due to its proximity to external forces, such as changes in temperature and pressure. CUA is characterised by progressive calcification of small blood vessels and the development of ischaemic necrosis of skin and soft tissues.

Given the rarity of CUA, treatment is often based on results from individual cases. Traditional treatment suggestions include debridement of necrotic tissue, antibiotic treatment to prevent or treat infection, nutritional support, correction of biochemical parameters,\textsuperscript{2} parathyroidectomy, cinacalcet, sodium thiosulphate (STS) and bisphosphonates.\textsuperscript{3-13} Bisphosphonates inhibit osteoclasts and bone resorption and are used in treating osteoporosis, Paget’s disease, multiple myeloma, and tumour-induced hypercalcaemia. In animal studies, bisphosphonates have been shown to have a beneficial effect on the prevention of arterial calcification.\textsuperscript{7} Because of these recent observations, bisphosphonates were recently introduced as CUA treatment, with good results.\textsuperscript{9-13} After undertaking preliminary studies, our unit began using bisphosphonates in 2002 as a treatment alternative for all patients with CUA. We present our series of CUA cases since 2002, all of which were successfully treated with bisphosphonates.

MATERIAL AND METHOD

Study population

Prospective study of the 8 patients diagnosed with CUA in our unit between 2002 and 2010. They included 4 men and 4 women with a mean age of 61±7 years. Five were on haemodialysis (3 following kidney graft loss) with time on dialysis ranging between 2 and 20 years. The other 3 had functioning kidney grafts (durations between 1 and 5 years). Demographic characteristics and risk factors are summarised in Table 1, and initial laboratory results are summarised in Table 2.

Relevant data: Previous history of high calcium-phosphorous product in 5 patients (75-157mg\textsuperscript{2}/dL\textsuperscript{2}), previous history of severe secondary hyperparathyroidism (>800pg/ml) in 6 patients (4 had undergone parathyroidectomy), history of high cumulative doses of steroids in 5 patients, and 6 patients undergoing treatment with dicoumarin derivatives (Sintrom\textsuperscript{®}) for a number of reasons (heart valve, atrial fibrillation or severe vascular access thrombosis problems). Only one patient had hepatitis C (HCV) and none were diabetic or obese. All of the patients had purple ulcerous skin lesions with a necrotic centre, erythematous edges and livedo reticularis in the entire area. The lesions were located on the inner thighs in 6 patients and in the tibial area in 3 patients (one had lesions in both locations). Diagnosis was based on clinical suspicion and a confirmatory biopsy was performed in 6 patients.

Treatment with bisphosphonates

All patients were treated with bisphosphonates. The first (patient 1) received oral alendronate 70mg/week; 4 patients (pa-
patients 2, 3, 4 and 5) received oral risedronate 35mg/week, and the last 3 (patients 6, 7 and 8) received intravenous ibandronate 6mg (1 dose) followed by a second 3mg dose after 15 days, followed by oral ibandronate 150mg/month during 6 months.

In patients on dicoumarin treatment, we decided to maintain the anticoagulant therapy for two reasons: to prevent thrombosis-related problems and determine whether the effect on calciphylaxis was due to the bisphosphonates alone.

Follow-up

In all patients, bisphosphonate treatment was maintained until all lesions had healed completely during at least 6 months. During the follow-up period, blood values of calcium, phosphorous, alkaline phosphatase and intact parathyroid hormone (iPTH) (Diasorin®) were measured monthly.

In the last 3 patients who received a second dose of ibandronate at 15 days, calcium levels were also measured prior to administering that dose. Renal function was also measured in the patients with functioning allografts.

RESULTS

In all cases, skin lesions stopped progressing after administration of bisphosphonates. After 2-4 weeks, the edges began healing and the size of the wound diminished. Gradual decrease in pain was recorded after 2-5 days. The decrease in pain and wound size was noted more quickly in patients treated with intravenous bisphosphonates. No other drugs were used (vitamin D, cinacalcet, phosphate binders) and previous treatment and dialysis regimes were not modified.

After follow-up periods ranging between 1 and 9 years, there have been no recurrences in any of the patients or death. After administration of bisphosphonates, no significant changes were reported in blood calcium and phosphorus levels in any of the cases (Figure 1). Similarly, there were no changes in iPTH or alkaline phosphatase. In patients with a functioning kidney transplant, renal function remained stable (Figure 2). The treatment was well tolerated in all cases and no relevant adverse effects were observed.

DISCUSSION

CUA develops mainly in patients with stage 3-4 CKD, in both dialysis and transplant patients. The incidence of CUA

Table 2. Baseline laboratory values

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.9</td>
<td>8.3</td>
<td>8.2</td>
<td>9.7</td>
<td>9.4</td>
<td>11.1</td>
<td>9.7</td>
<td>9.2</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>3.9</td>
<td>7.1</td>
<td>9.1</td>
<td>4.7</td>
<td>5.1</td>
<td>2.6</td>
<td>5.8</td>
<td>3.3</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>18</td>
<td>557</td>
<td>332</td>
<td>394</td>
<td>117</td>
<td>225</td>
<td>191</td>
<td>98</td>
</tr>
<tr>
<td>AP (U/l)</td>
<td>206</td>
<td>242</td>
<td>354</td>
<td>748</td>
<td>232</td>
<td>147</td>
<td>199</td>
<td>110</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.4</td>
<td>4.6</td>
<td>3.8</td>
<td>3.7</td>
<td>4.3</td>
<td>4.6</td>
<td>4.9</td>
<td>3.7</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>353</td>
<td>178</td>
<td>168</td>
<td>184</td>
<td>117</td>
<td>237</td>
<td>200</td>
<td>259</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>54</td>
<td>50</td>
<td>122</td>
<td>53</td>
<td>56</td>
<td>18</td>
<td>76</td>
<td>83</td>
</tr>
</tbody>
</table>

BUN: blood urea nitrogen; AP: alkaline phosphatase; iPTH: intact parathyroid hormone.
is being treated with high doses of steroids or with warfarin.1,2

Some authors have described a potent inhibitor of calcium and phosphorus product levels. On the other hand, most of our patients were being treated with steroids and acenocoumarol.

When CUA is diagnosed, priority treatment alternatives include normalising hypercalcaemia and hyperphosphataemia and avoiding intake of vitamin D and calcium salts. Topical treatment and beginning empirical antibiotic treatment may also be helpful.1,2 In patients with high PTH levels, parathyroidectomy was suggested as a good alternative, but results have been contradictory and risk of mortality may increase after surgery.1,2 Cinacalcet has been shown to be beneficial in some cases of CUA with secondary hyperparathyroidism, generally in combination with other treatments, such as hyperbaric oxygen and sodium thiosulphate (STS).1,3 Some cases of good response to hyperbaric treatment have been described, but this treatment is always combined with other alternatives.3

STS recently emerged as an interesting treatment option after publication of a few isolated cases and two clinical series with promising results. This compound seems to play a role in dissolving calcium deposits within tissues through the formation of soluble calcium thiosulphate complexes, and it may also act as an antioxidant to combat endothelial dysfunction. The most recent series, published in 2011, describes the use of STS in 6 patients. Authors reported pain relief and lesion healing in 4 patients, but 3 patients (including 2 of the 4 who responded to treatment) died less than 1 year after diagnosis.7 In addition, most of them had received at least 1 dose of IV pamidronate in the same month or the month prior to beginning STS treatment, and 2 patients were treated with cinacalcet. Only 1 of the patients did not develop adverse effects (vomiting or metabolic acidosis).

Another possible treatment alternative is the use of bisphosphonates, which are pyrophosphate analogues that are widely used in treating osteoporosis. The pyrophosphate (PPi) is a potent inhibitor of calcium and circulates in the bloodstream at levels that are high enough to prevent hydroxyapatite formation. It therefore serves as an endogenous calcification inhibitor.14,15 In particular, production of PPi by vascular smooth muscle cells may be an important defence mechanism against calcification of the vascular media. PPI has been shown to inhibit calcification of the arterial media in rats intoxicated with vitamin D.16 The effect of PPI is limited by its rapid in vivo hydrolysis. Bisphosphonates are non-hydrolysable PPi analogues which are able to inhibit vascular calcification at much lower doses.17 In recent years, bisphosphonates have been used in isolated cases as treatment for CUA, with a good response and good tolerance.9,13,17

At the pharmacological level, bisphosphonates inhibit hydroxyapatite crystallisation or reabsorption in vitro, depen-

seems to have increased in recent years; the reason for this is unknown, but it could be due to better record-keeping. It occurs in up to 4% of patients on dialysis.1,2

CUA should be suspected in the presence of very painful, necrotic cutaneous ulcers in a patient with long-standing CKD. In the beginning other cutaneous manifestations are present, such as indurated plaques or livedo reticularis, sometimes accompanied by palpable deposits of subcutaneous calcium. These lesions are usually located proximal (trunk) or distal (limbs), especially along the inner thigh.1

Simple high-sensitivity x-ray can reveal calcification of small blood vessels, but the diagnostic gold standard is still a skin biopsy of the lesions, despite the risk of spreading the ulcer. The typical histological finding is calcification of the small blood vessels with intimal proliferation and intravascular thrombosis, sometimes associated with panniculitis.1 Von Kossa staining can also reveal perivascular calcium deposits. Risk factors for developing CUA include: age (patients tend to be younger), female sex, high body mass index, diabetes mellitus, longer time on dialysis, high blood levels of calcium, phosphates, calcium-phosphorus product, alkaline phosphatase and PTH. Some authors have described a potential association with HCV, and another important risk factor is being treated with high doses of steroids or with warfarin (acenocoumarol).1,2

Our series includes equal numbers of men and women, dialysis patients with very different treatment durations, and kidney transplant recipients. There was only one patient with HCV and none of the patients were obese or diabetic. Elevated blood values of calcium, phosphorus and iPTH were found in 1 patient, 2 patients and 1 patient, respectively. It is true, however, that most had a history of very high calcium-phosphorus product levels. On the other hand, most of our patients were being treated with steroids and acenocoumarol.
GTP-binding proteins are necessary in post-translational modification of proteins, such as farnesyl pyrophosphate. Farnesyl pyrophosphate is necessary for the biosynthesis of isoprenoid compounds, including suppression of calcium salts, vitamin D and analogues, dicoumarin derivatives and precipitating factors, and by early administration of bisphosphonates or STS.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

REFERENCES


In conclusion, bisphosphonates may be a new, attractive treatment alternative for CUA treatment. Based on our experience, we recommend initial administration of an intravenous dose of bisphosphonate, preferably ibandronate, in patients with a suspected case of CUA. Treatment may then be continued depending on the definitive diagnosis or patient progress. We must keep in mind that CUA is potentially fatal, and it must be treated with all the means at our disposal, including suppression of calcium salts, vitamin D and analogues, dicoumarin derivatives and precipitating factors, and by early administration of bisphosphonates or STS.
Is there impact of mortality prior hemodialysis therapy in peritoneal dialysis patients?

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Nefrologia 2012;32(3):335-42

ABSTRACT

Aim: The aim of this study is to investigate the mortality and the factors which may affect it in patients who were transferred to peritoneal dialysis (PD) from hemodialysis (HD), compared to patients assigned to PD as first-line therapy. Material and Methods: A total of 322 patients treated with PD between 2001 and 2010 were evaluated retrospectively. Twenty three patients were excluded and the data of remaining 299 patients (167F, mean follow up time 38.5±26.8 months, mean age 44.7±15.9 years) were evaluated. Patients were separated into two groups according to their HD history. Group 1 and group 2 consisted of patients with (n=48) and without (n=251) a history of prior HD, respectively. Socio-demographic characteristics such as who helped administer the PD and the preference of patients (compulsory vs their preference) were obtained from the patient records. The clinical data obtained during the last clinical evaluation before the initiation of PD (blood pressure, daily urine volumes, daily ultrafiltration amounts and laboratory parameters) were recorded. Additional systemic diseases and information about the etiologies of the end stage renal disease (ESRD) of all patients were recorded. Frequencies of the infectious complications were recorded. Patient and technique survival were investigated and compared between groups.

Results: In group 1, the patients were older and had less urine amounts (p=.028 and .041 respectively). Thirty five patients (70%) and 25 patients (9.3%) have been transferred to PD due to vascular problems in group 1 and 2, respectively (p<.001). In group 1, 37 (74%) patients were carrying out PD treatment by themselves, compared to 222 (88.4%) patients in group 2 (p=.016). Incidences of peritonitis and catheter exit site/tunnel infection attacks were found 24.9±26.8 and 27.2±26.5 patient-months in group 1, and 27.4±22.4 and 33.4±24.5 patient-months in group 2, respectively (p=.50 and .12). In group 1, twenty three patients have death and 2 patients have discontinued the treatment due to transplantation. In group 2, 174 patients have discontinued the treatment (55 patients have died, 80 patients have been switched to hemodialysis and 39 patients have received renal transplantation). There were significant differences between groups according to the last condition (p<.001). Mean patient survival were found 22.9±4.2 and 55.5±2.8 patient-months in group 1 and group 2, respectively. The patient survival rates by Kaplan–Meier analysis were 50%, 40.9%, 27.3% and 9.1% at 1, 2, 3, and 4 years in group 1 and 90.9%, 81.6%, 73.9%, 64.9% and 53.1% at 1, 2, 3, 4 and 5 years in group 2, respectively. The mortality rate is higher in patients who have undergone HD before PD compared without HD history (log rank:<.001). In the Cox proportional hazards model analysis, preference of PD (RR: 7.72, p<.001), presence of diabetes (RR: 2.26, p=.01), pretreatment serum albumin level (RR: 0.37, p<.001) and catheter exit size infection attacks (RR: 0.34, p=.01) were identified as predictors of mortality.

Conclusion: Our data show that mortality in patients transferred to PD from HD was higher than in patients undergoing PD as first-line therapy. Compulsory choice such as vascular access problems and social factors were the most important causes of increasing mortality in patients transferred to PD from HD.

Keywords: Peritoneal dialysis. Mortality. Haemodialysis.

Impacto de la hemodiálisis previa al tratamiento con diálisis peritoneal en la mortalidad de los pacientes

RESUMEN

Objetivo: El presente estudio pretende analizar la mortalidad y los factores que pueden influir en ella en los pacientes que pasan de la hemodiálisis (HD) a la diálisis peritoneal (DP), en comparación con los pacientes a los que se les prescribe DP.
como tratamiento de elección. **Materiales y método:** Se evaluaron retrospectivamente 322 pacientes tratados con DP entre 2001 y 2010. Fueron excluidos del estudio 23 pacientes y se evaluaron los datos de los 299 restantes (167 mujeres, tiempo medio de seguimiento: 38,5 ± 26,8 meses edad media: 44,7 ± 15,9 años). Se formaron dos grupos de pacientes en función de su historial de HD. El grupo 1 y el grupo 2 indujeron, respectivamente, a pacientes con (n = 48) y sin (n = 251) historial de HD previo. Las características sociodemográficas como quién colaboraba en la administración de la DP y la preferencia de los pacientes (obligatoria frente a elegida) se recogieron de los historiales de los pacientes. Se registraron los datos clínicos obtenidos durante la última evaluación clínica antes de comenzar con la DP (presión arterial, volúmenes de orina diarios, cantidad de líquido ultrafiltrado diario y parámetros analíticos). Se procedió de igual manera con otras enfermedades sistemáticas e información sobre la etiología de la enfermedad renal de etapa terminal (ERET). Se hizo constar que cambiarían de HD a DP fue mayor que en los pacientes que cambian de HD a PD como tratamiento de elección.

**Resultados:** En el grupo 1, los pacientes eran de mayor edad y las cantidades de orina eran inferiores (p = 0,028 y 0,041 respectivamente). Treinta y cinco pacientes (70%) del grupo 1 y 25 (9,3%) del grupo 2 cambiaron a DP debido a problemas vasculares (p < 0,001). En el grupo 1, 37 pacientes (74%) se sometían a tratamiento de DP realizadas por ellos mismos, comparado con los 222 pacientes del grupo 2 (p = 0,016). Las incidencias de peritonitis y de infección del orificio de salida y del túnel del catéter peritoneal fueron 24,9 ± 26,8 y 27,2 ± 26,5 pacientes-meses en el grupo 1 y de 27,4 ± 22,4 y 33,4 ± 24,5 pacientes-meses en el grupo 2 (p = 0,50 y 0,12, respectivamente). En el grupo 1, fallecieron 23 pacientes y otros 2 suspendieron el tratamiento debido a un injerto. En el grupo 2, 174 abandonaron el tratamiento: 55 fallecieron, 80 cambiaron a hemodiálisis y 39 fueron sometidos a injerto renal, con importantes diferencias entre los dos grupos en función de esta última causa (p < 0,001). La supervivencia media de los pacientes fue de 22,9 ± 4,2 y 55,5 ± 2,8 pacientes-meses en el grupo 1 y grupo 2, respectivamente. Las tasas de supervivencia de los pacientes según los análisis de Kaplan–Meier fueron de 50%, 40,9%, 27,3% y 9,1% a los 1, 2, 3, y 4 años en el grupo 1 y de 90,9%, 81,6%, 73,9%, 64,9% y 53,1% a los 1, 2, 3, 4 y 5 años en el grupo 2. La tasa de mortalidad fue mayor en pacientes que se habían sometido a HD antes de la DP que en los pacientes que no tenían historia de HD (log rank < 0,001). En el análisis de los modelos de riesgos proporcionales de Cox, se identificaron la preferencia de DP (RR: 7,72, p < 0,001), la presencia de diabetes (RR: 2,26, p = 0,01), los niveles de albúmina sérica previos al tratamiento (RR: 0,37, p < 0,0001) y las infecciones del orificio de salida del catéter peritoneal (RR: 0,34, p = 0,01) como predictores de mortalidad. **Conclusión:** Los datos de nuestro estudio demuestran que la mortalidad en pacientes que cambian de HD a PD fue mayor que en los pacientes que recibían PD como tratamiento de elección. Las causas de la obligatoriedad del tratamiento como los problemas de acceso vascular y los factores sociales fueron las más importantes a la hora de aumentar la mortalidad en pacientes que cambiaron de HD a PD.

**Introducción**

There is no consensus in the literature regarding the most appropriate choice of dialysis method. Hemodialysis (HD) and peritoneal dialysis (PD) are interchangeable and complementary renal replacement therapy (RRT) modalities. Although there are advantages and disadvantages of both treatment methods, it is recommended to start the treatment with PD as the first-line renal replacement modality in the absence of special conditions (contraindications) and later switch to hemodialysis.

It was reported that PD was advantageous in terms of survival compared to HD in the first 2-3 years of treatment and afterwards the survival with PD was equal or worse than with HD. The studies reported a better duration and quality of life in patients who were transferred to HD following initiation with PD and receiving integrated care strategy, due to the complications such as further development of ultrafiltration problems, insufficient dialysis and/or peritonitis.

A much smaller proportion of patients change modality from HD to PD, predominantly due to vascular access problems, cardiac disease or patient preference. There are few data about the survival in this patient population.

**Material and method**

The purpose of this study was to identify the predictors of mortality and to evaluate the clinical outcome in peritoneal dialysis patients who were transferred to PD from HD due to various causes such as vascular access problems compared to patients receiving PD as first-line therapy.

**Resultados**

The records of 322 patients with end stage renal disease (ESRD) receiving PD therapy in our PD unit between 2001–2010 were evaluated retrospectively. Patients, younger than 18 years, had data missing, patients switching to another clinic, patients on PD for less than 90 days and patients who recovered renal function and no longer required dialysis were excluded. The data of the remaining 299 patients were evaluated.

The age, gender, educational levels of the patients and socio-demographic characteristics such as who helped administer the PD (by themselves, their children or other persons like health carers) and the nature of the decision to PD (patient preference, his/her own decision or other compulsory choice) were investigated in-depth from patient records.

In our country and unit, patients have the right to choose the appropriate treatment method after they are informed about renal replacement therapies. PD preference means; preferring of PD treatment by patients themselves or as a...
result of mandatory indication because of many causes (vascular problems, cardiac problems, attainability of the center, etc.).

Follow-up time of PD therapy, type of PD modality (CAPD, APD), presence of HD history before PD therapy and duration of the therapies were recorded. Duration of icodextrin and hypertonic solution usages during follow-up time were recorded. Additional systemic diseases (hypertension, coronary artery disease, cerebrovascular events, malignancy etc.) and information about ESRD etiologies of all patients were recorded.

Systolic and diastolic blood pressure measurements, daily urine volumes, daily mean ultrafiltration amounts, cardiothoracic indices all of patients were recorded at the beginning of the treatment and during the last visits of PD therapy. Serum urea, creatinine, calcium, phosphorus, albumin, parathormone, hemoglobin, transferrin saturation and ferritin values were recorded at the beginning of the treatment and during the last monitoring. Infectious complications such as peritonitis, catheter exit site/tunnel infections were recorded and their incidences were calculated.

Patients were divided into two groups. Group 1 consisted of patients who received PD treatment following hemodialysis (group 1: patients with HD history) and group 2 consisted of patients who received PD as first-line therapy (group 2: patients without HD history). Socio-demographic data, clinical courses and the infectious complications (peritonitis and catheter exit site/tunnel infections) of the two groups were compared, and the reasons for PD withdrawal were obtained. Survival analysis of all patients was performed and the effect of HD on mortality was investigated.

We performed statistical analyses with the Scientific Package for Social Science (version 11.0; SPSS Inc, Chicago, IL, USA). Chi-square and Mann-Whitney U test were used for nonparametric variables. Independent-samples T test for analyzing clinical and biochemical parameters between beginning and the last visit values. The Kaplan–Meier method for measuring patient survival rate was applied and a comparison of outcomes was based on the log rank test. We also analyzed the risk factors and calculated their hazard ratio (HR) for patient mortality using Cox proportional hazard model backward stepwise LR (Likelihood Ratio) method. Differences were considered statistically significant for p values less than 0.05.

RESULTS

The data of 322 patients were evaluated. Twenty three of them (13 patients have switched to another PD unit, 10 patients have been followed up for less than 90 days) were excluded. A total of 299 patients with a follow-up period of 10160 patient-months were evaluated. 167 of them were female, mean age at the onset of PD was 44.7±15.9 years and mean PD duration was 38.5±26.8 months.

A total of 48 patients, 31 of whom were female, had hemodialysis history before PD treatment (group 1), the mean age of the patients was 49.3±15.8 years, mean follow-up time 34.6±30.5 month and mean duration of hemodialysis before PD 32.8±34 (3-144) month.

Remain 251 patients, 136 of whom were females, had been assigned to PD treatment as first-line therapy without a hemodialysis history (group 2). Mean age was 43.8±15.8 years and mean follow-up time was 39.4±26 month in this group.

Group 1 patients were observed to be older (p=.028). The reason for switching to PD from HD in 35 patients (70%) in group 1 was found to be mandatory due to vascular reasons and for the remaining 13 patients it was due to patient decision or social problems. It was found that 37 patients (74%) in this group were performing their own PD treatment by themselves. In group 2, only 25 patients (9.3%) were found to have mandatory choices due to vascular reasons and 222 patients (88.4%) were detected to perform their own treatments by themselves.

There were significantly different according preference of PD (compulsory or own decision) and who helped administer the PD therapy (by themselves or other) between two groups (p<.001 and .016 respectively).

The major educational status of patients in both groups was a primary school (69% and 60.4% respectively). There was no significant difference between two groups (p=.69).

It was found that 42 patients (87.5%) in group 1 and 217 patients (86.4%) in group 2 started treatment with CAPD. Between the two groups no significant difference was found with regard to the type of PD modality (p=.274).

Socio-demographic characteristics of group 1 and 2 patients are shown in Table 1. At start of PD treatment, 18 patients in group 1 (37.5%) and 196 patients in group 2 (78%) had urine and mean urine volumes were 244±536 ml/day and 389±390 ml/day in group 1 and 2, retrospectively. Urine volume was significantly lower in group 1 patients at start of PD therapy (p = .041). Ten patients (20.8%) in group 1 had diabetes as the etiologic cause of ESRD, while there were 73 diabetic patients (29%) in group 2, and no statistically significant difference was found between the two groups in terms of diabetes (p=.70).

The biochemical and hemogram data are shown in Table 2 for both groups at the start of PD therapy and the last visit of all patients. The hemoglobin level was significantly higher...
Yener Koc et al. Is there impact of mortality prior hemodialysis therapy in peritoneal dialysis patients?

in group 1 (p=.013) at the start of PD, however this significance disappeared in time.

Peritonitis incidences and catheter exit site/tunnel infection attacks were 24.9±26.8 patient-months and 27.2±26.5 patient-months in group 1, respectively. Peritonitis incidences and catheter exit site/tunnel infection attacks were 27.4±22.4 patient-months and 33.4±24.5 patient-months in group 2, respectively. The frequency of peritonitis and catheter exit site infections were not significantly different between the two groups (p=.50 and p=.12, respectively).

The last status data and causes of them are shown in Table 3 for both groups. During the follow-up period 25 patients were withdrawn PD therapy, 23 of them had died and 2 patients were transplanted in group 1. Interestingly, no patient was re-transferred to HD in group 1. During the follow-up period 174 patients were withdrawn PD therapy, 55 of them had died, 80 of them were transferred to HD and 39 patients were transplanted in group 2. There was a significant difference between two groups with respect to the last status of patients (p<.001).

<table>
<thead>
<tr>
<th>Table 1. Socio-demographic features of all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Follow up time (months)</td>
</tr>
<tr>
<td>Systolic BP (at the beginning of PD) (mmHg)</td>
</tr>
<tr>
<td>Diastolic BP (at the beginning of PD) (mmHg)</td>
</tr>
<tr>
<td>Cardiothoracic index (at the beginning of PD) (%)</td>
</tr>
<tr>
<td>Urine volume (at the beginning of PD) (ml/day)</td>
</tr>
<tr>
<td>Systolic BP (at the last visit) (mmHg)</td>
</tr>
<tr>
<td>Diastolic BP (at the last visit) (mmHg)</td>
</tr>
<tr>
<td>Cardiothoracic index (at the last visit) (%)</td>
</tr>
<tr>
<td>Urine volume (at the last visit) (ml/day)</td>
</tr>
<tr>
<td>Kt/V urea</td>
</tr>
<tr>
<td>CrCL (L/week)</td>
</tr>
<tr>
<td>Peritonitis incidence (patient-months)</td>
</tr>
<tr>
<td>Catheter exit site infection incidence (patients-months)</td>
</tr>
</tbody>
</table>

BP: blood pressure; CrCL: creatinine clearance; NS: not significant; PD: peritoneal dialysis.

<table>
<thead>
<tr>
<th>Table 2. Laboratory datas of two groups</th>
</tr>
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<tbody>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>Creatinine (at the beginning of PD) (mg/dL)</td>
</tr>
<tr>
<td>Calcium (at the beginning of PD) (mg/dL)</td>
</tr>
<tr>
<td>Phosphorus (at the beginning of PD) (mg/dL)</td>
</tr>
<tr>
<td>Parathormon (at the beginning of PD) (pg/dL)</td>
</tr>
<tr>
<td>Albumin (at the beginning of PD) (g/dL)</td>
</tr>
<tr>
<td>Hemoglobin (at the beginning of PD) (g/dL)</td>
</tr>
<tr>
<td>Calcium (at the last visit) (mg/dL)</td>
</tr>
<tr>
<td>Phosphorus ( at the last visit) (mg/dL)</td>
</tr>
<tr>
<td>Parathormon (at the last visit) (pg/dL)</td>
</tr>
<tr>
<td>Albumin (at the last visit) (g/dL)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl) (at the last visit)</td>
</tr>
</tbody>
</table>

NS: not significant; PD: peritoneal dialysis.

The last status data and causes of them are shown in Table 3 for both groups. During the follow-up period 25 patients were withdrawn PD therapy, 23 of them had died and 2 patients were transplanted in group 1. Interestingly, no patient was re-transferred to HD in group 1. During the follow-up period 174 patients were withdrawn PD therapy, 55 of them had died, 80 of them were transferred to HD and 39 patients were transplanted in group 2. There was a significant difference between two groups with respect to the last status of patients (p<.001).
The most common causes of death were cardiovascular diseases (47.8%) and peritonitis and/or sepsis (34.7%) in group 1 and peritonitis and/or sepsis (47.2%) and cardiovascular diseases (32.7%) in group 2.

Mean patient survival time was 49.9±2.6 months in Kaplan–Meier analyses in patients transferred from HD to PD. The patient survival rates by Kaplan–Meier analyses were 50%, 40.9%, 27.3% and 9.1% at 1, 2, 3 and 4 years in group 1, respectively. Mean patient survival time was 55.5±2.8 months in group 2. The estimation of patient survival by Kaplan–Meier analyses was 90.9%, 81.6%, 73.9%, 64.9% and 53.1% at 1, 2, 3, 4 and 5 years, respectively in group 2. The mortality rate was found higher in patients with HD history before PD compared to patients without HD history (log rank: <.001) (Figure 1).

Age, preference of PD, who helped to administer the PD exchange, diabetic status, urine volume (>100ml/day or <100ml/day), pretreatment serum albumin levels, peritonitis and catheter exit site/tunnel infection attacks were analyzed using Cox proportional hazard model backward stepwise LR (Likelihood Ratio) to identify independent risk factors of mortality. Preference of PD, diabetic status, pretreatment serum albumin and catheter exit site/tunnel infection attacks were found to predict patient survival (Table 4). For each mg/dl decreases of albumin morality risk was elevated 3.3 times (RR: 3.376, 95% CI: 1.451-7.855, p=.003).

DISCUSSION

HD and PD are interchangeable and complementary renal replacement therapy modalities besides transplantation. In many PD programmes, a significant percentage of patients, ranging from 15 to 25%, have been transferred from HD due to problems experienced during this therapy or patient choice.3,7,8 Another study from our country established that 12.2% of patients begin with PD as a second-line renal replacement therapy modality.9 16% of the patients evaluated in our clinic are subjects transferred from HD to PD.

Many mortality studies have been published worldwide on both treatment modalities.3,4,10,21 According to these studies, PD is known in general to have a survival advantage in the first years.3,4 Nevertheless, there are less mortality studies investigating the effects of the interchange between the therapies and they are mostly related to patients transferred from PD to HD.12,13 Studies analyzing patients transferred from HD to PD are even scarcer.5,6,14

The majority of the published studies with patients who switched to PD from HD indicate that the mortality was found worse in patients transferred from HD,15-17 although there are some studies indicating similar mortality with those who primarily started with PD.6 In our study, mortality was found worse in patients transferred to PD from HD treatment, compared with the patients initially starting with PD.

Many studies, like ours, show that a previous history of hemodialysis has a negative impact on survival15,16,17 while some studies detect no influence on this parameter.6 Regarding the peritoneal dialysis, there are differences between the overall survival rates.

In peritoneal dialysis, overall survival rates show differences and this may be multifactorial reasons. Some evidences were shown to reflect the differences in mortality (particularly due to cardiovascular reasons) in general population of different countries.18,19 This discrepancy may also be the result of the demographic features (i.e. advanced age, diabetes, comorbidities, malnutrition, low residual kidney function, race, genetic factors, patient preference, etc.) of the study populations.20-23 It is well known, that the

**Table 3. The last status data and causes of death of all patients**

<table>
<thead>
<tr>
<th>Causes</th>
<th>Grup 1 (n=48)</th>
<th>Grup 2 (n=251)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exitus (n=78)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis/peritonitis</td>
<td>8(16.6%)</td>
<td>26(10.3%)</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>11(23.0%)</td>
<td>18(7.1%)</td>
</tr>
<tr>
<td>Malnutrition/PD insufficiency</td>
<td>3(6.2%)</td>
<td>9(3.5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1(2.1%)</td>
<td>2(0.8%)</td>
</tr>
<tr>
<td><strong>Transfer to hemodialysis (n=80)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis/peritonitis</td>
<td>0</td>
<td>50(19.9%)</td>
</tr>
<tr>
<td>PD insufficiency</td>
<td>0</td>
<td>24(9.5%)</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>0</td>
<td>3(1.2%)</td>
</tr>
<tr>
<td>His/her own decision</td>
<td>0</td>
<td>3(1.2%)</td>
</tr>
<tr>
<td>Transplantation (n=41)</td>
<td>2(4.2%)</td>
<td>39(15.5%)</td>
</tr>
<tr>
<td>Received PD treatment (n=100)</td>
<td>23(47.9%)</td>
<td>77(31%)</td>
</tr>
</tbody>
</table>

PD: peritoneal dialysis.
Yener Koc et al. Is there impact of mortality prior hemodialysis therapy in peritoneal dialysis patients?

The presence of diabetes and the serum albumin level at the onset of the therapy are factors influencing patient survival. Similar to the data of other studies we determined in our patients that advanced age, baseline serum albumin levels, presence of diabetes and frequent catheter exit site infections also increased the mortality.

The patient’s preference should be taken into account as the primary factor, since patient satisfaction, compliance with therapy and quality of life are better if the patient has been given the opportunity to make his/her own informed choice. The mandatory PD was associated with worse mortality rates among our patients. The main reasons for such transfers are vascular access problems or complications experienced during HD like intra- or postdialytic hypotension related predominantly to fluid loss during the procedure and aggravated by heart failure or cardiovascular neuropathy. Another study shows that most of the patients are transferred from HD to PD as a result of vascular problems. We found vascular problems as the cause of transfer to PD from HD in 70% of our patients. In other words, the vascular problems of patients treated with HD cause both mandatory transfer to PD and an increase in mortality because of continuing current cardiovascular problems.

Patients can be transferred from one modality to the other for various reasons and the reason of this transfer may closely affect the outcome. Cardiac and vascular problems are the most important causes for switching to PD from HD. In our unit, the most frequent causes of death were cardiovascular problems in patients transferred to PD from HD, while it was peritonitis/sepsis in patients without a history of HD.

RRF is very important in peritoneal dialysis, at least at the start of dialysis, because it directly affects the required dialysis dose. PD preserves residual renal function better than HD, and a clear correlation is known to exist between residual renal function and outcome. Re-analysis of the CANUSA data showed that the predictive power lays exclusively in the RRF, not in the peritoneal component, and each 250ml of daily urine output conferred a 36% reduction in mortality. Diaz-Buxo et al. analyzed the outcome of 1600 patients in the Fresenius database and reported that RRF, but not the dose of PD, predicted mortality. Van Biesen et al. discussed that HD patients which were transferred to PD usually had no RRF left and sufficient PD adequacy was more difficult to obtain in those patients. Urine outputs of patients transferred from HD to PD treatment in our unit were found to be significantly lower compared to the group that primarily initiated with PD treatment.

The initial haemoglobin level at the start of PD therapy was significantly lower in group 2. The primary reason for this difference may be the efficient erythropoietin therapy during HD treatment in group 1 and an inadequate erythropoietin substitution during predialysis period in the other group. This difference can be resolved by further erythropoietin use.

The main limitations of the present study are the retrospective design. Analysis of other factors that have also been associated with mortality, such as inflammation, renal clearance and peritoneal permeability. The presence of residual renal function were assessed by daily urine volume. Renal clearance was not calculated.

In conclusion, the mortality of patients transferred to PD from HD was found higher than of PD patients without prior HD history.

Table 4. Multivariate cox proportional hazards model for patient survival

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preference PD</td>
<td>7.724</td>
<td>3.974 – 15.012</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic status</td>
<td>2.261</td>
<td>1.185 – 4.312</td>
<td>0.013</td>
</tr>
<tr>
<td>Catheter exit site infection attacks</td>
<td>0.348</td>
<td>0.151 – 0.804</td>
<td>0.014</td>
</tr>
<tr>
<td>Pretreatment albumin level</td>
<td>0.371</td>
<td>0.220 – 0.628</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI: confidence interval; PD: peritoneal dialysis; RR: relative risk.
HD history. The most common causes of increased mortality in patients transferred to PD from HD were compulsory choice due to vascular access problems and social reasons. The most important cause of death in patients transferred to PD from HD were cardiovascular events, whereas infectious complications were the most important cause of death in patients for whom PD was the first-line modality.

Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

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Erythropoietin resistance and survival in non-dialysis patients with stage 4-5 chronic kidney disease and heart disease

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Nefrologia 2012;32(3):343-52

ABSTRACT

Introduction: Patients with chronic kidney disease (CKD) frequently suffer from heart disease as well. The combination of the two processes can exacerbate inflammation, resulting in increases in both resistance to erythropoietin (EPO) and mortality. Objectives: The aim of this study was to determine the prevalence of heart disease in a representative group of non-dialysis patients with stage 4-5 CKD, and the influence of that entity on EPO requirements and on mortality during a period of 36 months. Methods: 134 patients (68% on EPO at the beginning, increasing to 72.3% during follow-up) were monitored for 36 months. To evaluate the dose-response effect of EPO therapy, we used the erythropoietin resistance index (ERI) calculated as the weekly weight-adjusted dose of EPO divided by the haemoglobin level. The ERI was determined both initially and during the last six months before the end of the study. Results: 39 patients (29.1%) had history of heart disease; 22 (16.4%) had suffered from heart failure (HF). The ERI was higher in patients with a history of heart disease or HF and those treated with drugs acting on the renin-angiotensin system (ACE inhibitors or ARBs). Using ERI as the dependent variable in the multivariate analysis, the variables that composed the final model were ferritin, haemoglobin, glomerular filtration rate and history of HF. The 36 month mortality rate (n=39 patients) was higher in the group having ERI above the median (2.6IU/week/kg/gram of haemoglobin in 100ml) (P=0.002), and in the groups with heart disease (P<0.001) or HF (P=0.001) according to the Kaplan-Meier survival analysis. Conclusions: Patients with history of heart disease or HF have a higher ERI, and all of these characteristics are associated with lower survival. ERI can be considered a marker for risk of death in the short to-medium term.


RESISTENCIA A ERITROPLOYETINA Y SUPERVIVENCIA EN PACIENTES CON ENFERMEDAD RENAL CRÓNICA 4-5 NO-D Y ENFERMEDAD CARDÍACA

RESUMEN

Antecedentes: Los pacientes con enfermedad renal crónica (ERC) tienen con frecuencia patología cardíaca asociada. La coincidencia de ambos procesos puede potenciar la inflamación, aumentando los requerimientos de eritropoyetina (EPO) y empeorando la supervivencia. Objetivos: Conocer la prevalencia de patología cardíaca, su influencia en la dosis de EPO y la de ambos factores sobre la mortalidad en pacientes con ERC 4-5 no-D (no diálisis). Métodos: 134 pacientes (68% con EPO al inicio y el 72,3% a lo largo del seguimiento) seguidos durante 36 meses. Para evaluar la respuesta a la EPO se utilizó su índice de resistencia a la eritropoyetina (IRE): dosis de EPO semanal/peso/hemoglobina (Hb); el IRE se estimó basándose en los datos del estudio. Resultados: 39 pacientes (29,1%), antecedentes de cardiopatía; 22 (16,4%), episodios de insuficiencia cardíaca (IC). El IRE fue superior en los pacientes con antecedentes de cardiopatía, con...
IC and in the treated with inhibitors of the enzyme convertido- 
ra of angiotensin/angiotensin II receptors of angio-
tensin II; in the analysis multivariate (IRE as a variable de-
pending) they were the model for analysis: ferritin, Hb, 
function renal and episodes of IC. During the period of follow-
maintenance, 39 patients fell. The supervivencia (Kaplan-
Meier) to the 36 months was inferior in the patients with an IRE 
superior to the median (2.6 UI week/kg/g of Hb in 100 ml) 
(p = 0.002), those who had suffered episodes of IC (p = 0.001) 
y the ones that had antecedents of cardiopathy (p <0.001). Con-
clusions: Patients with antecedents cardiological en 
general and of IC in particular have an IRE augmented. Tan-
to the presence of these antecedentes como a mayor IRE se 
asoció a la disminución de la supervivencia, pudiendo consi-
derarse el IRE como marcador de riesgo de muerte a corto-
medio plazo.

Palabras clave: Erithropoyetina. Índice de resistencia a 
eritropoyetina. Enfermedad renal crónica estadio 4-5 no 
diálisis. Resistencia a eritropoyetina. Síndrome cardiorrenal. 
Insuficiencia cardiaca. Mortalidad.

INTRODUCTION

The main factor causing the anaemia associated with 
chronic kidney disease (CKD) is a decrease (both absolute 
and relative) in the synthesis of erythropoietin (EPO). 
Inadequate response to treatment with exogenous EPO is 
described in 10% of patients with CKD. Anaemia is also 
common in patients with heart disease in general and heart 
failure (HF) in particular; the most common form is anaemia 
associated with chronic disorders. In this case, we 
observe a relative EPO deficit — resistance to 
endogenous EPO — in conjunction with inhibition of iron 
uptake, and both conditions are largely provoked by an 
increase in cytokines. Inflammatory processes are usually 
accompanied by an increase in hepcidin which impedes 
the release of iron by intestinal cells and those in the 
mononuclear phagocyte system. Inflammation is an 
important factor in HF and CKD. In the latter process, the 
increase in hepcidin is favoured by the reduction in the 
amount excreted by the kidney. In both conditions (CKD 
and HF), decreased availability of Fe is a factor that 
exacerbates anaemia.

In patients who suffer from both conditions simultanea- 
ously (chronic cardiorenal syndrome types IV and V, according to the Ronco classification), EPO 
resistance is logically more common. These patients 
need to take larger doses of EPO in order to maintain 
similar haemoglobin (Hb) levels, as seen in prior 
studies conducted in patients on haemodialysis with a 
history of HF.

This study has a dual purpose: a) to examine the prevalence 
of heart diseases in general and HF episodes in particular, 
and determine their influence on the EPO doses administered 
in a representative sample of our stage 4-5 CKD patients; b) 
use this CKD population to prospectively study the influence 
of pre-existing heart disease and EPO requirements on patients’ 3 year survival rates.

MATERIAL AND METHOD

The study was both cross-sectional (for the prevalence 
analysis) and longitudinal (for the survival analysis), and 
included all patients attended in sequential order in our 
Advanced Chronic Kidney Disease (ACKD) Unit from the 
beginning of January to the end of February 2008. The 
follow-up period ended on 28 February 2011 and included 
the patient’s status at the end of that period (outpatient 
monitoring, on dialysis, transplant recipient or deceased). No 
patients were excluded from the overall study of heart 
disease prevalence and survival. We recruited 134 patients, 
representing 16% of the 824 patients attended in our Unit 
throughout 2008. One patient was positive for the hepatitis B 
virus and another for hepatitis C. We excluded 2 patients 
from the baseline analysis of the subgroup of patients on 
EPO treatment (n=91) due to severe associated conditions 
(cirrhosis of the liver with advanced portal hypertension in 1 
case; chronic infectious process associated with an 
enterocutaneous fistula following radiotherapy in the other) 
and who required EPO doses higher than 20000IU/week. 
The baseline study therefore contained the remaining 89 
patients. In addition, 6 patients who were not being treated 
with EPO at the time of recruitment either began or returned 
to treatment throughout the 3-year follow up period. The 
study of survival according to EPO dose therefore contained 
97 patients. In summary, 89 patients participated in the 
baseline study and 97 participated in the study of survival 
according to EPO dose.

Using patients’ medical histories, we recorded demographic 
and anthropometric data, mean blood pressure, CKD 
aetiology, history of heart disease including ischaemic heart 
disease (acute myocardial infarction or angina diagnosed and 
monitored by the Cardiology department), severe valvular 
heart disease or arrhythmia (atrial fibrillation in all cases) 
and history of heart failure episodes, defined as left 
ventricular failure manifesting as dyspnoea of cardiac origin 
which required hospital treatment, and was considered or 
diagnosed as such in the patient’s medical history. We also 
gathered data regarding treatment with angiotensin converter 
enzyme inhibitors (ACE inhibitors) or angiotensin II 
receptor blockers (ARB), date of death and cause of death 
when known. During follow-up, 39 patients died (33 in the 
outpatient monitoring programme and 6 after beginning 
dialysis).
All patients undergoing treatment received subcutaneous EPO (erythropoietin beta). EPO requirements were measured using the erythropoietin resistance index (ERI): weekly units of EPO/weight in kg/Hb in g per 100ml. The baseline ERI recorded at the beginning of the study was used to analyse survival in patients who started dialysis or died during the first year of follow-up. For patients who began dialysis or died after the first year, we used mean ERI, referring to the arithmetic mean of the baseline ERI and final ERI. The latter refers to indices calculated with data gathered during the 6 months prior to death, initiation of dialysis or the end of the follow-up period. As a result, mean ERI corresponds in some cases to baseline ERI and in others to the mean of baseline ERI and final ERI in the survival study.

We analysed the following parameters: C-reactive protein (CRP), homocysteine, haemogram, Fe deposits, renal function as measured by creatinine clearance in urine over 24 hours and the estimate given by the Cockcroft-Gault equation normalised according to body surface area (calculated using the Mosteller formula), uric acid, Ca-P metabolism, parathyroid hormone and proteinuria. The Charlson comorbidity index was used to indicate comorbidity.

Statistical analysis was performed using IBM SPSS software version 18. The descriptive population study used absolute and relative frequencies for categorical variables; quantitative variables were represented by the median and typical deviation for the total population, while median, 25th percentile and 75th percentile were used in study subgroups since they did not follow a normal distribution. When comparing groups according to ERI being above or below the median, we used the Mann-Whitney U-test for quantitative variables and chi-squared for qualitative variables. Spearman’s rank correlation coefficient was used to study correlations between EPO dose and different variables. Variables with an effect on ERI were analysed using forward stepwise linear regression, with ERI as a dependent variable. The survival study was carried out using Kaplan-Meier curves (log-rank test).

RESULTS

Causes of CKD among the 134 patients in the study (51% men, 49% women) were as follows: 36% vascular nephropathy; 27% diabetic nephropathy; 10% tubulo-interstitial nephritis of different aetiologies; 10% unknown causes; 8% chronic glomerular disease diagnosed by renal biopsy; 4% polycystic renal disease; 5% systemic conditions (systemic lupus erythematosus, rheumatoid arthritis, Sjögren’s syndrome, atypical haemolytic-uraemic syndrome). At the beginning of the follow-up period, 91 patients were being treated with EPO (68%); 97 received treatment at some point during that period (72.3%). High blood pressure was present in 96% of patients, and 75.7% of these patients were treated with ACE inhibitors/ARB. A history of heart disease was present in 39 patients (29.1%) and 22 patients (16.4%) had a history of HF episodes. According to echocardiographic data, 61 patients (45.5%) had left ventricular hypertrophy, 49 (42.6%) had diastolic dysfunction and 11 (9.2%) had systolic dysfunction. Table 1 lists this data and other data of interest for the entire group.

### Table 1. Patient characteristics (full group)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SD, n=134</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69±12</td>
</tr>
<tr>
<td>Survival (months)</td>
<td>27±7</td>
</tr>
<tr>
<td>MBP (mm Hg) [n]</td>
<td>94±11 [126]</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29±4 [130]</td>
</tr>
<tr>
<td>Proteinuria (g/day) [n]</td>
<td>1.0±1.1 [132]</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>37±4.2</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>12±1.5</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>139±118</td>
</tr>
<tr>
<td>TSAT (%) [n]</td>
<td>24±10 [133]</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/ml) [n]</td>
<td>170±197 [131]</td>
</tr>
<tr>
<td>Homocysteine (µmol/l) [n]</td>
<td>25±10 [96]</td>
</tr>
<tr>
<td>CRP (mg/l) [n]</td>
<td>9±18 [112]</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>6±2.2</td>
</tr>
<tr>
<td>nCrCl-CG (ml/min/1.73 m²)</td>
<td>20±7</td>
</tr>
<tr>
<td>% LV ejection fraction</td>
<td>58±1 [35]</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>40/134(29.4%)</td>
</tr>
<tr>
<td>History of heart disease</td>
<td>39/134(29.1%)</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>22/134(16.4%)</td>
</tr>
<tr>
<td>LV hypertrophy (%)</td>
<td>61/134(45.5%)</td>
</tr>
<tr>
<td>Systolic dysfunction</td>
<td>11/119(9.2%)</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>49/115(42.6%)</td>
</tr>
<tr>
<td>Treatment with ACE-i/ARB</td>
<td>97/128 (75.7%)</td>
</tr>
<tr>
<td>Treatment with erythropoietin</td>
<td>91/134 (68%)</td>
</tr>
</tbody>
</table>

ARBs: angiotensin II receptor blockers; SD: standard deviation; ACE-i: angiotensin-converting enzyme inhibitors; BMI I: body mass index; TSAT: transferrin saturation index; nCrCl-CG: creatine clearance estimated by the Cockcroft-Gault equation and normalised for a body surface area of 1.73 m²; MBP: mean blood pressure; CRP: C-reactive protein; LV: left ventricle.
Subgroup of patients with erythropoietin

Baseline data for the subgroup of 89 patients (56% women, 43% men) treated with EPO at the outset of the study, after exclusion of the 2 patients mentioned previously, are shown in Table 2.

When comparing these patients according to whether baseline ERI was above or below the median (2.6 IU/kg/g Hb in 100ml) (Table 3) we find significant differences in their cholesterol levels ($P<.001$), renal function estimated using the Cockcroft-Gault equation normalised for a body surface area of 1.73 m$^2$ ($P=.04$) and Hb ($P=.007$). TSAT and the Charlson comorbidity index almost reached the statistical significance level ($P=.06$ in both cases).

Comparison of different qualitative variables revealed that the percentage of patients with a history of HF was higher in the group whose ERI was above the median ($P=.04$). There were no significant differences with regard to sex, percentage of diabetes mellitus, history of heart disease in general, echocardiographic abnormalities, or in the percentage of patients treated with ACE inhibitors/ARB. However, patients treated with ACE inhibitors/ARB had a higher baseline ERI than the untreated group: median 2.3 (p25-75: 1.1-4.9) vs 3.6 (p25-75: 2.5-7) IU/kg/g Hb in 100ml ($P=.01$).

We found a significant correlation for baseline ERI which was positive for P levels ($r=0.246; P=.02$) and negative for CrCl ($r=-0.373; P<.001$), Hb ($r=-0.323; P=.002$), haematocrit ($r=-0.216; P=.04$), cholesterol ($r=-0.442; P<.001$) and triglycerides ($r=-0.200; P<.03$).

Multivariate analysis was conducted using forward stepwise linear regression and the range of variables traditionally related to each dose of EPO (measured by the baseline ERI): Charlson comorbidity index, Hb, ferritin, transferrin saturation index, renal function estimated using the Cockcroft-Gault equation normalised for body surface area, history of HF (analysed as absence of HF history) and history of heart problems in general, diabetes mellitus and sex. Of the variables listed above, ferritin, Hb, renal function and lack of history of HF were the variables used in the final model (Table 4).

Evolution at 36 months

During the 36 month period in which 134 patients were monitored, 31 (23%) began dialysis, 4 received pre-emptive transplants (3%) and 66 (49%) remained in the ACKD Unit. There were 39 deaths (29%): 33 in an ACKD unit outpatient monitoring programme and 6 after beginning renal replacement therapy. None of the patients receiving transplants died. Causes of death among all 39 patients were as follows: cardiovascular, 18 (46%); infection, 7 (18%); neoplasia, 6 (15%); other, 2 (5%) (1 patient due to cirrhosis and the other due to digestive tract haemorrhage); cause unknown in 6 (15%) (occurred at home or another hospital, or we were unable to contact the family, or the family did not know cause of death).

As mentioned in the “Material and Method” section, when analysing 3 year survival according to EPO dose, measured as mean ERI (97 patients, mean: 3.3±2.5 IU/kg/g Hb in 100ml; range: 0.5-13.1 IU/kg/g Hb in 100ml; median: 2.5 IU/kg/g Hb in 100ml) we considered all patients receiving EPO treatment at the time of recruitment plus the other 6 who began EPO treatment at a later date, for a total of 97 patients.
The Kaplan-Meier survival study showed that patients whose mean ERI was higher than the median (2.6 IU/kg/g Hb in 100ml) had lower survival rates (log-rank $P=.002$) (Figure 1). Likewise, patients with a history of HF also had lower survival rates: log-rank $P=.001$ (Figure 2), as did patients with a history of general heart disease, with log-rank $P<.001$ (Figure 3).

**Patients not treated with erythropoietin**

Different quantitative and qualitative variables were compared between the groups of patients treated with EPO (97 patients) and those who never received EPO (37 patients) during the 3 year follow-up or prior to that follow-up period. Statistically significant differences were found for levels of Hb, Hct (both higher in patients without EPO), ferritin (lower in patients without EPO) and renal function (higher in patients without EPO). There were also lower percentages of diabetes mellitus (DM) and history of HF among patients without EPO treatment. Results are shown in Table 5.

There were no statistically significant differences between survival of patients treated with EPO and survival of untreated patients according to the Kaplan-Meier survival study (log-rank test $P=.1$).

### Table 3. Erythropoietin resistance index (ERI)> or ≤ 2.6 IU week/kg/g Hb per 100 ml

<table>
<thead>
<tr>
<th></th>
<th>ERI&gt;2.6</th>
<th>ERI≤2.6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (p25-p75)</td>
<td>Median (p25-p75)</td>
</tr>
<tr>
<td>Age</td>
<td>74 (68-80)</td>
<td>71 (60-80)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 (24-31)</td>
<td>29 (26-32)</td>
</tr>
<tr>
<td>Proteinuria (g/day) [n]</td>
<td>0.5 (0.2-1.5) [42]</td>
<td>0.5 (0.2-1.6) [45]</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>6.7 (6.5-7.8)</td>
<td>6.6 (5.6-7.8)</td>
</tr>
<tr>
<td>Weekly EPO dose (IU)</td>
<td>5000 (3000-6000)</td>
<td>1000 (1000-2000)</td>
</tr>
<tr>
<td>Baseline ERI (IU week/kg/g Hb in 100 ml)</td>
<td>5.2 (3.9-7.7)</td>
<td>1.3 (1-2.3)</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>11.6 (10.6-12.1)</td>
<td>12 (11-13)</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>35 (33-37)</td>
<td>36 (35-38)</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>117 (63-179)</td>
<td>115 (64-217)</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>21 (14-28) [41]</td>
<td>23 (20-31)</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/ml) [n]</td>
<td>119 (59-238)</td>
<td>112 (76-228)</td>
</tr>
<tr>
<td>Cholesterol (mg/dl) [n]</td>
<td>161 (143-184) [42]</td>
<td>182 (165-202) [44]</td>
</tr>
<tr>
<td>Triglycerides (mg/dl) [n]</td>
<td>126 (84-154)</td>
<td>145 (105-189) [45]</td>
</tr>
<tr>
<td>Homocysteine (µmol/l) [n]</td>
<td>22 (20-28) [28]</td>
<td>24 (18-28) [36]</td>
</tr>
<tr>
<td>CRP (mg/l) [n]</td>
<td>5.4 (2.7-9.1) [33]</td>
<td>3.5 (2.4-6.3) [40]</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>7 (6-8)</td>
<td>6 (4-8)</td>
</tr>
<tr>
<td>nCrCl-CG (ml/min/1.73m²)</td>
<td>17 (13-22)</td>
<td>22 (13-27)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14/29 (48.2%)</td>
<td>15/29 (51.7%)</td>
</tr>
<tr>
<td>History of heart disease</td>
<td>15/27 (55.5%)</td>
<td>12/27 (44.4%)</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>13/19 (68.4%)</td>
<td>6/19 (31.5%)</td>
</tr>
<tr>
<td>LV hypertrophy (%)</td>
<td>21/40 (52.5%)</td>
<td>19/40 (47.5%)</td>
</tr>
<tr>
<td>Systolic dysfunction</td>
<td>4/8 (50%)</td>
<td>4/8 (50%)</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>14/33 (42.4%)</td>
<td>19/33 (57%)</td>
</tr>
<tr>
<td>Treatment with ACE-i/ARB</td>
<td>38/67 (56.7%)</td>
<td>29/67 (43.2%)</td>
</tr>
</tbody>
</table>

(p25-p75): 25th to 75th percentile; ARBs: angiotensin II receptor blockers; EPO: erythropoietin; ACE-i: angiotensin-converting enzyme inhibitors; BMI: body mass index; ERI: erythropoietin resistance index; TSAT: transferrin saturation index; nCrCl-CG: creatine clearance estimated by the Cockcroft-Gault equation and normalised for a body surface area of 1.73m²; ns: not significant; CRP: C-reactive protein; LV: left ventricle.
DISCUSSION

This study shows that a representative sample of non-dialysis CKD patients in stages 4-5 undergoing regular monitoring by our ACKD Unit had high comorbidity - 6 on the Charlson index - and a high prevalence rate for heart disease. The sample is representative because it consists of patients seen at the clinic in sequential order, without any type of selection process. Atherosclerosis increases with age; CKD may be just another sign of that process, as is true for atherosclerosis in other locations (heart, brain, peripheral arteries). Ageing of the population as life expectancy increases is also extending exposure time to CKD risk factors, and this causes the alarming increase in CKD worldwide.8,9

Response to EPO was evaluated by using ERI, as has been done in prior studies.10,11 This index relates the dose administered per kg body weight with the Hb level achieved; high values indicate the presence of mechanisms that slow erythrocyte response. It also serves a prognostic purpose, since increased EPO resistance is associated with increased risk of death among patients on haemodialysis.7,11 Our study also confirms its usefulness in ACKD outpatients with HF. This tendency is confirmed by the survival analysis. A recent article,13 drawing on data from the TREAT study14 conducted in diabetic patients with stage 3-4 CKD, evaluates response to darbepoetin by means of the percentage of change in Hb after the first 2 doses. The article observed increased mortality and increased incidence of cardiovascular events among patients in the lowest quartile for Hb response to darbepoetin.

When we analyse and compare different characteristics between patients with and without EPO treatment, we observe that patients with EPO have lower incidence rates of HF and DM, as well as higher Hb levels. However, having this patient profile, which is theoretically healthier, does not result in differences in survival, or at least this is true in our group. We cannot rule out the possibility that in a larger sample, patients who do not need EPO could show better survival rates than those treated with EPO.

Although CRP level, which is considered an inflammation parameter, was higher among patients with a more elevated baseline ERI, the difference was not significant. This fact could be explained by a considerable dispersion among the values that were recorded; the median CRP value in patients with a higher ERI was clearly superior to that in the lower ERI group. The study mentioned above, which made use of TREAT study data from diabetic patients with stage 3-4 CKD also observed higher CRP levels in patients with the most moderate response to the first doses of darbepoetin. Likewise, this relationship between EPO response and inflammation has also been observed with levels of endogenous EPO. A recent study analysed endogenous EPO levels in patients with DM and CKD (mean CrCl 50cc/min), examining different parameters and their effect on mortality after a 7 year follow-up period. That study showed higher endogenous EPO levels in patients with higher CRP levels and a history of cardiovascular disease, as well as increased mortality in that patient group.15

### Table 4. Forward stepwise linear regression analysis

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>95% CI</th>
<th>P</th>
<th>Tolerance</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>15.069</td>
<td>8.770; 1.368</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nCrCl-CG (ml/min/1.73m²)</td>
<td>-0.097</td>
<td>-0.170; -0.024</td>
<td>.010</td>
<td>0.950</td>
<td>1.052</td>
</tr>
<tr>
<td>No history of heart failure</td>
<td>-2.258</td>
<td>-3.633; -0.882</td>
<td>.002</td>
<td>0.952</td>
<td>1.051</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>-0.718</td>
<td>-1.230; -0.206</td>
<td>.007</td>
<td>0.929</td>
<td>1.076</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>0.005</td>
<td>0.001; 0.010</td>
<td>.016</td>
<td>0.987</td>
<td>1.014</td>
</tr>
</tbody>
</table>

a Dependent variable: ERI (erythropoietin resistance index)
R²: 0.298; Durbin-Watson: 2.195
B: regression coefficient estimates; VIF: variation inflation factor; CI: confidence interval; nCrCl-CG: creatine clearance estimated by the Cockcroft-Gault equation and normalised for a body surface area of 1.73m²; P: significance level.
Homocysteine levels tend to be high during renal failure because of the decrease in urinary elimination. Although increase in homocysteine levels is associated with higher vascular risk, we found no significant differences in patients with a higher ERI. This could be because the factor with the greatest effect on homocysteine serum levels is renal function, and this was similar in both groups.

Baseline ERI was negatively correlated with renal function (also true in the linear regression model), as might be expected, since synthesis of endogenous EPO is primarily renal and depends on critical functioning renal mass. However, a study carried out in patients with stage 3-4 CKD in which response to EPO was evaluated at doses of less than 100IU/kg/week did not find this inverse relation between EPO dose and renal function. This could be explained by the fact that these patients had higher glomerular filtration rates (25-60ml/minute) than our own patients. Given these levels of renal function, other factors (age, prior Hb level, Fe deposits, ACE inhibitor treatment, body mass index, proteinuria) could have a greater influence on response to EPO.

In our study, treatment with renin-angiotensin system blockers was shown to have an effect on ERI, which is higher in patients receiving such treatments. This effect was previously described both in patients on EPO, who needed higher doses, and in patients who developed anaemia after beginning ACE inhibitor or ARB treatment. Although the underlying mechanism is not completely understood, we know that angiotensin II regulates circulating EPO levels in both normal individuals and CKD patients, and that activation of the RAS increases EPO levels. Therefore, using renin-angiotensin system blockers will decrease endogenous EPO levels, exacerbate anaemia and increase the need for exogenous EPO.

The serum cholesterol level was inversely correlated with baseline ERI. This relationship has been described in patients on haemodialysis, and the reason is that low cholesterol levels are a marker for the presence of malnutrition and inflammation. In this turn would explain lower survival in these patients, which is contrary to what occurs in the population without CKD. The same trend occurs with obesity among haemodialysis patients (this has not been found consistently among patients on peritoneal dialysis). In this group, obesity does not increase cardiovascular risk, unlike what happens in the general population; this is part of the so-called “reverse epidemiology” described by the DOPPS study.

When evaluating the relationship between EPO dose, ERI and Hb level in patients with CKD and HF, it is important to keep in mind the complexity of administering EPO treatment in this situation, which is becoming increasingly common.

Figure 1. Survival analysis
A) Kaplan-Meier survival analysis for patients with an erythropoietin resistance index above (dotted line) or equal to/below (solid line) the median (2.6IU week/kg/g Hb in 100ml) by log-rank test.
B) Kaplan-Meier survival analysis of patients with a history of heart disease (dotted line) compared to patients with no history of heart disease (solid line) by log-rank test.
C) Kaplan-Meier survival analysis of patients with a history of heart failure (dotted line) compared to patients with no history of heart failure (solid line) by log-rank test.
CE: history of heart disease; HF: heart failure; ERI: erythropoietin resistance index.
The Hb level may fall and rise in an “unreal” way depending on the intensity of diuretic treatment and the simultaneous presence of oedemas (haemoconcentration and haemodilution). Due to these reasons, the EPO dose may change without variation in the real mass of red blood cells, and therefore the nephrologist must adjust the EPO dose for these patients, while considering the effect which changes in plasma volume will have on the Hb concentration.23-25

One of this study’s limitations is that it contains a small number of patients. It does, however, have the advantage of being homogenous, since it was conducted in one centre with a single observer and a consecutive array of patients who had the same therapeutic criteria, and these characteristics reduce population and observer biases. To compensate for the bias occurring from correlating baseline ERI with a patient’s evolution over 3 years of follow-up, we took a second ERI measurement (in the 6 months prior to exitus, beginning dialysis or the end of follow-up for patients still treated on an outpatient basis) and used the mean ERI for studying survival. With this approach, we are able to reconcile ERI with the evolution we observed. All things considered, this study and its conclusions have the same limitations as any survival analysis, including the low rate of events in some groups which does not permit us to calculate median survival, risk over time, etc.

Table 5. Patients with or without erythropoietin treatment

<table>
<thead>
<tr>
<th></th>
<th>NO EPO Median (p25-p75)</th>
<th>EPO Median (p25-p75)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71 (60-77)</td>
<td>72 (63-80)</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28 (25-30) [36]</td>
<td>29 (26-31)</td>
<td>ns</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>0.5 (0.2-1.3) [35]</td>
<td>0.5 (0.2-1.2) [95]</td>
<td>ns</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.8 (4.8-8)</td>
<td>6.6 (5.5-7.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>13 (12-14)</td>
<td>12 (11-13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>39 (37-41)</td>
<td>36 (34-38)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>75 (46-142)</td>
<td>115 (63-182)</td>
<td>.03</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>25 (17-30)</td>
<td>22 (18-30)</td>
<td>ns</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/ml)</td>
<td>103 (73-145)</td>
<td>115 (70-227)</td>
<td>ns</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>162 (148-189)</td>
<td>176 (155-199)</td>
<td>ns</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>117 (91-156)</td>
<td>126 (93-170)</td>
<td>ns</td>
</tr>
<tr>
<td>Homocysteine (µmol/l)</td>
<td>23 (17-28) [27]</td>
<td>20 (14-29) [69]</td>
<td>ns</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>3.8 (1.7-8.5) [32]</td>
<td>3.2 (2.2-6.6) [80]</td>
<td>ns</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>6 (5-7)</td>
<td>6 (5-8)</td>
<td>ns</td>
</tr>
<tr>
<td>nCrCl-CG (ml/min/1.73m²)</td>
<td>23 (18-28)</td>
<td>20 (14-26)</td>
<td>.03</td>
</tr>
</tbody>
</table>

(p25-p75): 25th to 75th percentile; EPO: erythropoietin; HF: heart failure; BMI: body mass index; TSAT: transferrin saturation index; nCrCl-CG: creatinine clearance estimated by the Cockcroft-Gault equation and normalised for a body surface area of 1.73m²; ns: not significant; CRP: C-reactive protein; LV: left ventricle.
Although some of the findings from studies of patients on dialysis mirror those in earlier stages of CKD, important differences are present. ERI and EPO dose per kg in non-dialysis CKD stage 4-5 are much lower to those recorded for patients on haemodialysis. In the article by López Gómez' describing a multi-centre Spanish study of patients during the first year of inclusion in a haemodialysis programme, mean ERI was 10.2±7.3 IU/kg/g Hb in 100ml, while ERI in our study was 3.7± 3 IU/kg/g Hb in 100ml, just over a third of the other index. It is likely that better renal function among our patients and absence of the negative effects of haemodialysis are the main factors accounting for this difference, since comorbidity (the Charlson comorbidity index), the percentage of heart disease and age are quite similar.

As a group, patients with CKD and a high ERI have the following profile: history of heart disease in general or, more specifically, episodes of HF; higher Charlson index, the percentage of heart disease and age are quite similar.

In summary, this study shows a high prevalence of heart disease among patients attended by the ACKD outpatient unit. Simultaneous presence of CKD and HF increases the need for EPO, both in terms of absolute value and with regard to Hb levels, expressed as the resistance index. Likewise, both a history of heart disease/HF episodes and high ERI seem to be associated to poorer survival, and both may be considered markers of increased risk of mortality over the short to medium term. High ERI may be a marker for patients requiring increased diagnostic and therapeutic intensity.

**Conflicts of interest**

The authors affirm that they have no conflicts of interest related to the content of this article.

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Factors associated with early peritoneal dialysis catheter replacement in Veracruz, Mexico

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Nefrologia 2012;32(3):353-8

ABSTRACT

Introduction: Catheter-related complications in patients on peritoneal dialysis lead to decreased effectiveness and discontinuation of the technique, conversion to haemodialysis, hospitalisation, and surgical interventions to replace the catheter. Objectives: Determine risk factors for early catheter dysfunction that result in the need for replacement. Methods: We analysed 235 catheters placed by open surgery using an infra-umbilical midline incision. Possible risk factors included the following: age, sex, body mass index, body surface area, diabetes, polycystic kidney disease, previous surgery, time of surgical procedure, omentectomy, omentopexy, wound infection and postoperative incisional hernia. Results: During the first year, 47 patients (20%) required a catheter replacement due to poor function. The most common complications were catheter migration and peritonitis (4.3% in both cases), followed by obstruction from omental wrapping (3.7%). Univariate analysis showed that patients with catheter dysfunction or requiring catheter replacement were younger, with a lower body mass index and body surface area (P<0.05). There was a significant association of wound infection and post-operative incisional hernia with catheter replacement. Omentectomy was associated with a low incidence rate of catheter dysfunction/replacement in the univariate and logistical regression analyses (odds ratio: 0.275; 95% confidence interval: 0.101-0.751; P<.012). Conclusions: Our catheter placement technique offers a low complication rate and good results in the first year after surgery. Except for omentectomy, we did not discover any risk factors for catheter replacement in our study population. Omentectomy had a protective effect in terms of catheter replacement.

Keywords: Peritoneal dialysis. Surgery. Risk factors. Complications. Outcome.

INTRODUCTION

Continuous ambulatory peritoneal dialysis (PD) has become an established option for treating patients with end-sta-
Open surgical approaches can involve midline,2,4 paramedian infra-umbilical laparotomy5,6 or multiple laparoscopic approaches.7,10 Although laparoscopy has become the surgical method of choice for placing PD catheters, open surgery techniques remain as an important option when laparoscopic resources are limited, whether due to the lack of laparoscopic equipment in different hospitals due to costs, or due to operator limitations.

Several studies have identified characteristics that increase the risk of developing complications, making an examination of pre-existing conditions necessary.3,5,7,18-20

The aim of this article was to present the results from our experience in the insertion of PD catheters and to determine which factors involve a higher risk for early catheter dysfunction and affect 1-year survival rates.
RESULTS

Patient and surgical registry characteristics

During the study period, a total of 235 patients were placed catheters (118 women and 117 men). Mean patient age was 51.4±17.5 years (range: 13-86 years), mean body mass index (BMI) was 26.3±4.2kg/m² (range: 14.4-40), and mean body surface area (BSA; Mosteller) was 1.7±0.1m² (range: 1.06-2.1). Some 43% of patients (n=101) had diabetic nephropathy, and only 3% (n=7) had autosomal dominant polycystic kidney disease.

Forty-six of the 235 patients (19.6%) had a history of previous abdominal surgery. Of these, only 26 had previously undergone one surgical procedure before, 12 patients had undergone two previous surgical procedures, 4 had undergone three previous surgical procedures, and 4 patients had undergone more than 3 previous surgical procedures. Regional anaesthesia was used in 95.8% of cases (n=225) during catheter placement; and general and local anaesthesia protocols were used evenly (2.1%, n=5 each). Mean duration of surgery was 43.7±14 minutes (range: 15-120). An omentectomy was performed in 37.9% of catheter placements (n=89), and an omentopexy was performed in 10 patients (4.3%). Dialysis was started within 24 hours of catheter placement in 97% of patients (n=230).

Peritoneal dialysis catheter complications and results

Catheter dysfunction that eventually required catheter replacement occurred in 47 patients (20%), and 80% of catheters were incident-free after one year.

Catheter dysfunction appeared after a mean 6.8±22.6 days (range: 0-120). The most common causes of catheter dysfunction were migration (4.3%, n=10) and peritonitis (4.3%, n=10), followed by obstruction of the catheter by omental wrapping in 9 patients (3.7%). Eight patients (3.4%) suffered surgical wound infection, and all of them required catheter replacement at some point. Other causes for changing the catheter included bleeding (haemoperitoneum) (2.1%, n=5) and fibrin clots in the catheter (2.1%, n=5). The 8 patients with surgical wound infections (3.4%) also had dialysate fluid leaks. Four patients (1.7%) had only one dialysate fluid leak and did not require PD catheter replacement. Another complication that did not require catheter replacement was granuloma in the exit site with subcutaneous tunnel infection in 1.7% of patients (n=4). Ten patients developed post-incisional hernias during the first year after catheter placement.

Factors associated with catheter dysfunction

We compared patients with and without catheter dysfunction, searching for factors associated with this phenomenon (Table 1). Patients with dysfunction were younger, with lower BMI and BSA than those without dysfunction (P<.05). There were no differences between groups with and without diabetes and autosomal dominant polycystic kidney disease. We did not find any correlation between previous abdominal surgery and catheter dysfunction, or the duration of the surgical procedure when using a 45-minute cut-off point. Patients that underwent an omentectomy had a lower incidence of catheter dysfunction (11.2%) than patients that did not undergo an omentectomy (25.3%) (P<.009). We did not observe a similar association for omentopexy. Patients that developed a post-incisional hernia developed catheter dysfunction in half of all cases (P<.03), and all patients with surgical wound infection required catheter replacement (P<.0001). The logistic regression analysis showed that having undergone an omentectomy was a statistically significant protective factor against catheter dysfunction (P<.05). No other variables that were significant in the univariate analysis for catheter dysfunction had a significant positive or negative impact on risk factors in the multivariate analysis (Table 2).

DISCUSSION

Our study showed a considerable level of effectiveness and safety in PD catheter placement using an open surgical approach with an infra-umbilical midline incision. In addition, certain patient variables, such as age, BMI, BSA, and surgical aspects, such as wound infection and post-incisional hernia, were associated with early catheter dysfunction and catheter replacement, contrasting with the protective effect of an omentectomy, which reduced the probability of catheter dysfunction.

We observed a wide range of complications that affected the incidence of catheter replacement. The incidence of catheter migration (4.3%) was lower than that of 7.6% reported by Liu et al., and those high rates (22%-24%) reported in other studies. In a similar manner, omentum or fibrin obstruction occurred at a combined incidence of 5.8%, lower or similar to rates reported in other studies.
As regards infectious complications, our rate of surgical wound infection was lower than in other studies, and few patients in our study had peritonitis, as compared to an unusual rate of 30% reported in other studies.\textsuperscript{3,5} However, we must be cautious in interpreting our results, taking into account that the majority of our complications resulted in catheter replacement, except for 4 patients with dialysate fluid leaks and those patients with complications at the catheter exit site. This may reveal suboptimal salvage manoeuvres, such as anti-infection treatment and catheter recovery using fluoroscopic guidance.

One of the intrinsic properties of the omentum is that, when it comes into contact with a foreign body, it attempts to surround and isolate it. Omental wrapping was a very common cause of catheter dysfunction in our study (3.7%). Some authors have suggested performing an omentectomy during catheter placement to avoid wrapping and the need for secondary procedures.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No dysfunction</th>
<th>Dysfunction</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>88 (75.2%)</td>
<td>29 (24.8%)</td>
<td>.068*</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.6±4.02kg/m(^2)</td>
<td>25.05±4.8kg/m(^2)</td>
<td>.023*</td>
</tr>
<tr>
<td>Body surface area</td>
<td>1.7±0.19m(^2)</td>
<td>1.66±0.19m(^2)</td>
<td>.006*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>83 (82.2%)</td>
<td>18 (17.8%)</td>
<td>.469*</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>5 (71.4%)</td>
<td>2 (28.6%)</td>
<td>.629*</td>
</tr>
<tr>
<td>Previous abdominal surgery</td>
<td>35 (76.1%)</td>
<td>11 (23.9%)</td>
<td>.459*</td>
</tr>
<tr>
<td>Surgery duration</td>
<td>77 (78.6%)</td>
<td>21 (21.4%)</td>
<td>.643*</td>
</tr>
<tr>
<td>Omentectomy</td>
<td>79 (88.8%)</td>
<td>10 (11.2%)</td>
<td>.009*</td>
</tr>
<tr>
<td>Omentopexy</td>
<td>8 (80%)</td>
<td>2 (20%)</td>
<td>.679*</td>
</tr>
<tr>
<td>Wound infection</td>
<td>0 (0%)</td>
<td>8 (100%)</td>
<td>.0001*</td>
</tr>
<tr>
<td>Post-incisional hernia</td>
<td>5 (50%)</td>
<td>5 (50%)</td>
<td>.03*</td>
</tr>
</tbody>
</table>

\textsuperscript{*} \chi\(^2\) test, \textsuperscript{b} Student’s t-test, \textsuperscript{c} Fisher’s exact test.
dary interventions, since 27% of patients that do not undergo an omentectomy develop catheter obstruction. We also observed a significant difference in catheter dysfunction and replacement when an omentectomy was performed. In our study, omentectomy had a protective effect against catheter dysfunction and replacement in both univariate and multivariate analyses, probably due to the reduced rate of obstruction from omental wrapping.

The majority of studies assessing PD catheter placement place special emphasis on a previous history of abdominal surgery as a potential risk for PD complications. Tiong et al. analysed several factors related to catheter dysfunction and found that patients with a background of diabetes, glomerulonephritis, or previous abdominal surgery had a higher probability (OR: 3.24; 6.52; 3.42, respectively) of early progression analysis. Crabtree et al. observed that abdominal scarring and previous history of peritonitis did not predict the severity of adherences and should not be used for deciding whether or not to use PD. We did not observe any relationship with other aspects of surgery, such as previous abdominal surgery or pre-existing medical conditions (for example, diabetes mellitus, polycystic kidney disease) that might affect selection criteria for entering our PD program in the future. Currently, we do not assess patients based on previous abdominal surgery in order to use PD as a replacement therapy, despite the low prevalence of previous abdominal surgery as potential surgical complications. Omentectomy had a protective effect against catheter dysfunction and replacement in both univariate and multivariate analyses. Another study examining hernias as a potential complication of PD catheter placement found that patients with polycystic kidney disease had a 2.5 times higher risk of complications, and that female sex was a protective factor against the occurrence of hernias. Although we observed several factors, including age, BMI, BSA, wound infection, and post-incisional hernia that were associated with catheter dysfunction in the univariate analysis, none were associated with a higher risk of catheter dysfunction and replacement in the logistic regression analysis. Crabtree et al. observed that abdominal scarring and previous history of peritonitis did not predict the severity of adherences and should not be used for deciding whether or not to use PD.

In conclusion, PD catheter placement using an open surgical approach with an infra-umbilical midline incision offers good results with few surgical complications after one year. In our study, we did not find significant risk factors for early catheter replacement. Omentectomy had a protective effect against catheter dysfunction and replacement. A prospective, randomised study evaluating omentectomy and PD catheter placement would confirm our conclusions.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

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Factors determining a low dose of haemodialysis as measured by ionic dialysance in critical patients with acute kidney injury

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Nefrologia 2012;32(3):359-66

ABSTRACT

Background: Estimating the dialysis dose is a requirement commonly used to assess the quality of renal replacement therapy (RRT) in patients with chronic kidney disease (CKD). In patients with acute kidney injury (AKI), this value is not always evaluated and it has been estimated that the prescribed dose is seldom obtained. Reports addressing this issue in AKI individuals are scarce and most have not included an adequate number of patients or treatments, nor were patients treated with extended therapies. Kt values obtained by the ionic dialysance method have been validated for the evaluation of the dialysis dose and it has also been shown that, compared with Kt/V, this is the most sensitive strategy for revealing inadequate dialysis treatment in critically ill AKI individuals. The main aim of this study was to assess the difference between the prescribed and the administered dialysis dose in critically ill AKI patients, and to evaluate what factors determine this gap using Kt values assessed through ionic dialysance.

Material and Method: Data from 394 sessions of renal replacement therapy in 105 adult haemodialysis (HD) patients with oliguric acute kidney injury and admitted to ICU were included in this analysis. RRT was carried out with Fresenius 4008E dialysis machines equipped with on-line clearance monitoring (OCM® Fresenius), which use non-invasive techniques to monitor the effective ionic dialysance, equivalent to urea clearance. The baseline characteristics of the study population as well as the prescription and outcome of RRT were analysed. These variables were included in a multivariate model in which the dependent variable was the failure to obtain the threshold dose (TD).

Results: The main baseline characteristics of the study population/treatments were: age 66±15 years, 37% female, most frequent cause of AKI: sepsis (70%). Low BP and/or vasoactive drug requirement (71%), mechanical ventilation (70%) and average individual severity index: 0.7±0.26. Two hundred and one intermittent HD (IHD) and 193 extended HD (EHD) sessions were performed; the most frequently used temporary vascular access was the femoral vein catheter (79%). Prescribed Kt was 53.5±14L and 21% of prescriptions fell below the TD. Sixty-one percent of treatments did not fulfill the TD (31±8L) compared with 56±12L obtained in the subgroup that achieved the target. Compared to IHD, EHD provided a significantly larger Kt (46±16L vs 33L±9L). Univariate analysis showed that inadequate compliance was associated with age (>65y), male gender, intra-dialytic hypotension, low Qb, catheter line reversal, and IHD. The same variables with the exception of age and gender were independently associated in the multivariate analysis.

Conclusions: The dialysis dose obtained was significantly lower than that prescribed. EHD achieved values closer to the prescribed KT and significantly higher than in IHD. Ionic Kt measurement facilitates monitoring and allows HD treatments to be extended based upon a previously established TD. Besides the chosen strategy to dispense the dose of dialysis, a well-functioning vascular access allowing for optimal blood flow and other approaches aimed at avoiding hemodynamic instability during RRT are the most important factors to achieve TD, mainly in elderly male patients. The dialysis dose should be prescribed and monitored for all critically ill AKI patients.

Factores determinantes de una baja dosis de hemodiálisis establecida por dialisancia iónica en pacientes críticos con insuficiencia renal aguda

RESUMEN

Introducción: En la insuficiencia renal aguda (IRA), la dosis administrada no suele controlarse y se estima que resulta inferior a la prescrita. Objetivo: Evaluar la diferencia entre la dosis prescrita y la dosis administrada en pacientes con IRA en Unidades de Cuidados Intensivos (UCI), así como los factores que la determinan, utilizando la determinación del Kt por dialisancia iónica. Material y método: Se incluyeron 394 terapias de reemplazo renal (TRR) en 105 pacientes adultos, con IRA oligúrica ingresados en UCI, con requerimiento de TRR, tratados con hemodiálisis intermitente (HDI) y/o extendida (HDE). Las TRR fueron realizadas con un monitor de aclaramiento on line (OCM®, Fresenius) para la determinación del Kt. Se registraron las características de los pacientes, la prescripción y el desarrollo de TRR. Todas estas variables fueron incluidas en un modelo uni y multivariado, teniendo como variable dependiente la incapacidad de lograr la dosis umbral objetivo (DU). Resultados: Edad 66 ± 15 años, 37% del sexo femenino, etiología más frecuente: sepsis (70%), hipotensión y/o requerimientos de inotrópicos (71%), asistencia respiratoria mecánica (70%); el índice de severidad individualizado promedio fue de 0,7 ± 0,26. Se efectuaron 201 HDI y 193 HDE, la vía de acceso vascular más frecuente fue la femoral (79%). El Kt prescrito fue de 53,5 ± 14 litros, y un 21% de las prescripciones estaban por debajo de DU. En el 61% no se logró el nivel de cumplimiento de la DU (31 ± 8 litros), vs. 56 ± 12 litros en el subgrupo que logró el nivel de cumplimiento. El Kt obtenido por las HDE fue significativamente mayor (46 ± 16 litros vs. 33 ± 9 litros en HDI). En el análisis univariado, el nivel de cumplimiento insuficiente estuvo relacionado con la edad (≥ 65 años), el sexo (masculino), la presencia de hipotensión intradialítica, no lograr el flujo de sangre prescrito, la inversión de las ramas del catéter y la HDI. Las mismas variables estuvieron independientemente relacionadas en el modelo multivariado, con excepción de la edad y el género. Conclusiones: La dosis de dialisancia administrada fue significativamente inferior a la prescrita. Las HDE exhibieron un Kt más cercano a DU y significativamente mayor que las HDI. El funcionamiento adecuado del acceso vascular, sin la necesidad de inversión de las ramas del catéter, y el hecho de evitar la inestabilidad hemodinámica durante la TRR constituyen dos de los factores más importantes para lograr la DU, particularmente en ancianos y varones. Debe prescribirse y controlarse la dosis de dialisancia en pacientes críticos con IRA.


INTRODUCCIÓN

Acute kidney injury (AKI) is a highly prevalent entity among patients admitted to intensive care units (ICU); AKI occurs in 5%-15% of these patients, according to the at-risk population being studied and the definition used for AKI.1,2

Although more than 60 years have passed since the first haemodialysis session was successfully carried out in patients with AKI, the mortality rates associated with this condition in critical patients still range between 30% and 60%,3,4 particularly in patients requiring some type of renal replacement therapy (RRT),5 making AKI an independent risk factor for mortality in this group.3,4,5

The different types of RRT used in AKI patients can be classified into intermittent (IHD), extended or hybrid (EHD), continuous, or peritoneal dialysis.7 This last technique is not commonly applied in adult patients, and patients treated with continuous methods are rare in Spain, with IHD and EHD being the most common, taking first and second place, respectively.4

While haemodialysis dosage is important for patients on chronic dialysis, threshold doses (TD) for RRT in patients with AKI in the ICU have not been established.9,12 A study at one hospital showed higher survival and renal recovery rates in patients with daily IHD sessions13; however, the dose administered per session was 0.94Kt/V, far below the recommendations for patients with chronic kidney disease (CKD). A multi-centre study showed that, above a Kt/V of 1.3, no benefits were observed in terms of reduced patient mortality.14 As such, the TD in patients with AKI is generally considered to be close to the applicable target values in patients with CKD, which entails a Kt/V equal to or greater than 1.2, a percent reduction in urea (PRU) equal to or greater than 65%, or a Kt greater than 45 or 40 in males and females, respectively.15,16

However, in normal clinical practice, in contrast to patients with CKD, the doses administered to AKI patients go uncontrolled, and it is widely estimated that we do not reach the prescribed dose.18,19 Few studies have evaluated this issue as a primary objective in patients on IHD with an adequate number of patients and treatments, and none has performed such an evaluation in EHD. In this context, critical patients would be at an even greater risk of not receiving the prescribed dose.20

The most commonly used methods for evaluating the dose administered in patients with AKI have been the Kt/V formula or URR. The Kt/V formula, which is routinely used in CKD patients, has limited applications in critical patients, since this group tends to have a varying and unpredictable urea distribution volume.21 While determining URR is a simple process, the calculation is made retrospectively,
Our research team was composed of members of the Nephrology, Cardiology, and Intensive Care departments, and the study took place in the Intensive Care Unit (ICU) and Intensive Coronary Care Unit (ICCU) at the Hospital Italiano de Buenos Aires. The study was conducted according to the regulations established by good clinical practices and the Declaration of Helsinki with the modifications established by the Nuremberg and Tokyo Conventions, and was approved by an Institutional Review Board (IRB) - Comité de Protocolos de Investigación (CEPI) - Hospital Italiano.

This was a prospective and observational study involving RRT-requiring adult AKI individuals admitted to the ICU or ICCU, and being treated with intermittent and/or extended haemodialysis. Patients in the ICCU were included due to the extensive cardiological care provided at the Hospital Italiano de Buenos Aires. All baseline characteristics, including sequential organ failure assessment (SOFA), aetiology and classification of the AKI, and the severity of AKI using the individual severity index (ISI) were recorded. The type and duration of dialysis was not modified for the purposes of the study, and was administered according to the indications by the attending physician and the type of treatment (intermittent or extended dialysis), registering all of the different parameters of the prescription. Patients were administered dialysis using Fresenius 4008 S monitors equipped with OCM® biosensors (On-line Clearance Monitoring, Fresenius Medical Care AG), devices that use non-invasive methods to measure effective ionic dialysance with conductivity probes. Water used for haemodialysis was obtained through a portable reverse osmosis device (FG Ingenieria). The dialysate flow rates for IHD and extended dialysis were 500ml/min and 300ml/min, respectively. Sterile bicarbonate powder was also used. In all cases, RRT was administered using Fresenius FX® 60 dialysers (helixone filters of 1.4m², KoA urea 960ml/min).

In all cases, the vascular access used were non-tunelled central venous catheters of 11.5Fr, placed using the Seldinger technique in the femoral vein or internal jugular vein, at 19cm or 16cm, respectively. In the absence of any contraindications, patients were administered standard anticoagulation using sodium heparin in a continuous infusion with a loading dose of 1000 units and a maintenance dose of 500 units per hour. Kt was automatically determined through the aforementioned method, and calculated prescribed Kt based on the type of RRT, blood flow, and time prescribed on dialysis along with in vivo dialysate clearance, which was previously determined in a series of CKD patients on stable haemodialysis.

The following parameters were registered throughout each dialysis session: type of RRT, compliance with the duration prescribed, temporary or definitive suspension, ultrafiltration (millilitres), nominal blood flow, type and location of vascular access, need for catheter line reversal, recirculation of the vascular access, intra-dialysis hypotension (defined as a drop in mean blood pressure of 10mm Hg), need for hypotension treatment (defined as an increase in inotropic drugs and/or saline solution), use of heparin, and coagulation of the dialysate or system. Recirculation of the vascular access was measured by determining plasma urea levels in arterial, venous, and peripheral lines using the low-flow method.

All data are expressed as mean ± standard deviation or proportions, unless otherwise indicated.

Considering a target Kt of 40 for women and 50 for men, we determined compliance with this target for both the prescribed dose and administered dose in each case. We performed a univariate analysis with the dependent variable of compliance and the independent variables were components of the RRT performed and patient characteristics. A p-value <.05 was considered statistically significant. All variables that had statistical significance or clinical relevance were included in a multiple logistic regression model, with level of compliance with dosage as the dependent variable. Taking into account the number of variables mentioned, we estimated a minimum number of 200 RRT sessions with Kt measurements. We used STATA software version 8.0 for all statistical analyses.

RESULTS

A total of 395 RRT sessions were recorded in 105 patients with AKI in the ICU (3.7±3.96 sessions per patient) from June 29, 2010 through May 24, 2011. Table 1 summarises...
the characteristics of the study population: mean age: 66±15 years, 37% female, 97% with oliguric AKI, and the most common aetiology was sepsis (70%). These were critical patients, the majority of which had hypotension and/or requirements for inotropic drugs (71%) and required mechanical ventilation (70%). The mean ISI was 0.7±0.26, and the mean SOFA score was 12±4.

A total of 201 IHD and 193 EHD sessions were performed, and the most commonly used vascular access was the femoral vein (79%). Serum levels of urea at the start of each haemodialysis session were 101±58mg/dl, and the haematocrit was 24±8 %. Heparin was not administered in 165 sessions (42%), the treatment duration was 317±102 minutes (extended: 408±73 minutes), and the blood flow was 223±62ml/min (extended: 186±17ml/min) whereas the total ultrafiltration per session was 1036±684ml (62% above 1000ml). Vascular access recirculation occurred in 21±19% of cases, with a recirculation of more than 15% in 53% of accesses evaluated. Catheter line reversal was required in 22% of procedures, and recirculation was significantly more common in this instance than when the reversal was not required (recirculation: 25±21 vs 20±18; P<.05). Intra-dialysis hypotension occurred in 20% of RRT sessions, requiring an increased dosage of inotropic drugs in 17% and/or saline solution in 8%. Coagulations occurred in the dialyser in 23 sessions, 11 required temporary suspensions of treatment and then completed the indicated effective time, and 2 required definitive suspension (Table 2).

Mean prescribed Kt was 52.26±13 litres, and 21% of all prescriptions were below the dosage compliance level (lower than 40 litres in women and 45 litres in men). There were no significant differences between the proportion of men and women with a prescribed Kt below the level of dosage compliance (21% in women vs 23% in men).

As regards the dose of Kt administered with an adequate prescription, 185 sessions (61%) did not comply with the prescribed dose, with mean Kt in this sub-group being 31±8 litres vs 56±12 litres in the sub-group that did reach the compliance level.

The Kt obtained in EHD sessions was significantly higher than in IHD: 46±16 litres vs 33±9 litres, respectively (Figure 1).

In the univariate analysis, an insufficient level of compliance was significantly correlated with age (older than 65 years), sex (male), severity of illness, anaemia (haematocrit <25), failure to achieve the prescribed blood flow, catheter line reversal, and the type of RRT (IHD) (Table 3).

In the multivariate analysis, an insufficient level of compliance was independently correlated with the presence of intra-dialysis hypotension, failure to achieve the prescribed blood flow, catheter line reversal, and intermittent haemodialysis (Table 4).

**DISCUSSION**

This study demonstrates that a substantial proportion of RRT sessions in critical patients with AKI are inadequately prescribed, and that an even greater proportion does not reach full compliance with the dose prescribed. This is the first study in which ionic dialysance has been applied in a
Guillermo Rosa-Diez et al. Factors affecting dialysis dose in AKI

As regards our method of measurement for the dosage of dialysis, we believe that it is adequate for this type of patient and treatment. Urea kinetic modelling assumes stability characterised by a neutral nitrogen balance and similar pre-dialysis urea values for each cycle of treatment (haemodialysis). However, this is not valid for patients with AKI, since the majority of critical patients are hyper-catabolic and have a negative nitrogen balance. Regional blood flow abnormalities, particularly in unstable patients receiving vasoactive drugs, can produce a disequilibrium. In the intercompartmental distribution of urea, which would invalidate the normal single-compartment models for urea, over-estimating the dose of dialysis when calculated through blood samples. This disequilibrium would be lower in the case of patients treated with extended dialysis, and so calculating dialysis dosage through urea kinetic modelling could not be used to compare between intermittent and extended therapies. In contrast, ionic dialysance, using the same principle of direct measurements of solute purification in the dialysate, is an applicable, sensible method that allows for comparing doses between IHD and EHD.

In our study, all variables that could be related to an inadequate dialysis dose were taken into account; the fact that none of these were correlated with non-compliance in both univariate and multivariate analyses (for example, not using heparin) does not imply that these are not important. With regard to the severity of the patients’ conditions, while this has been associated with a greater proportion of insufficient dialysis doses, our patients were in severely critical states, since this was part of the primary objective of our study, and this variable is also masked by the type of treatment provided, since the severity of the patient’s condition at the start of treatment was higher in EHD than IHD (ISI: 0.83±0.16 vs 0.69±0.26; and SOFA: 15±3 vs 7±3, respectively).

Age and sex were correlated in the univariate model; a previous study showed that male sex was associated with a higher risk of insufficient dialysis, but both variables were not significantly associated in our multivariate model.

The vascular access is of fundamental importance. All patients with AKI require temporary catheters, and, as demonstrated by our results, these imply a high rate of recirculation, regardless of the location of insertion. While recirculation was more common in femoral catheters than...
jugular catheters, this difference was not significant, and recirculation was higher than 15% in both cases (22±19% vs 19±19%, respectively). Line reversal, which is a common practice when we are unable to achieve proper flow rates, was a prevalent cause for inadequate dialysis, with a high rate of recirculation regardless of the site of insertion. These factors, together with an incapacity to achieve the prescribed blood flow rate, makes the vascular access one of the most important factors in considering the dialysis dose to prescribe in critical patients. As such, when faced with an inability to achieve optimal flow rates, we must consider modifying the treatment regimen by increasing the duration of the session and/or the frequency of treatments, or consider using longer catheters (equal to or longer than 20cm for femoral vein insertion) or wider catheters (13Fr).

Independently of other variables, haemodynamic instability during dialysis, which is a common complication in these patients, was another primary cause of inadequate dialysis. This was significantly more common in patients on EHD (23% vs 10% in IHD), which is probably due to the severity of the patient’s conditions, not to the type of RRT per se.

Finally, patients on EHD reached a higher level of compliance than those on IHD. A multi-centre study did not observe this difference, but this study had the bias of being a controlled study, since the primary objective was to reach a specific dialysis dosage. Our study attempted to reflect what actually occurs in daily practice, and together with the aforementioned study, supports the arguments set forth by expert opinion: regardless of the controversy surrounding thresholds and methodologies in measuring dialysis dosage, it must indeed be controlled and monitored. However, EHD is not without its disadvantages; in a secondary analysis, patients on EHD had a significantly higher proportion of dialyser coagulations (Figure 1). However, we should point out that the indication for EHD is related to the haemodynamic state and overall severity of the patient, and this type of RRT allows for reaching objective dosage even in critical patients, with the resources normally available in IHD. In our experience, the duration and compliance with time prescriptions for RRT are very important.

Our study had certain limitations, most notably the fact that it was carried out at one single hospital, did not incorporate body weight and surface area for the patients analysed, possibly involved a certain level of heterogeneity in the study population, and Kt was considered to be optimal at its lower limit; however, we used an adjusted fit model, and no previous studies exist in the medical literature of this

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>Standard error</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly (&gt; 65 years)</td>
<td>2.14</td>
<td>0.51</td>
<td>.002</td>
<td>1.33-3.43</td>
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<tr>
<td>Male</td>
<td>1.92</td>
<td>0.46</td>
<td>.006</td>
<td>1.25-3.08</td>
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<tr>
<td>Severity (ISI &gt; 0.7)</td>
<td>0.56</td>
<td>0.15</td>
<td>.034</td>
<td>0.33-0.95</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>0.6</td>
<td>0.2</td>
<td>.124</td>
<td>0.31-1.15</td>
</tr>
<tr>
<td>Pre-dialysis hypotension</td>
<td>1.04</td>
<td>0.3</td>
<td>.892</td>
<td>0.59-1.83</td>
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<tr>
<td>Haematocrit &lt; 25%</td>
<td>0.56</td>
<td>0.14</td>
<td>.018</td>
<td>0.35-0.90</td>
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<tr>
<td>Ultrafiltration (&gt; 1000 ml)</td>
<td>0.81</td>
<td>0.2</td>
<td>.340</td>
<td>0.50-1.32</td>
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<tr>
<td>Location of catheter insertion (femoral)</td>
<td>0.71</td>
<td>0.22</td>
<td>.282</td>
<td>0.38-1.32</td>
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<tr>
<td>Vascular access recirculation &gt; 15%</td>
<td>0.85</td>
<td>0.20</td>
<td>.503</td>
<td>0.53-1.36</td>
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<tr>
<td>Blood flow obtained</td>
<td>0.32</td>
<td>0.09</td>
<td>.000</td>
<td>0.21-0.57</td>
</tr>
<tr>
<td>Catheter line reversal</td>
<td>2.49</td>
<td>0.78</td>
<td>.04</td>
<td>1.34-4.62</td>
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<tr>
<td>Procedure without heparin</td>
<td>1.26</td>
<td>0.30</td>
<td>.34</td>
<td>0.78-2.01</td>
</tr>
<tr>
<td>Thrombosis of the dialyser</td>
<td>1.50</td>
<td>0.82</td>
<td>.46</td>
<td>0.51-4.38</td>
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<tr>
<td>Intra-dialysis transfusion</td>
<td>2.24</td>
<td>1.30</td>
<td>.163</td>
<td>0.72-6.99</td>
</tr>
<tr>
<td>Intra-dialysis hypotension requiring action</td>
<td>1.65</td>
<td>0.50</td>
<td>.097</td>
<td>0.91-2.98</td>
</tr>
<tr>
<td>Temporary suspension</td>
<td>2.24</td>
<td>1.30</td>
<td>.163</td>
<td>0.72-6.99</td>
</tr>
<tr>
<td>Type of RRT (extended)</td>
<td>0.11</td>
<td>0.03</td>
<td>.000</td>
<td>0.07-0.20</td>
</tr>
</tbody>
</table>

Univariate analysis of an insufficient level of compliance. Bold values are significant.
MRA: mechanical respiratory assistance; CI: confidence interval; ISI: individual severity index; OR: odds ratio; RRT: renal replacement therapy.
magnitude in which Kt was used as a measurement of the dialysis dose in critical patients with AKI. Prospective studies that include a comparison of the duration of hospital stay and mortality with weekly Kt doses might better respond to the question of limits for Kt dosage in critical patients with AKI.

In conclusion, the prescribed dialysis dose in critical patients with AKI should be monitored. Ionic dialysance facilitates such supervision, as well as the estimation of extended treatments based on target doses and TD. In addition to the method used for measuring and controlling dialysis dosage, a better functioning vascular access (ensured optimal blood flow without the need for catheter line reversal) and haemodynamic stability during RRT would be the most important factors for achieving TD and other objectives in critical patients with AKI.

Conflicts of interest

The authors have no conflicts of interest to declare.

REFERENCES


Table 4. Multivariate analysis of insufficient compliance

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>Standard error</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly (&gt; 65 years)</td>
<td>1.25</td>
<td>0.35</td>
<td>.424</td>
<td>0.72-2.17</td>
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<tr>
<td>Male</td>
<td>1.43</td>
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<td>.21</td>
<td>0.82-2.48</td>
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<tr>
<td>Haematocrit &lt; 25%</td>
<td>0.76</td>
<td>0.21</td>
<td>.319</td>
<td>0.44-1.31</td>
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<tr>
<td>Severity (ISI &gt; 0.7)</td>
<td>0.61</td>
<td>0.43</td>
<td>.487</td>
<td>0.16-2.43</td>
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<tr>
<td>Catheter insertion location (femoral)</td>
<td>0.99</td>
<td>0.36</td>
<td>.989</td>
<td>0.49-2.03</td>
</tr>
<tr>
<td>Catheter line reversal</td>
<td>2.41</td>
<td>0.85</td>
<td>.012</td>
<td>1.20-4.79</td>
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<tr>
<td>Vascular access recirculation &gt; 15%</td>
<td>0.85</td>
<td>0.23</td>
<td>.55</td>
<td>0.49-1.45</td>
</tr>
<tr>
<td>Flow obtained</td>
<td>3.73</td>
<td>1.66</td>
<td>.003</td>
<td>1.56-8.91</td>
</tr>
<tr>
<td>Intra-dialysis hypotension requiring action</td>
<td>2.07</td>
<td>0.72</td>
<td>.035</td>
<td>1.05-4.09</td>
</tr>
<tr>
<td>Type of RRT (extended)</td>
<td>0.11</td>
<td>0.36</td>
<td>.000</td>
<td>0.54-0.21</td>
</tr>
</tbody>
</table>

Multivariate analysis of insufficient compliance. Bold values are significant.
CI: confidence interval; ISI: individual severity index; OR: odds ratio; RRT: renal replacement therapy.


Discrepancies among consensus documents, guidelines, clinical practice and the legal framework for the treatment of type 2 diabetes mellitus patients

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Nefrologia 2012;32(3):367-73

ABSTRACT

In this paper we analyse the discrepancies that exist in the widespread prescription of metformin in patients with type 2 diabetes and the lack of guidelines concerning its prescription in the different stages of renal failure. This cross-sectional study includes 304 patients with type 2 diabetes treated with oral antidiabetic drugs (ADOs) and a glomerular filtration rate (estimated GFR) <60ml/min/1.73m². Patients were attended in consecutive visits to primary health centres or in hospital departments of endocrinology or nephrology during 2010. We studied the frequency of metformin and other ADO prescriptions according to renal function and the department in which the patient was treated. The ADO most frequently prescribed was metformin (54.9%), followed by repaglinide (47.7%), DPP4 inhibitors (28.6%), and sulfonylureas (18.4%). However, in nephrology departments, repaglinide was more frequently prescribed than metformin (P<.001), whereas in primary health centres, the prescription of DPP4 inhibitors increased. In patients with an estimated GFR of 15-29ml/min/1.73m², metformin (13.3%) and sulfonylureas were the least prescribed, whereas metformin was much more frequently prescribed (70.0%) when estimated GFR was 45-59ml/min/1.73m² (P<0.001). In contrast, patients with an estimated GFR of 15-29ml/min/1.73m² were mainly prescribed repaglinide (76.7%), as opposed to patients with an estimated GFR of 45-59ml/min/1.73m² (38.9%) (P<0.001). Substantial evidence suggests that the recommendations for the use of ADO should be modified. This would lead to safely prescribing ADO in patients with an estimated GFR<60ml/min/1.73m², and more importantly in medical practice, according to the law.


INTRODUCTION

There is a complex arsenal of therapeutic options for the treatment of patients with type 2 diabetes mellitus (DM),
including metformin, sulfonylureas, glinides, thiazolidinediones, disaccharidase inhibitors, dipeptidyl peptidase (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP1) receptor antagonists, which, along with insulin, can be used in monotherapy or combined treatment. These drugs must be used after careful consideration of their technical data sheets. The choice depends on several different inter-related patient aspects, the ability of the drug to achieve treatment targets, associated diseases and complications, the risk of adverse effects, tolerance, and cost.1

The main national (Spanish Society of Diabetes [SED]) and international2,3 consensus documents and guidelines for the treatment of type 2 DM recommend using metformin as the first line of treatment, along with hygienic and dietary modifications, from the moment a diagnosis of DM is confirmed. However, there are no standard criteria for its use in the different stages of renal failure.

The SED1 and the American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on Type 2 DM (AACE/ACE) contraindicate the use of metformin in patients with a glomerular filtration rate (GFR) <60ml/min/1.73m², whereas Canadian and Australian guidelines place the cut-off point at GFR<30ml/min/1.73m², and recommend caution in prescribing this drug in patients with GFR<60ml/min/1.73m², which is in agreement with the consensus document from the American Diabetes Association and the European Society for the Study of Diabetes.4

The results from the UKPDS study already demonstrated the capacity of metformin to reduce glycaemia and the risk of micro and macroangiopathic complications in overweight patients.5 Additionally, metformin presents a series of advantages that provide an added value: it does not induce hypoglycaemia,2 has a neutral impact (or slight decrease) on body weight,3 improves lipid profiles,7,8 and also improves insulin resistance,3 all while maintaining a low cost. The limitations for its use are primarily derived from digestive intolerance, renal failure, liver failure, and acute/chronic pathologies that may cause tissue hypoxia.9

The aim of our study was to analyse the prescription of oral antidiabetics (ADO), especially metformin, which is the most commonly used ADO, by a group of health professionals from different specialties (primary care, endocrinology, and nephrology) in patients with renal failure and a MDRD-4 (Modification of Diet in Renal Disease-4) estimated GFR<60ml/min/1.73m², as they do not fall within the technical data sheet indications, the legal document that serves as the basis for drug prescription.10

MATERIAL AND METHOD

We performed a cross-sectional study of patients diagnosed with type 2 DM in consecutive visits during 2010 in primary care, endocrinology, and nephrology departments. Patients were only included in the study with an estimated GFR<60ml/min/1.73m², according to laboratory results, and who were receiving treatment with ADO. The variables collected were age, sex, last serum creatinine measurement (mg/dl), GFR calculated using the MDRD-4 formula, and latest measurements of glycosylated haemoglobin (HbA1c) and albuminuria/proteinuria. We also recorded all antidiabetic drugs prescribed: metformin, sulfonylureas, DPP-4 inhibitors, and repaglinide. The possible concomitant use of insulin and treatment compliance were also taken into account.

Quantitative variables are expressed as mean ± SE, and were compared using Student’s t-tests or Mann-Whitney U-tests, based on their distribution. Categorical variables were analysed using chi-square tests. A P-value <.05 was considered statistically significant, and we used G-Stat statistical software, version 2.0, for the analyses.

RESULTS

We analysed a total of 304 patients diagnosed with type 2 DM and treated with ADO, all of which had a GFR<60ml/min/1.73m² (MDRD-4) and a mean age of 74.2±9.0 years; of these, 128 were male (42.1%) and 176 were female (57.9%). Mean creatinine was 1.42±0.48mg/dl (range: 0.90-3.67mg/dl), with a mean GFR (MDRD-4) of 45.5±11.1ml/min/1.73m². Some 180 patients (59.2%) had a GFR of 30-44ml/min/1.73m², 94 (30.9%) had a GFR of 15-29ml/min/1.73m², and 30 (9.9%) had a GFR of 15-29ml/min/1.73m².

Patients were from primary care (128), outpatient endocrinology and nutrition (86), and outpatient nephrology units (90). The characteristics of each group are summarised in Table 1. Patients derived from primary care were on average older, the endocrinology group had a higher proportion of female patients, and those from nephrology had higher creatinine and proteinuria rates and a lower GFR.

The most commonly used ADO was metformin (167 patients, 54.9%) followed by repaglinide (145 patients, 47.7%). DPP-4 inhibitors were prescribed in 87 patients (28.6%), and 56 (18.4%) received sulfonylureas, with glimepiride being the most commonly prescribed. The ADO prescribed was associated with insulin in 80 patients (26.3%). Statistically significant differences were observed in the prescription of ADOs between the three groups: metformin was used less frequently and repaglinide was used to a greater extent in patients derived from nephrology, DPP-4 inhibitors were used more frequently in primary care, and 70% of these cases involved metformin. Endocrinology patients were most
commonly prescribed ADO with insulin, and were less frequently prescribed sulfonylureas (Table 2).

As regards the use of the different types of ADO according to severity of GFR, metformin was the least commonly used drug with a GFR of 15-29ml/min/1.73m² (4/30 patients, 13.3%), along with sulfonylureas, but it was the most commonly prescribed drug in patients with a GFR of 45-59ml/min/1.73m² (126/180 patients, 70.0%) (P<.001). The opposite occurred in the case of repaglinide, as this was the most commonly prescribed drug in patients with a GFR of 15-29ml/min/1.73m² (23/30 patients, 76.7%), but was less commonly prescribed at 45-59ml/min/1.73m² levels (70/180 patients, 38.9%) (P<.001). DDP-4 inhibitors were less frequently prescribed at lower GFR values, although this difference did not reach statistical significance (P=.07), and GFR had no apparent correlation with the use of sulfonylureas (Table 3).

**DISCUSSION**

In recent years, several different consensus documents and guidelines have been published that coincide on the recommendation to use metformin as the glucose-lowering drug of choice for patients with type 2 DM. However, no such agreement exists as regards the level of renal damage from which the use of this drug is contraindicated due to the potential risk of lactic acidosis (LA), a rare but severe complication that can arise.1-5

With the objective of evaluating and comparing medical practice among different groups of health care professionals (primary care, endocrinology, and nephrology departments) in our health area, and in light of the information provided in the available consensus documents and guidelines, we have reviewed the characteristics of treatment with ADO in a group of 304 patients diagnosed with type 2 DM and a GFR (MDRD-4) <60ml/min/1.73m², focusing primarily on the use of metformin. Overall, metformin was the most commonly used ADO, followed by repaglinide, DPP-4 inhibitors, and sulfonylureas (mainly glimepiride).

Upon analysis of the data by department, we observed that the most commonly used drug was metformin in primary care and endocrinology units, with a significantly lower rate of use by nephrologists, which also occurred with sulfonylureas. We also observed that sulfonylureas and DPP-4 inhibitors were less frequently prescribed at lower GFR values, although this difference did not reach statistical significance (P=.07), and GFR had no apparent correlation with the use of sulfonylureas (Table 3).

Table 1. Characteristics and differences between the three patient groups according to origin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary care</th>
<th>Endocrinology</th>
<th>Nephrology</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>128</td>
<td>86</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>75.9±8.8</td>
<td>72.7±9.3</td>
<td>73.3±8.5</td>
<td>P&gt;.05</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>56/72</td>
<td>28/58</td>
<td>44/46</td>
<td>P&gt;.05</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.24±0.27</td>
<td>1.31±0.41</td>
<td>1.79±0.59</td>
<td>P&gt;.001</td>
</tr>
<tr>
<td>GFR (MDRD)</td>
<td>49.8±8.3</td>
<td>49.0±9.2</td>
<td>35.8±10.2</td>
<td>P&gt;.001</td>
</tr>
<tr>
<td>HbA₁c</td>
<td>8.1±1.2</td>
<td>7.2±1.5</td>
<td>7.1±1.3</td>
<td>P&gt;.001</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>80±195</td>
<td>223±686</td>
<td>762±1572</td>
<td>P&gt;.001</td>
</tr>
</tbody>
</table>

* Primary care vs the other two groups; † Endocrinology vs the other two groups; ‡ Nephrology vs the other two groups. M: male; HbA₁c: glycosylated haemoglobin; F: female; GFR: glomerular filtration rate.

Table 2. Differences in the use of oral antidiabetic drugs by health care department

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary care</th>
<th>Endocrinology</th>
<th>Nephrology</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>65.6%</td>
<td>68.6%</td>
<td>26.7%</td>
<td>P&lt;.001</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>32.0%</td>
<td>3.5%</td>
<td>13.3%</td>
<td>P&lt;.001</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>32.0%</td>
<td>46.5%</td>
<td>71.1%</td>
<td>P&lt;.001</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>43.8%</td>
<td>19.8%</td>
<td>15.6%</td>
<td>P&lt;.001</td>
</tr>
<tr>
<td>Combined with insulin</td>
<td>18.8%</td>
<td>38.4%</td>
<td>25.6%</td>
<td>P&lt;01</td>
</tr>
</tbody>
</table>

DPP-4: dipeptidyl peptidase 4.
4 inhibitors were more commonly used in primary care, repaglinide was more commonly used in nephrology units, and repaglinide in combination with insulin in endocrinology departments. The more intensive use of DPP-4 inhibitors in primary care was associated with the simultaneous use of metformin (70%), with appearance of these associations (vildagliptin/sitagliptin with metformin) occurring in recent years. The lower rate of use of metformin in nephrology units can be explained by the higher mean plasma creatinine level (1.79±0.59mg/dl) and significantly lower GFR (10.2±35.8ml/min/1.73m²) as measured by MDRD-4 than in the other groups. Furthermore, sulfonylureas were used at a lower rate and repaglinide was used more frequently by nephrologists, as repaglinide has a short half-life and can be used in patients in advanced stages of renal failure.1

Upon analysis of the use of metformin and its correlation with GFR (MDRD-4), we found that the majority of patients (70%) had a GFR of 45-59ml/min/1.73m², 39.4% had a GFR of 30-44ml/min/1.73m², and only 13.3% had a GFR of 15-29ml/min/1.73m². As such, no patient fell within the recommendations made by the SED and AACE/ACE, which contraindicate the use of metformin at GFR<60ml/min,1,2 although it is in line with the recommendations from Canadian and Australian clinical guidelines4,5 and with the non-explicit recommendations from other consensus documents.3 In any case, most doctors consider a cut-off point of 30ml/min to be an absolute contraindication for the use of metformin.

Metformin and sulfonylureas were prescribed in 13.3% of patients with a GFR<30ml/min/1.73m², even though the use of these drugs in patients with such a low GFR is contraindicated and does not fall within the ranges observed in clinical recommendations. This trend is reported in other studies as well, in which as many as 27% of patients that received metformin had some contraindication for its use.12-14 In these studies, no mention is made to the reasons justifying the use of metformin in patients with contraindications for the drug, although doubts are raised as to the maintenance of this therapy in many patients (41%-75%), despite these contraindications.12-14 The four patients that received metformin with a GFR<30ml/min/1.73m² were 69-95 years old and had a plasma creatinine level of 1.9-2.2mg/dl (GFR: 23-28ml/min/1.73m²).

The basis for different levels of metformin prescribed according to GFR lies in the possible increase of risk for LA in patients with renal failure, since lactic acid is eliminated through filtration and active tubular secretion. The association between LA and renal failure in patients with type 2 DM is currently under debate, to say the least. In a review of the Cochrane database,15 no cases of fatal or non-fatal LA were observed when combining the information for 206 comparative trials performed with a total of 47 846 patients/year treated with metformin and 38 221 patients/year treated without metformin. In a systematic literature review, again no differences were observed when analysing the incidence of LA between patients treated with and without metformin, although in this study, the mean incidence of LA was 8.4 cases/patient/year in the group with metformin, and 9 cases/patient/year in the other,16 which is higher than the rates reported elsewhere (3.3 cases/patient/year in groups treated with metformin vs 4.8 cases/patient/year in groups treated with other sulfonylureas).17 These studies concluded that there is no increased risk of LA, and that the primary cause for this condition is systemic dysfunction.

Table 3. Differences in the use of oral antidiabetics according to glomerular filtration rate

<table>
<thead>
<tr>
<th>Drug</th>
<th>GFR 45-59</th>
<th>GFR 30-44</th>
<th>GFR 15-29</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>70.0%</td>
<td>39.4%</td>
<td>13.3%</td>
<td>P&lt;.001</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>19.4%</td>
<td>18.1%</td>
<td>13.3%</td>
<td>ns</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>38.9%</td>
<td>55.3%</td>
<td>76.7%</td>
<td>P&lt;.001</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>33.3%</td>
<td>23.4%</td>
<td>16.7%</td>
<td>ns (P=.07)</td>
</tr>
</tbody>
</table>

DDP-4: dipeptidyl peptidase 4; ns: non-significant; GFR: glomerular filtration rate.
necessary. However, they maintained the absolute contraindication for prescribing metformin when GFR<30ml/min.20

In the last 15 years, we have diagnosed only 2 patients with LA, and in neither case had metformin been prescribed when GFR<60ml/min/1.73m². Both cases were triggered by dehydration from severe gastroenteritis and prerenal acute renal failure.

Upon reviewing the technical data sheet for metformin, which is the legal document regulating its use, we found that explicit contraindications are stated for its use in patients with renal failure or renal dysfunction (creatinine clearance <60ml/min), although no reference is made to adjusting the measure to body surface area.9

Although no randomised studies have been performed in patients with a GFR>60ml/min/1.73m², as expressed in consensus documents, guidelines, studies, and medical practice, suggest the possibility of modifying the technical data sheet for metformin, not only in terms of contraindications for its use in patients with renal failure, but also regarding the use of creatinine clearance as a parameter for measuring renal function. We understand that this is a complex and costly process in which scientific associations should play a greater role. New evidence, studies, experience, and better understanding are necessary to change the recommendations and contraindications established for a drug. We should also conduct studies in patients with renal failure, who are normally excluded from clinical trials, in order to fully understand this issue.

Currently, the nephrological scientific community does not consider creatinine clearance to be the most adequate parameter for measuring GFR. In 2002, the National Kidney Foundation (NKF) – Kidney Disease Outcomes Quality Initiative (KDOQI) published a guideline for the evaluation, classification, and stratification of chronic kidney disease, and recommended estimating GFR, the currently used method in clinical practice, to evaluate the level of renal dysfunction and its progression through time, using formulas that take into account serum creatinine, such as Cockcroft-Gault (CG) and MDRD.21 Spanish Society of Nephrology guidelines also recommend the use of CG and MDRD for calculating GFR (level B evidence).22

Although the comparison between CG and MDRD is under debate, primarily based on the characteristics of the population studied and the method used for calculating serum creatinine,23 which results in underestimation of GFR>60ml/min/1.73m²,24 the majority of authors and scientific associations have used the MDRD-4 formula as the reference method due to its ease of application in clinical laboratories and the fact that patient weight is not needed.25 The laboratory at our hospital uses the MDRD-4 formula as the reference method for measuring renal function (KDOQI); in addition, the percentages of patients included in each stage of renal failure would vary considerably when compared to using MDRD as the reference method, decreasing the potential number of patients that could use metformin.27

Later studies in different study populations appear to confirm these data.29,30 The recommendations for using metformin in patients with a GFR of 30-60ml/min/1.73m², as expressed in consensus documents, guidelines, studies, and medical practice, suggest the possibility of modifying the technical data sheet for metformin, not only in terms of contraindications for its use in patients with renal failure, but also regarding the use of creatinine clearance as a parameter for measuring renal function. We understand that this is a complex and costly process in which scientific associations should play a greater role. New evidence, studies, experience, and better understanding are necessary to change the recommendations and contraindications established for a drug. We should also conduct studies in patients with renal failure, who are normally excluded from clinical trials, in order to fully understand this issue.

We conclude that metformin, a drug recommended by various consensus documents and guidelines for the treatment of patients with DM, is a safe, useful, and cheap ADO. However, its current technical data sheet, a document establishing legal constraints, contraindicates its use in patients with creatinine clearance <60ml/min. Although no randomised studies have been performed in populations with renal failure, meta-analyses and retrospective and observational studies suggest that metformin can be used with caution, instructing the patient, and reducing the dosage in patients with a GFR of 30-60ml/min/1.73m².
Currently, creatinine clearance has been replaced by MDRD as the method of choice for estimating GFR, although it underestimates GFR in patients with GFR>60ml/min/1.73m² and is not validated for all populations, including many of the patients that we see on a regular basis. The nephrological community should develop formulas for estimating GFR with greater accuracy in all types of patients, as well as standardise the technical data sheets for drugs in terms of reference parameters used for measuring renal function. We believe that scientific associations, the ministry of health, and pharmaceutical laboratories should review the potential modification of the technical data sheet for metformin, with the goal of allowing health professionals to work within the legal framework established for this drug.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

REFERENCES


Advances in immunosuppression for kidney transplantation: new strategies for preserving kidney function and reducing cardiovascular risk

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Nefrologia 2012;32(3):374-84

ABSTRACT

The development of new immunosuppressants for renal transplantation is aimed not only at improving short-term outcomes, but also at achieving better safety, cardiovascular, and metabolic profiles and at decreasing nephrotoxicity. Belatacept is a fusion protein that inhibits T cell activation by binding to CD80 and CD86 antigens. Clinical trials, particularly the BENEFIT and BENEFIT-EXT studies, have shown that belatacept preserves function and structure in renal grafts. The effects of belatacept provide long-term, sustained results, and the safety and efficacy of this drug have been demonstrated in cases of renal transplantation from expanded criteria donors. Compared to calcineurin inhibitors, belatacept is associated with a lower incidence of chronic allograft nephropathy and a more favourable cardiovascular and metabolic profile.

Keywords: Belatacept. Renal function. Kidney transplantation.

INTRODUCTION

The objective of immunosuppression in kidney transplantation is to prevent and treat acute rejection and avoid chronic graft damage, thus minimising the adverse effects of immunosuppressants. The introduction of cyclosporine, tacrolimus, and mycophenolate mofetil (MMF) reduced rates of acute rejection and improved short and mid-term graft survival,¹² as reported by data from the Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients (SRTR) in the United States,¹ and the Grupo Español para el Estudio de la
However, the decrease in acute rejection rates has not been associated with increased long-term graft survival. Results from the OPTN/SRTR 2009 report showed no significant differences over time (Table 1). As such, strategies are still being sought that can increase long-term graft survival and patient survival.

Chronic graft dysfunction continues to be a common cause of graft loss. In the Spanish ICEBERG epidemiological study, 55.5% of patients developed chronic allograft nephropathy during a follow-up period of 8 years, average. In a Spanish study involving 1029 kidney recipients between 1997 and 2007, no significant differences in graft survival were observed after 5 and 10 years when only analysing cases where the graft had already survived more than 12 months. In the second phase of the study by the Spanish Chronic Allograft Nephropathy Study Group, patients that received a kidney transplant in 2002 were also included. Twelve months after the transplant, mean estimated glomerular filtration rate (eGFR) was 51.7±18.8ml/min/1.73m². During the follow-up period that lasted a mean 74.0±43.9 months, eGFR decreased by a mean 1.6±6.24ml/min/year. This decrease was more pronounced in patients treated with cyclosporine (n=3163) than those treated with tacrolimus (n=1044) and the difference was even greater with respect to those not receiving calcineurin inhibitors (n=133; drugs not specified). Cardiovascular disease following a kidney transplant was researched by the Spanish group Forum Renal, which created a prospective, multi-centre database of 2600 kidney transplantations during the period of 2000-2002. The rate of acute rejection at 12 months was 14.8%. After 4 years, graft and patient survival were 85.6% and 91.7%, respectively. The leading cause of death was cardiovascular disease, mainly coronary disease during the first year. The primary causes of graft loss were: vascular disease and thrombosis during the first year, death with a functioning graft in the second and third years, and chronic allograft nephropathy in the fourth year.

In addition to chronic allograft nephropathy and cardiovascular morbidity and mortality rates, infectious morbidity and mortality, metabolic complications, and a high frequency of tumours all impede long-term success. The primary interest in developing new immunosuppressants no longer involves simply improving short-term results, but also improving the safety profile, lowering nephrotoxicity, and improving cardiovascular and metabolic profiles.

NEW IMMUNOSUPPRESSANTS FOR KIDNEY TRANSPLANTS

The currently used immunosuppressant regimens are designed to block the activation, proliferation, and functioning of T cells (TC). The activation and proliferation of TC depends on three signals. The first is given by the interaction between the TC receptor and class II molecules, expressed in antigen presenting cells (APC). Calcineurin is activated at this point, and this is where calcineurin inhibitors, such as cyclosporine and tacrolimus, come into play. The second signal, or costimulatory signal, depends on the interaction of CD80/86 in the APC and CD28 expressed in the TC surface. Belatacept inhibits this interaction. The

| Table 1. Evolution of graft and patient survival between 1998 and 2007, according to the OPTN/SRTR 2009 report |
|--------------------------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Deceased donor | Living donor | Deceased donor | Living donor |
| Graft survival (%) | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| 1 year | 3 years | 5 years | 10 years | 1 year | 3 years | 5 years | 10 years | 1 year | 3 years | 5 years | 10 years |
| 1998  | 88.8  | 78.2  | 66.9  | 42.8  | 94.7  | 88.1  | 80.4  | 58.9  | 94.8  | 88.6  | 81.7  | 61.5  | 97.8  | 94.8  | 90.1  | 76.8  |
| 2003  | 89.1  | 78.5  | 68.6  | na    | 95.4  | 88.4  | 81.0  | na    | 94.5  | 88.2  | 81.4  | na    | 98.2  | 94.9  | 90.8  | na    |
| 2005  | 90.0  | 80.3  | na    | na    | 95.1  | 89.2  | na    | na    | 94.6  | 88.7  | na    | na    | 98.0  | 95.2  | na    | na    |
| 2007  | 91.5  | na    | na    | na    | 96.6  | na    | na    | na    | 95.9  | na    | na    | na    | 98.7  | na    | na    | na    |
first and second signals activate transduction pathways that generate transcription factors for the synthesis of cytokines. Among these, interleukin 2 (IL-2) stands out, as it induces the third signal, allowing for the proliferation of TC clones (this is where immunosuppressants that interfere with the cell cycle play a role). Several strategies have been developed for improving kidney transplant results using traditional immunosuppressants, but the rates of chronic transplant nephropathy and cardiovascular and metabolic risk oblige us to continue seeking out alternatives.

Several different drugs and biological agents are being evaluated in clinical trials or have recently been approved for immunosuppression in kidney transplants. These new immunosuppressants have different mechanisms of action. Some inhibit enzymes such as protein kinase C (PKC) or Janus kinase 3 (JAK3), and others act on key components of the lymphocyte activation process, such as the LFA3-CD2 or CD28-CD80/86 pathways (Figure 1).

Sotrastaurin is a potent and selective inhibitor of classic (α and β) and new (δ, ε, η and θ) isoforms of PKC. These isoforms play a key role in the first and second signals for TC activation. By inhibiting these isoforms, sotrastaurin blocks the initial activation of T cells, although it does not affect the lymphocyte proliferation that is mediated by IL-2. Two phase II trials were interrupted due to an increase in acute rejection. In another phase II trial, sotrastaurin was compared to tacrolimus in 125 patients that received a kidney transplant (de novo recipients). After 3 months, sotrastaurin was significantly less effective than tacrolimus using the primary evaluation criteria (acute rejection confirmed by biopsy, graft loss, death, or loss to follow-up).

CP-690550 or tofacitinib (previously referred to as tasocitinib) is a selective inhibitor of JAK3 kinase which plays a central role in signal transduction for cytokine receptors. In phase II trials, tofacitinib has demonstrated comparable efficacy to tacrolimus in terms of acute rejection and renal function. In a pilot trial, the lower dose of CP-690550 had similar safety and efficacy profile to tacrolimus in kidney transplant recipients. Later, a multi-centre, randomised study was carried out in which 322 kidney transplant recipients were randomised to receive CP-690550 or cyclosporine for 12 months. The incidence of acute rejection was similar in both groups, although severe infections were more common with CP-690550 than with cyclosporin. However, eGFR improved with CP-690550 from the 1st month, and the effect was maintained throughout the study, with significantly different results from cyclosporine (P<.05 for both regimens of CP-690550).

Alefacept is a humanised anti-CD2 monoclonal antibody. It is a LFA3-IgG1 fusion protein that inhibits the adhesion of T cells. The results of alefacept in kidney transplants in primates were very promising, which led to further phase I and II trials, administering the drug orally along with tacrolimus in kidney transplants. However, the results from a randomised, double-blind, placebo controlled, multi-centre, phase II trial with 212 kidney transplant recipients did not confirm these expectations. Alefacept did not result in significantly superior outcomes than the placebo, except for in the activation of CD4+ and CD8+ T cells, with no differences in graft survival, patient survival, or renal function.

**BELATACEPT**

Belatacept is a selective T-cell blocker. It is a human fusion protein that combines a modified extracellular portion of cytotoxic T-cell antigen 4 (CTLA-4) and the fragment crystallisable region of human IgG1 (Fc region). It blocks the costimulatory signal by binding to APC CD80 and CD86 antigens, thus inhibiting the complete activation of T cells and promoting anergy and apoptosis. This drug is derived from abatacept, a fusion protein that is effective in autoimmune disorders such as rheumatoid arthritis. The belatacept molecule includes two replaced amino acids that confer a greater binding ability to CD80 and CD86, greater binding strength to T cells, and greater efficacy in prophylaxis against rejection.

In June 2011, the European Medicines Agency (EMA) approved belatacept for combined use with steroids and mycophenolic acid in prophylaxis against graft rejection.
adult patients that had received a kidney transplant. This is the first biological agent to be approved for this indication, and is the first immunosuppressant in a decade to offer a new mechanism of action.

Belatacept has linear pharmacokinetics in healthy volunteers and kidney transplant recipients. Patient exposure to the drug is proportional to dosage, with very little day to day variability. Drug levels in the body are predictable based on the doses administered intravenously, regardless of sex, age, race, renal function, albuminemia, diabetes, and dialysis treatment. In clinical trials, the minimum concentration was maintained stably up to 5 years following the transplant.

The saturation of CD 86 receptors inhibit the T-cell alloresponse. In vitro studies have demonstrated alloresponse inhibition with the minimum concentration of belatacept necessary to saturate CD86 receptors. In patients treated with belatacept, free CD86 receptor levels are significantly lower than before treatment, and are also lower than in healthy volunteers and patients treated with cyclosporin. The extension to 5 years of a phase II trial involving patients treated with belatacept or cyclosporine, CD86 receptor saturation with belatacept was maintained throughout the follow-up period. However, belatacept saturation in patients treated every 4 weeks (74%) was significantly higher than in patients treated with belatacept every 8 weeks (56%) ($P<.05$), confirming that saturation of CD86 receptors depends on the frequency and dosage of belatacept administered.

**Phase II trials**

A randomised, partially blinded study with parallel groups carried out in 22 centres in Europe, USA, and Canada, and involving 216 patients, compared belatacept administered in more intensive (MI) or less intensive (LI) treatment schedules vs cyclosporine in the prevention of rejection within 6 months of transplantation. The incidence of acute rejection within 6 months was similar between the three groups: 7% with MI belatacept, 6% with LI belatacept, and 8% with cyclosporine. There were no cases of rejection after 6 months. Directly measured GFR was higher with belatacept after 12 months (Figure 2). The best correlations between GFR and eGFR were achieved using the Modification of Diet in Renal Disease (MDRD) equation. Chronic allograft nephropathy was less frequent with belatacept (Figure 3). Patients with chronic allograft nephropathy that received belatacept had a higher eGFR than the group that received cyclosporine. In terms of cardiovascular and metabolic profiles, blood pressure, and lipid levels in patients treated with belatacept were similar or slightly lower than in the group treated with cyclosporine, despite the greater use of anti-hypertensive and lipid-lowering drugs in this group.

This study demonstrated that belatacept was not inferior to cyclosporine, and even suggested that belatacept could preserve GFR and reduce the incidence of chronic allograft nephropathy.

In order to evaluate the long-term efficacy and safety of belatacept, 102 patients treated with belatacept (90%) and 26 treated with cyclosporine (51%) from the previous study completed 60 months of treatment. The percentages of participation show good acceptance of belatacept. Renal function remained stable throughout the study in patients treated with belatacept, with an eGFR (MDRD) of 75.8±20.1ml/min/1.73m$^2$ 12 months after the transplant, and 77.2±22.7ml/min/1.73m$^2$ after 5 years. In contrast, eGFR decreased in the group treated with cyclosporine.
As regards cardiovascular risk factors, there was a slight increase in systolic and diastolic blood pressure between months 24 and 60 in patients treated with cyclosporine, with final values of 138±18.9mm Hg and 76±10.1mm Hg, respectively, compared to 125±13.9mm Hg and 76±10.1mm Hg with belatacept (note: no P-values are available, data extracted from Table 1 in Vincenti, 2010). The levels of non-HDL cholesterol decreased in both groups, although the use of lipid-lowering drugs was lower in patients treated with belatacept. When the study period was extended to a long-term period, the frequency of new-onset diabetes after transplantation (NODAT) was similar in the two groups.

The incidence rates of death/graft loss and acute rejection were low. The incidence of severe infections was 16% with belatacept and 27% with cyclosporine. Neoplasia occurred in 12% of patients in both groups, with only one case of post-transplant lymphoproliferative disorder (PTLD) in the cyclosporine group and none in the belatacept group. Coronary disease was more common in the cyclosporine group (12% vs 2% with belatacept).

The study demonstrated good compliance with treatment, stable renal function, a high level of safety, and predictable pharmacokinetics with belatacept during a 5-year follow-up period. No new cases of PTLD occurred with belatacept. In an open, randomised, controlled phase II trial, kidney transplant recipients were treated with belatacept/MMF (n=33), belatacept/sirolimus (n=26), or tacrolimus/MMF (n=30) for 12 months. The incidence of acute rejection after 6 months was 12% with belatacept/MMF, 4% with belatacept/sirolimus, and 3% with tacrolimus/MMF. Renal function was better with the two different belatacept regimens, with a mean eGFR (MDRD) that was 8.10ml/min/1.73m² higher than in the tacrolimus/MMF group. There were no significant differences in terms of safety, including cardiovascular risk profile.

This same study demonstrated a potent inhibitory activity in the combination of belatacept/sirolimus, which can be as effective as a calcineurin inhibitor (CNI) in halting the antigen-specific and T-cell response. In the first year of the study, the percentage of regulatory T cells (Treg) in the memory T-cell compartment was significantly higher in patients treated with belatacept/sirolimus. The combination of depleted T cells, costimulatory blockade, and mTOR inhibition appears to be effective in preserving Treg and inhibiting immune responses.

Another open and randomised phase II trial compared the replacement of a CNI (cyclosporine or tacrolimus) with belatacept against continuing treatment with the CNI in 175 patients that had received a kidney transplant 6-36 months ago and had stable graft function. After 12 months, 6 patients that had converted to belatacept had developed acute rejection, but no graft losses occurred. Graft survival was 100% in the group treated with belatacept and 99% in the group treated with a CNI. Belatacept produced a mean increase in eGFR (MDRD) of 7.0±11.99ml/min/1.73m², whereas the mean increase with a CNI was 2.1±10.34ml/min/1.73m² (P=0.0058). The switch from a CNI to belatacept improved renal function and was associated with a low rate of acute rejection.

In order to evaluate whether the benefits of belatacept were maintained over long periods, the follow-up protocol was expanded to 2 years in 162 patients from the previous study. Mean eGFR was higher with belatacept (62.0ml/min/1.73m²) than with CNI (55.4ml/min/1.73m²). The mean change in eGFR from the start of the study was much higher with belatacept (8.8ml/min/1.73m²) than with calcineurin inhibitors (0.3ml/min/1.73m²). The benefit of belatacept on renal function was observed in patients previously treated with cyclosporine (7.8ml/min/1.73m²) or tacrolimus (8.9ml/min/1.73m²), and it was independent of renal function at the start of the study. There were also differences in the incidence of acute rejection; rejection occurred in 4.9% of the cases treated with belatacept, and only during the first year, whereas the rate was 3.7% with CNI, all cases occurring in the second year. The safety profile was similar for all groups, and no cases of PTLD were observed.

### Phase III trials

In the international BENEFIT study (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial), MI and LI regimens of belatacept were compared to cyclosporine (Table 1) as maintenance immunosuppression therapy in 666 kidney recipients. The primary evaluation criteria were patient and transplant survival, along with a composite endpoint involving renal deterioration and incidence of acute rejection. After 12 months, patient/grant survival was similar in the three treatment groups (95%, 97%, and 93%, respectively). However, renal function was significantly better with both belatacept regimens. The composite endpoint of renal deterioration was reached in 55% of MI belatacept patients and 54% of LI belatacept patients, as compared to 78% of patients with cyclosporine (P≤.001 for MI or LI vs cyclosporine). Mean eGFR was 65ml/min/1.73m² and 63ml/min/1.73m² for MI and LI belatacept, respectively, whereas it was 50ml/min/1.73m² for cyclosporine (P≤.001 for MI or LI vs cyclosporine). EGFR was calculated using the MDRD equation. Acute rejections were more common with belatacept (22% MI and 17% LI) than with cyclosporine (7%). Safety was similar with both drugs, although more cases of PTLD occurred with belatacept.
In the phase III BENEFIT-EXT study (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial-EXTended criteria donors), 543 kidney transplant recipients were evaluated that had received kidneys from expanded criteria donors. The primary evaluation criteria were the same as in the BENEFIT study.

There were no significant differences in patient/graft survival: 71% with MI, 77% with LI, and 85% with cyclosporine ($P = .002$ for MI vs cyclosporine and $P = .06$ for LI vs cyclosporine). Renal function was significantly better with belatacept, with an eGFR that was 4-7 ml/min/1.73 m$^2$ higher ($P = .008$ for MI vs cyclosporine and $P = .1309$ for LI vs cyclosporine). Cardiovascular and metabolic profiles were better with belatacept. The incidence of acute rejection was similar between groups (18% for MI and LI and 14% for cyclosporine).

The combined data analysis from the BENEFIT and BENEFIT-EXT studies after 2 years of treatment included 840 patients. The proportion of surviving patients with a functioning graft was similar between all treatment groups. Belatacept continued to provide superior results to cyclosporine in terms of renal function, with an eGFR that was a mean 16-17 ml/min/1.73 m$^2$ higher in the BENEFIT study and 8-10 ml/min/1.73 m$^2$ higher in the BENEFIT-EXT study as compared to cyclosporine. Very few episodes of acute rejection occurred in the second year of the trials. Cardiovascular and metabolic profiles were better with belatacept than with cyclosporine. The incidence of PTLD is greater in patients with negative serology tests for Epstein-Barr virus (EBV-), and so the efficacy of this drug was specifically analysed in EBV+ patients, with coinciding results with those from the overall study population. No new adverse effects were observed. The authors concluded that the LI regimen of belatacept was preferable to the MI regimen, since it provided a better balance between efficacy and safety.

The 3-year results from both trials showed that belatacept maintains its effects on a long-term basis, with high patient and graft survival rates, even in recipients of kidneys from expanded criteria donors.

In the BENEFIT study, renal function was better with belatacept than with cyclosporine from the third month until the end of the three-year study. Treatment with belatacept was associated with a greater probability of improved renal function. In the combined analysis of renal function results from the BENEFIT and BENEFIT-EXT studies, belatacept was superior (Figure 4 and Figure 5). Change in mean eGFR (ml/min/year) between months 3 and 36 was 1.0 (MI belatacept), 1.2 (LI belatacept), and -2.0 (cyclosporine) in the BENEFIT study, and -0.9, -0.6, and -1.9, respectively, for the BENEFIT-EXT study. Advanced chronic renal failure (eGFR<30ml/min) was more common in patients treated with cyclosporine in both studies: 20% in the BENEFIT study and 44% in the BENEFIT-EXT study as compared to MI or LI belatacept: 9% and 10% in the BENEFIT study and 27% and 30% in the BENEFIT-EXT study. In another analysis, renal function results were compared by donor type (deceased or living donor), with no significant differences observed in GFR improvement amongst patients treated with belatacept.

### Safety of belatacept

Clinical studies have demonstrated good tolerance with belatacept. The safety profile of belatacept was evaluated in an analysis of the pooled data from the three key belatacept studies in kidney recipients. The data for 1425 patients were analysed, with a mean follow-up time of 2.4 years. With LI belatacept, the death rate (5%) was lower than with cyclosporine or MI belatacept (7% each), which also occurred with the rate of neoplasia (32% vs 36% and 37%).

---

**Table 2. Treatments in the BENEFIT study**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI belatacept</td>
<td>0-3 months: 10mg/kg on days 1 and 5 and weeks 2, 4, 6, 8, 10, 12</td>
</tr>
<tr>
<td></td>
<td>4-6 months: 10mg/kg on weeks 16, 20, 24</td>
</tr>
<tr>
<td></td>
<td>7-12 months: 5mg/kg every 4 weeks</td>
</tr>
<tr>
<td>LI belatacept</td>
<td>0-1 month: 10mg/kg days 1 and 5 and weeks 2, 4</td>
</tr>
<tr>
<td></td>
<td>2-3 months: 10mg/kg weeks 8, 12</td>
</tr>
<tr>
<td></td>
<td>3-12 months: 5mg/kg every 4 weeks</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Initial dose: 4-10mg/kg</td>
</tr>
<tr>
<td></td>
<td>0-1 month: adjust dosage to achieve a concentration of 150-300ng/ml</td>
</tr>
<tr>
<td></td>
<td>2-12 months: adjust dosage to achieve a concentration of 100-250ng/ml</td>
</tr>
</tbody>
</table>

LI: least intensive treatment; MI: most intensive treatment. (Source: reference No. 47.)
respectively). The rate of infection was similar between patients treated with belatacept and with cyclosporine. One case of progressive multifocal leukoencephalopathy was observed in a patient treated with belatacept at higher doses than recommended, and who was also receiving IL-2 receptor antagonists, MMF, and steroids. The tolerance to the infusion was good, which facilitated compliance with the treatment protocol, and no cases of anaphylaxis or hypersensitivity were reported. According to the results from this analysis, the LI regimen is preferable to the MI, since it provides a better safety profile that MI and the same efficacy.

The safety profile analysis for belatacept after 3 years of treatment in the BENEFIT and BENEFIT-EXT studies included the data from 1209 patients. LI belatacept was associated with fewer deaths and cases of severe infection than MI belatacept and cyclosporine (Table 3). The risk of PTLD with belatacept (1% for each treatment schedule) was within the expected incidence rate following a kidney transplant, and decreased after 18 months.

Cases of PTLD have arisen in phase II and III trials. There were 16 cases of PTLD: 8 under the MI regimen (2%), 6 under the LI regimen (1%), and 2 with cyclosporine (0.4%). 9 cases having central nervous system (CNS) problems among those treated with belatacept (6 with MI and 3 with LI). The risk for developing this condition was greater in the first 18 months of treatment, in patients on the MI belatacept regimen and in those with EBV- serology at the time of transplant. In a later analysis of biopsies by a central pathologist, two of the cases described as graft PTLD, both in LI patients, were later diagnosed as acute rejection in one case and non-specific T-cell proliferation in the other.

Calcineurin inhibitors increase the risk of infection by cytomegalovirus (CMV) by inhibiting specific memory T cells. Results from in vitro studies and seropositive volunteers for CMV suggest that belatacept protects against transplant rejection, but does not alter the response of CMV-specific memory T cells. As a result, belatacept does not increase the risk of infection by CMV, which is known to be a risk factor for developing PTLD when coexisting with an EBV infection.

The cardiovascular risk profile for belatacept could be more favourable than currently used immunosuppressants. In the BENEFIT and BENEFIT-EXT trials, belatacept was superior to cyclosporine in the parameters evaluated. Mean systolic blood pressure was 6-9mm Hg lower, and mean diastolic blood pressure was 3-4mm Hg lower in patients treated with belatacept than in those treated with cyclosporine (P≤.002).

Non-HDL cholesterol levels were lower with belatacept (P<.01 with MI or LI belatacept compared to cyclosporine in both studies), and a similar trend occurred in serum triglycerides (P<.02 with MI or LI belatacept compared to cyclosporine in both studies).

In prespecified pooled analysis, NODAT was significantly less frequent with MI or LI belatacept (5%) than with cyclosporine (10%) (P<.05 for MI or LI belatacept compared to cyclosporine). The results from the BENEFIT and BENEFIT-EXT trials showed that belatacept provides a better cardiovascular and metabolic profile than cyclosporin.

In one of the phase II trials, blood samples were taken at least every 12 months before the belatacept infusion. The samples were analysed in a sensitive electrochemiluminescence immunoassay that was validated for the detection of anti-belatacept antibodies directed against the whole molecule or the modified CTLA-4 portion of belatacept. This type of antibody was detected in six patients treated with the 4-week treatment regimen and in ten
patients treated with the 8-week regimen, although only two of the patients in the first group and six in the second still had positive test results on the last follow-up check. Two of the patients from the 8-week group developed neutralising antibodies, but none continued treatment. None of the patients with anti-belatacept antibodies had graft loss or acute graft rejection, and none died or suffered severe adverse autoimmune side effects or conditions related to the infusion.41

In contrast to other immunosuppressants used as the background treatment in organ transplantation, belatacept does not require monitoring of drug levels in the body, since it does not have a narrow therapeutic range.

The risk of interaction with other drugs is very low, since, in contrast with other immunosuppressants used in transplants, belatacept is a fusion protein that is not metabolised by cytochrome P450 enzymes (CYP) or UDP-glucuronosyltransferase.40

**COMMENTS**

Belatacept is the first drug in a new class of immunosuppressants. The data from clinical trials comparing belatacept to cyclosporine suggest that they have similar efficacy, but belatacept preserves renal graft structure and function, and is associated with lower rates of chronic allograft nephropathy. In long-term treatment regimens, renal function remained stable, which contrasts with the annual decrease of 1-3 ml/min/m² that is usually observed with calcineurin inhibitors at stable doses, and is consistent with 1st year results.61,62 The recommended initial dose is 10 mg/kg on days 1 (before the intervention), 5, 14, and 28, and after weeks 8 and 12 following the transplantation. In the maintenance phase, the recommended dose is 5 mg/kg every 4 weeks (±3 days), starting at the end of the 16th week following the transplant.63

Belatacept offers a more favourable cardiovascular and metabolic profile than calcineurin inhibitors. According to the results from a systematic review of randomised and controlled studies, patients treated with belatacept had a 69% lower probability of death, compared to those treated with tacrolimus.64 Cardiovascular disease is the most common cause of death in patients with kidney transplants and functioning grafts. In clinical trials such as BENEFIT and BENEFIT-EXT, the incidence of NODAT with belatacept has been lower than in patients treated with calcineurin inhibitors, and belatacept has demonstrated a better cardiovascular and metabolic profile than currently used immunosuppressants. In summary, belatacept can provide a better cardiovascular and metabolic profile than current immunosuppressants.

Kidney transplants from expanded criteria donors are becoming more and more frequent due to the increased demand for organs. However, the risk of graft loss or dysfunction is higher in these donors, who tend to be older and have associated morbidity. Graft survival after one year is lower than in normal organ donors, and survival in later years is even lower, mainly due to chronic allograft nephropathy.62,63 The BENEFIT-EXT study demonstrated that belatacept is effective in recipients of kidneys from expanded criteria donors, and its use in this context could prevent nephrotoxicity associated with calcineurin inhibitors.41

In clinical trials, the primary risk of treatment with belatacept has been PTLD, especially in the first 18 months of treatment. A relationship has been suggested between the intensity of immunosuppression and PTLD, since patients treated with MI belatacept suffered from CNS-related events more frequently and had a higher risk of CNS infections. It was proposed that the risk of PTLD could be reduced by administering the LI regimen of belatacept and avoiding treatment in EBV-infected patients or those with unknown serology,65 since the primary risk factor is an EBV-serology but CMV infection and T-cell depletion therapy also increases the risk. Currently, the technical data sheet for belatacept states that it is contraindicated in patients with EBV- or unknown serology.64

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**Table 3. Safety profile in the BENEFIT and BENEFIT-EXT studies**

<table>
<thead>
<tr>
<th></th>
<th>Li belatacept (n=401)</th>
<th>MI belatacept (n=403)</th>
<th>Cyclosporine (n=405)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>25 (6%)</td>
<td>31 (8%)</td>
<td>32 (8)</td>
</tr>
<tr>
<td>Severe adverse effects</td>
<td>270 (67%)</td>
<td>282 (70%)</td>
<td>296 (73%)</td>
</tr>
<tr>
<td>Severe infections</td>
<td>144 (36%)</td>
<td>151 (38%)</td>
<td>157 (39%)</td>
</tr>
<tr>
<td>Neoplasia (overall)</td>
<td>19 (5%)</td>
<td>16 (4%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Post-transplant lymphoproliferative disorder</td>
<td>6 (1%)</td>
<td>5 (1%)</td>
<td>1 (&lt; 1%)</td>
</tr>
</tbody>
</table>

LI: least intensive treatment; MI: most intensive treatment. (Source: reference No. 56).
Since CNS involvement in PTLD is more common with belatacept than cyclosporine, we must keep this possibility in mind when treating kidney recipients with belatacept who develop neurological, cognitive, or behavioural symptoms.64

The use of belatacept as the background therapy in kidney recipients preserves renal function and is associated with a lower incidence of cardiovascular risk factors and NODAT. The inclusion of belatacept in immunosuppression protocols for kidney transplants could facilitate a major improvement in patient and graft survival.

Acknowledgements

The authors would like to thank Content Ed Net Communications for their editorial assistance.

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Infliximab in the treatment of amyloidosis secondary to Crohn’s disease

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Nefrologia 2012;32(3):385-8

ABSTRACT

Secondary amyloidosis (AA) is a severe complication of progressed Crohn’s disease (CD) for which no effective treatment exists. We present the exceptional case of a 33-year-old male with moderate renal failure and proteinuria, who was simultaneously diagnosed with AA amyloid nephropathy and oligosymptomatic CD. He was treated with infliximab at 5mg/kg/8 weeks for 4 years, azathioprine at 1-1.5mg/kg/day (first year) and renin-angiotensin-aldosterone system blockers, with no complications. Treatment caused a decrease in proteinuria, improved renal function, and improved inflammatory parameters over time. Inspired by this case, we performed a review of the medical literature and found that infliximab could be a useful tool in the early treatment of amyloidosis secondary to CD.

Keywords: Infliximab. Secondary amyloidosis. Crohn’s disease.

INTRODUCTION

Secondary amyloidosis or AA is a rare but severe complication associated with Crohn’s disease (CD). The deposition of amyloid material in AA amyloidosis mainly affects the kidneys and the major clinical manifestations are proteinuria and renal failure. The progression of chronic kidney disease associated with amyloidosis secondary to CD in the absence of an effective treatment leads to high morbidity and mortality rates.1-3

However, anti-tumour necrosis factor-alpha (anti-TNFα) agents, infliximab in particular, have been successfully used in recent years to treat AA amyloidosis in some inflammatory rheumatic diseases4 and also in some cases of CD.5-8

We present the case of a patient simultaneously diagnosed with oligosymptomatic CD and AA renal amyloidosis, successfully treated with infliximab over 4 years with a good response and absence of complications.

CASE REPORT

A 33-year-old male was referred to the nephrology unit in late 2006 due to elevated serum creatinine (SCr) levels,
1.4mg/dl. He had no history or clinical manifestations of urological or kidney disease. Five years previously, his SCr had been measured at 0.9mg/dl.

At 18-years-old, he was diagnosed with iron-deficiency anaemia and gastro-oesophageal reflux. In the past 4 years he reported suffering from dysphagia and postprandial heaviness, without any other gastrointestinal manifestations; and mechanical back pain. He had no febrile episodes, joint inflammation, skin lesions, serositis, or problems with any other body organs or systems.

He had a family history of ankylosing spondylitis in several males on his father’s side; a paternal uncle was also diagnosed with stage 5 chronic kidney disease secondary to nephropathy caused by analgesic use.

Normal physical examination, blood pressure: 130/79mm Hg, body mass index: 21kg/m².

Diagnostic tests


Urine test: proteinuria: 200mg/24h; albuminuria: 47mg/24h, with no monoclonal free light chains. Normal urine sediment.

Chest and spine x-rays showed no significant alterations. Ultrasound scans of the abdomen, kidneys and urinary passages: normal. Analysis by the rheumatology department ruled out ankylosing spondylitis.

Repeat tests after two months showed: SCr: 1.64mg/dl; eGFR (MDRD-4): 52ml/min/1.73m²; proteinuria: 316mg/24h; albuminuria: 163mg/24h. And 4 months later: SCr: 1.77mg/dl; eGFR (MDRD-4): 47ml/min/1.73m²; proteinuria: 640mg/24h. The iron, vitamin B12 and folic acid deficiencies were partially corrected with oral supplements.

In light of the persistent gastrointestinal symptoms (dysphagia, dyspepsia) and suspected intestinal malabsorption (iron and vitamin deficiency), we decided to perform an endoscopy of the digestive tract and take biopsies. The main alterations found in the mucosa of the terminal ileum were compatible with CD: ulcerated villi, lymphoplasmacytic inflammation in the lamina propria, neutrophil infiltration (crypt abscesses) and epithelioid histiocyte granulomas. A deposit of material with staining characteristics (Congo red and immunohistochemical) of AA amyloidosis, and no signs of inflammation, was found in the rectal mucosa, in the blood vessel walls of the lamina propria.

A percutaneous renal biopsy was also performed in light of the unfavourable progression of the renal parameters (renal function and proteinuria), which showed: 7 glomeruli, 3 with virtually global glomerulosclerosis and the remaining 4 with small eosinophilic deposits in the hilum of the glomerulus; patchy areas of interstitial fibrosis; and eosinophilic deposits in the walls of the blood vessels that were larger and more intense than the glomerular ones. The deposits tested positive for Congo red with green birefringence under polarised light and immunohistochemical staining detected the presence of amyloid A protein.

In the subsequent evolution of this case, the patient had no symptoms or clinical signs suggestive of any other type of inflammatory, infectious or tumour disease, or familial Mediterranean fever.

With the diagnosis of CD and secondary AA amyloidosis, it was decided to pursue aetiological treatment of the CD based on intravenous infliximab at 5mg/kg every 2 months, azathioprine at 1-1.5mg/kg/day (for the first year only, suspended due to leucopenia) and renin-angiotensin-aldosterone system blockers. The renal parameters improved (Figure 1), as did the inflammatory markers (CRP: 5mg/l, and serum amyloid A protein <5mg/l), and are maintained after 4 years of monitoring. There have been no major complications of the CD or side effects from the medication.

DISCUSSION

Between 0.9% and 3% of patients with CD develop secondary amyloidosis, a rate that is 2.5-3 times higher in men. The average time from the diagnosis of CD to the appearance of amyloidosis is 10-15 years in exceptional cases, the diagnosis of both clinical entities occurs simultaneously and it has even been suggested that amyloidosis can precede CD in rare cases. In our patient, both entities were diagnosed at the same time, although minor and non-specific digestive manifestations had been present for several years. In the two longest studies published to date, two thirds of people with...
amyloidosis secondary to CD had previous suppurative complications (fistulas or abscesses), and half or more had extraintestinal manifestations; from which we can deduce that AA amyloidosis in CD can also develop in the absence of chronic infections or extraintestinal complications, as in our case. In line with the foregoing, it would appear that AA amyloid nephropathy can first appear as an early complication in CD and not necessarily be associated with a clinically manifest, extensive and aggressive disease.

The main objectives of secondary renal amyloidosis treatment are to induce and maintain the remission of the primary disease, prevent renal deposition of amyloid A proteins, and stop or reverse the progression of chronic kidney disease. The effect of intestinal resection to prevent or treat renal amyloidosis in DC is controversial, and the majority of authors advocate drug treatment as the treatment of choice. Drugs like colchicine, azathioprine and dimethyl sulfoxide can slow down the progression of amyloid nephropathy, but their effectiveness has not been fully demonstrated. Eprodisate, the first drug in a new class of compounds, inhibits amyloid protein polymerisation and deposition in tissues and slows down the decline in the glomerular filtration rate in AA amyloidosis patients, but it has little effect on proteinuria and survival.

In recent years, the anti-TNFα agent infliximab has been used successfully to treat isolated cases of renal amyloidosis secondary to CD. We conducted a PubMed search with the words “systemic or secondary amyloidosis, Crohn’s disease, infliximab” and selected those cases published in English not associated with other rheumatic inflammatory or infectious diseases or with familial Mediterranean fever. The main clinical characteristics of the four cases found in addition to our own are summarised in Table 1. In all these cases, treatment with infliximab was started soon after the diagnosis with amyloidosis and was followed by rapid and maintained clinical improvement of the intestinal disease and the laboratory inflammatory parameters, a rapid decrease in proteinuria and improved renal function with no complications associated with the medication. One of these studies showed a decrease in the amyloid deposits in the intestinal mucosa after 5 years of treatment with infliximab.

The most common adverse effects relating to ongoing infliximab use in patients with amyloidosis and rheumatic diseases are an increased susceptibility to infections and the drug’s loss of effectiveness. In cases of resistance or loss of effectiveness or adverse effects in patients with CD, another anti-TNFα, adalimumab, can be used as an alternative.

It has been hypothesised that anti-TNFα agents can improve amyloid nephropathy in inflammatory diseases through two mechanisms: 1) by reducing the glomerular inflammation and the increase in the glomerular permeability to albumin induced by TNFα cytokines and interleukin-6; and 2) by reducing the synthesis of acute-phase proteins mediated by the same cytokines. Indeed, it has been demonstrated that the serum amyloid A protein level reached is a prognostic factor in AA amyloidosis; mean levels below 10mg/l are associated with a higher likelihood of regression of the amyloid deposits and higher survival rates.

To conclude, AA renal amyloidosis can first appear as an early complication in patients with CD, even in those patients with a disease that presents mild clinical symptoms. It would appear appropriate to recommend renal function and urinary protein excretion tests for patients diagnosed with CD at the time of diagnosis and at regular intervals thereafter with a view to diagnosing and, where applicable, starting early treatment on any associated kidney disease. Infliximab could be a useful and effective tool in the early treatment of amyloidosis secondary to CD and provides encouraging prospects.

**Conflicts of interest**

The authors affirm that they have no conflicts of interest related to the content of this article.
Table 1. Evolution of the renal parameters of 5 patients with AA amyloidosis and Crohn’s disease treated with infliximab

<table>
<thead>
<tr>
<th>Autor (reference)</th>
<th>Sex/age</th>
<th>Organ affected by amyloidosis</th>
<th>CD and Amyloidosis latency (years)</th>
<th>Treatment (duration)</th>
<th>Clinical evolution and inflammatory parameters</th>
<th>UPE (gr/24h) Before Trmt.</th>
<th>UPE (gr/24h) After Trmt.</th>
<th>S Creatinine (mg/dl) Before Trmt.</th>
<th>S Creatinine (mg/dl) After Trmt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boscá M (6)</td>
<td>M/26</td>
<td>Rectum</td>
<td>11</td>
<td>Azathioprine (4y)+ Colchicine (5y)+ Infliximab (5y)</td>
<td>Improvement</td>
<td>8-20</td>
<td>4 (1.º y) 0.85 (4.º y)</td>
<td>1.7</td>
<td>Not stated</td>
</tr>
<tr>
<td>Lizuka M (7)</td>
<td>M/34</td>
<td>Kidney Gastro-I</td>
<td>14</td>
<td>Infliximab 5mg/kg 1 dose (46 days)</td>
<td>Improvement</td>
<td>Not reported</td>
<td>Not reported</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Park YK (8)</td>
<td>M/34</td>
<td>Kidney Gastro-I</td>
<td>11</td>
<td>Infliximab 5mg/kg 3 doses (8wk)</td>
<td>Improvement</td>
<td>7.3</td>
<td>2.7</td>
<td>2.2</td>
<td>2</td>
</tr>
<tr>
<td>Lizuka M (9)</td>
<td>M/35</td>
<td>Kidney Gastro-I</td>
<td>13</td>
<td>Infliximab 5mg/kg/8wk (1y)</td>
<td>Improvement</td>
<td>2</td>
<td>0.24</td>
<td>1.88</td>
<td>1.1</td>
</tr>
<tr>
<td>This case</td>
<td>M/33</td>
<td>Kidney Gastro-I</td>
<td>0</td>
<td>Azathioprine (1 a)+ Infliximab 5mg/kg/8wk (4y)</td>
<td>Improvement</td>
<td>0.6</td>
<td>0.08</td>
<td>1.7</td>
<td>1.5</td>
</tr>
</tbody>
</table>


REFERENCES


Sent to review: 8 Jan. 2012 | Accepted: 19 Feb. 2012
Analysis of concordance between the bioelectrical impedance vector analysis and the bioelectrical impedance spectroscopy in haemodialysis patients

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Nefrología 2012;32(3):389-95

ABSTRACT

Introduction: The values of body composition provided by the two most commonly used bioelectrical impedance systems in Spain, single-frequency bioelectrical impedance vector analysis (SF-BIVA) and multi-frequency bioelectrical impedance spectroscopy (MF-BIS) are different and not comparable. Objective: Analyse whether the inter-method variability is due to bioelectrical variables measured by the different monitors, or rather due to the equations used to calculate body volume and mass. Another objective was to determine whether, despite the inter-method variability, the classification of hydration status by the two methods is consistent. Material and Methods: Bioelectrical impedance was measured by SF-BIVA and MF-BIS immediately before a dialysis session in 54 patients on haemodialysis. In 38 patients, the study was repeated by SF-BIVA at the end of the same dialysis session. Results: Resistance and phase angle values provided by the two monitors at a frequency of 50kHz were consistent. For resistance, variability was 1.3% and the intra-class correlation coefficient was 0.99. For phase angle, variability and the intra-class correlation coefficient were 11.5% and 0.92, respectively. The volume values for total body water, extracellular water, fat mass and body cell mass were biased, with a level of variability that would not be acceptable in clinical practice. The intra-class correlation coefficient also suggested a poor level of agreement. SF-BIVA systems define overhydration or dehydration as a vector below or above the tolerance ellipse of 75% on the longitudinal axis. MF-BIS uses two criteria for pre-dialysis hyper-hydration: overhydration (OH) greater than 2.5 litres, or greater than 15% of extracellular water. The degree of equivalence with the results of the SF-BIVA monitor was better with the second criterion (kappa: 0.81, excellent agreement) than with the first one (kappa: 0.71, acceptable agreement). The MF-BIS system defines post-dialysis normal hydration as a difference between OH and ultrafiltration volume between –1.1 and 1.1 litres and agreement with the SF-BIVA system for this parameter was acceptable (weighted kappa index: 0.64). Conclusions: The MF-BIS and SF-BIVA systems provide similar readings for bioelectrical parameters, and the wide variation in the quantification of volume and body mass must be attributed to the different equations used for calculation. Furthermore, the criteria used by both systems to define both pre- and post-dialysis hydration have an acceptable level of equivalence.

Keywords: Bioimpedance vector analysis. Multifrequency bioimpedance spectroscopy. Haemodialysis.

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INTRODUCTION

Bioelectrical impedance analysis allows us to quantify the different human body compartments and provides useful information for evaluating nutrition and hydration status. Simple, easy to use monitors with an accessible price range have led to the current widespread use of this technology in nephrology departments. This is evidenced by the large number of reports regarding bioelectrical impedance that were presented at the last three national conferences in this medical specialty.

Bioelectrical impedance monitors obtain electrical parameters from the human body (resistance, reactance, and phase angle), and calculate body mass and volume using predictive equations that take into account electrical data and other variables, such as weight, height, age, and sex. These equations vary between the different types of monitors. The majority only takes into account resistance, and on many occasions they are difficult to learn.1-6

Multi-frequency bioelectrical impedance spectroscopy (MF-BIS) and single-frequency bioelectrical impedance vector analysis (SF-BIVA) are the two most commonly used bioelectrical impedance systems in Spain.7,8 Comparative studies reported that the two systems provide different results for the body compartments and methods are not interchangeable due to the high inter-method variability.6,8-12

The aim of our study was to determine whether inter-method variability is due to differences in the way monitors read bioelectrical variables, or due to the equations used by each system to calculate body mass and volume. Another objective was to test whether, despite the inter-method variability, the classification of a patient’s hydration status was consistent across the two different systems. This study was performed in patients with stage 5 chronic kidney disease being treated with haemodialysis.

MATERIAL AND METHODS

Ours was a cross-sectional study of 54 patients on periodic haemodialysis who underwent bioelectrical impedance analysis using both MF-BIS and SF-BIVA. The mean patient age was 69±14 years (range: 34-92 years); 36 patients were male and 18 were female. All patients were clinically stable, with no signs or symptoms of heart failure. Mean body mass index was 26.5±3.9 (range: 18.3-38.3; confidence interval: 25.5-27.6). The bioelectrical impedance analysis was performed before the haemodialysis session, with the patient lying in a supine position, placing electrodes at the wrist and ankle of the side of the body free from vascular accesses, following standard protocol. We first took measurements with the SF-BIVA monitor, which used a 50kHz frequency (ElectroFluidGraph [EFG] analyser, Akern SRL, Florence, Italy), and then with the MF-BIS device (BCM monitor, Fresenius Medical Care, Bad Homburg, Germany), which took readings at 50 frequencies with a range of 5kHz-1000kHz. In 38 patients, we repeated the bioelectrical impedance analysis using SF-BIVA after completing the haemodialysis treatment. We used the same electrodes, which were left in place throughout the session.

The SF-BIVA monitor provides values for resistance, reactance, and phase angle at a 50kHz frequency. The MF-BIS monitor provides values for resistance and phase angle for each frequency used. In order to compare the
bioelectrical data from the two monitors, we used the results from phase angle and resistance produced by the MF-BIS system at 50kHz. In order to analyse hydration status, we assigned a score (ordinal scale) from 1 to 7 to the results produced by the SF-BIV A monitor (from -3 to +3) along the major axis of the three tolerance ellipses (95%, 75%, and 50%) from the lower pole of greater hydration to the upper pole of less hydration, as proposed by Piccoli.1 With the MF-BIS monitor, hydration status was determined using the pre-dialysis hyper-hydration value (overhydration: OH) provided by the monitor. Post-dialysis OH was calculated by subtracting the ultrafiltration volume from the OH value (post-HD OH).

Hydration status was defined using the following criteria. With the MF-BIS monitor, we used two criteria to define pre-dialysis overhydration: an OH volume greater than 15% the extracellular water volume (ECW)13 and a total OH volume greater than 2.5 litres.14 Post-dialysis hydration status was considered normal when post-HD OH was between -1.1 litres and 1.1 litres; overhydration: OH>1.1 litres, and dehydration: OH<-1.1 litres.15 When using the SF-BIV A monitor, hydration was considered normal when the impedance vector on the hydration axis was within the 75% tolerance ellipse in pre- and post-dialysis measurements.16 Under this criteria, we defined pre-dialysis overhydration as an impedance vector in the pre-dialysis measurement below the 75% tolerance ellipse (on the ordinal hydration scale, this corresponds to values +3 and +2). In the post-dialysis assessment, the same criteria were used to define overhydration; normal hydration in the post-dialysis period was defined as a post-dialysis impedance vector within the 75% tolerance ellipse (values +1, 0, and -1 on the ordinal scale) and dehydration was defined as a post-dialysis impedance vector above the 75% tolerance ellipse (corresponding to values -2 and -3 on the ordinal scale).17

For our statistical analysis, we presented results in terms of mean ± standard deviation. Our data had a normal distribution (Kolmogorov-Smirnov test), and so we only used parametric tests. The difference between SF-BIV A and MF-BIS values for each parameter was defined as the bias between the two systems. This same difference in absolute values expressed as a percentage of the arithmetic mean for both values (relative difference) allowed us to examine the variability between the two measurement methods. The correlation between the two different methods was measured using Pearson’s coefficients. For quantitative variables, we performed an intra-class correlation analysis,18 which varied between 0 (no agreement) and 1 (total agreement). For binary and ordinal variables, we used kappa index and weighted kappa index tests.19 For the kappa index, a level of agreement >0.40 was considered acceptable, and excellent at values >0.75. We compared means using Student’s t-tests and ANOVA, as necessary. A P-value <.05 was considered statistically significant.

RESULTS

Table 1 shows resistance and phase angle values produced by SF-BIV A and MF-BIS monitors at a frequency of 50kHz, and the body composition values obtained using the two methods. The values for resistance have a minimal variability, and the intra-class correlation coefficient suggests that the inter-method agreement is almost absolute. However, the values for phase angle were statistically different. Even so, the level of variability is acceptable from a clinical standpoint (11.5%), and the intra-class correlation coefficient of 0.92 indicates excellent inter-method agreement.

Of the different body composition variables measured by the two systems, only intracellular water volume (ICW) had an acceptable level of variability between the values for the two different types of monitors (13%); in all other variables, bias and variability are very high. Although the Pearson’s correlation coefficient suggests that there is a good correlation between the values obtained by the two systems, the intra-class correlation coefficient indicates that the level of agreement is mediocre.

Table 2 displays the MF-BIS parameters associated with hydration status (OH and the OH/ECW ratio) for the 7 different levels of the ordinal scale that measure hydration in the SF-BIV A monitor, showing good correlation between the two different methods.

The classification of patients according to pre- and post-dialysis hydration status is expressed in Table 3 and Table 4. In pre-dialysis patients, the kappa index for diagnosing overhydration was 0.81 if the diagnostic criterion of overhydration with the MF-BIS system was an OH/ECW>0.15 (excellent agreement) and 0.71 if the diagnostic criterion was an OH>2.5 (acceptable agreement). In post-dialysis measurements, the mean weighted kappa index was 0.64 (acceptable agreement).

DISCUSSION

The different manufacturers of bioelectrical impedance monitors assure us that the procedures they use to calculate body mass and volume are validated against reference methods, both in healthy subjects and patients suffering a wide range of pathologies, but the results obtained with the different bioelectrical impedance systems demonstrate a substantial inter-method variability.6,8-12 The aim of our study was to determine whether this inter-method variability was due to different results obtained in the measurement of bioelectrical parameters, or due to the equations used by each system to quantify body compartments.
The measurements of resistance and phase angle provided by SF-BIVA and MF-BIS monitors at a frequency of 50kHz have a high level of agreement. The mean variability for resistance was only 1.3%, similar to the intra-individual variability rate. The intra-class correlation coefficient (0.99) suggests that the agreement between the two systems is virtually absolute. The measurements of phase angle were different from a statistical point of view, but the mean variability (11.5%) could be negligible from a clinical standpoint, and the intra-class correlation coefficient (0.92) indicates a high level of agreement. We can conclude that the two monitor systems make very similar measurements of bioelectrical parameters at a frequency of 50kHz.

The measurements of total body volume, extracellular water, intracellular water, fat mass, and body cell mass, showed high variability and bias. As in other studies performed using these same monitors, we observed that the SF-BIVA system yields higher values than the MF-BIS system for all compartments analysed, except for fat mass. The best correlation between the two systems occurred in ICW (mean bias: 2.2 litres; mean variability: 13%; intra-class correlation coefficient: 0.80), which is acceptable. For all other compartments, the bias and variability were not negligible, and the intra-class correlation coefficient indicates that only a mediocre equivalence exists between the two systems. We can conclude that the two monitor systems make very similar measurements of bioelectrical parameters at a frequency of 50kHz.

Table 1. Resistance and phase angle values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SF-BIVA</th>
<th>MF-BIS</th>
<th>Mean difference (CI)</th>
<th>Relative difference %</th>
<th>Pearson’s coefficient</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance (ohm)</td>
<td>510.1±75.6</td>
<td>515.4±78</td>
<td>-5.3 (-55.3; 25.2)</td>
<td>1.3±1.7</td>
<td>r=0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Phase angle (°)</td>
<td>4.7±0.9</td>
<td>4.2±1</td>
<td>0.5 (0; 1.3)</td>
<td>11.5±6.5</td>
<td>r=0.97</td>
<td>0.92</td>
</tr>
<tr>
<td>TBW (l)</td>
<td>38.7±7.8</td>
<td>32.1±6.3</td>
<td>6.6 (2.6; 17.8)</td>
<td>18.4±6.1</td>
<td>r=0.95</td>
<td>0.65</td>
</tr>
<tr>
<td>ECW (l)</td>
<td>20.3±4.5</td>
<td>16.2±3.3</td>
<td>4.2 (0.3; 10.1)</td>
<td>22.5±9.1</td>
<td>r=0.89</td>
<td>0.55</td>
</tr>
<tr>
<td>ICW (l)</td>
<td>18.1±4.6</td>
<td>15.9±3.4</td>
<td>2.2 (-3.5; 6.2)</td>
<td>13±6.3</td>
<td>r=0.96</td>
<td>0.80</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>22.1±6.2</td>
<td>28.1±8.4</td>
<td>-6 (-19.2; 0.8)</td>
<td>23.6±13</td>
<td>r=0.91</td>
<td>0.65</td>
</tr>
<tr>
<td>BCM (kg)</td>
<td>22.8±6.5</td>
<td>16.1±5.1</td>
<td>6.7 (-2; -18.2)</td>
<td>35.8±13.5</td>
<td>r=0.86</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Table 2. Relationship between hydration status according to the SF-BIVA monitor and overhydration according to the MF-BIS monitor

<table>
<thead>
<tr>
<th>SF-BIVA</th>
<th>MF-BIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH (l)</td>
<td>OH/ECW (%)</td>
</tr>
<tr>
<td>+3 (n=2)</td>
<td>6.5±0.3</td>
</tr>
<tr>
<td>+2 (n=13)</td>
<td>2.9±1.2</td>
</tr>
<tr>
<td>+1 (n=17)</td>
<td>1.7±0.7</td>
</tr>
<tr>
<td>0 (n=15)</td>
<td>1.1±0.9</td>
</tr>
<tr>
<td>-1 (n=4)</td>
<td>0.3±0.3</td>
</tr>
<tr>
<td>-2 (n=2)</td>
<td>-0.7±0.3</td>
</tr>
<tr>
<td>-3 (n=1)</td>
<td>-0.9</td>
</tr>
</tbody>
</table>

ANOVA P<.001 ANOVA P<.001

MF-BIS: multi-frequency bioelectrical impedance spectroscopy; SF-BIVA: single-frequency bioelectrical impedance vector analysis; ECW: extracellular water; OH: overhydration.
The majority of equations that determine body volume and mass only use resistance as the bioelectrical parameter.1,3,5 Since the level of agreement in the readout for resistance at a frequency of 50kHz is virtually absolute, we must assume that the inter-method variability observed is attributable to the different bioelectrical models and equations used by each bioelectrical impedance device.

In addition to quantifying body mass and volume, the different bioelectrical impedance systems utilise certain criteria to classify patients based on hydration status. For pre-dialysis values, the MF-BIS system uses the parameter of OH, expressed in litres,14 or in a percentage of ECW13;and for post-dialysis values, the estimated post-dialysis OH in litres.15 The SF-BIVA system defines pre- and post-dialysis hydration status by applying an ordinal scale to tolerance ellipses.1,17 Upon analysing the equivalence of the two systems for classifying patients according to hydration status, we observed that the level of agreement was good both for defining pre-dialysis overhydration status and post-dialysis normal, over-, and dehydration. Although the results for the different body water compartments obtained from the two systems are not interchangeable, the criteria used to define hydration status had a very high level of correlation in classifying patients.

Phase angle is a bioelectrical parameter associated with nutrition, and has a prognostic value in patients with renal failure.21-24 When evaluating this parameter, we must keep in mind that phase angle varies with hydration status,25,26 and increases following haemodialysis sessions.16,27 Our study suggests that in the pre-dialysis period, the two monitor systems have an acceptable level of agreement, and that phase angle obtained by either device can have the same

| Table 3. Pre-dialysis hydration status. Concordance between the definition criteria used by SF-BIVA and MF-BIS systems |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| MF-BIS overhydration (OH/ECW>15%)              | SF-BIVA overhydration ( +3 and +2 on ord. scale) | SF-BIVA no overhydration (rest of ord. scale) | Total                                               |
| MF-BIS no overhydration (OH/ECW<15%)           | 12                                              | 1                                               | 13                                                |
| Total                                           | 15                                              | 39                                              | 54                                                |
| Kappa index                                     | 0.81                                            |                                                 |                                                   |
| MF-BIS overhydration (OH>2.5l)                  | 11                                              | 2                                               | 13                                                |
| MF-BIS no overhydration (OH<2.5l)              | 4                                               | 37                                              | 41                                                |
| Total                                           | 15                                              | 39                                              | 54                                                |
| Kappa index                                     | 0.71                                            |                                                 |                                                   |

MF-BIS: multi-frequency bioelectrical impedance spectroscopy; SF-BIVA: single-frequency bioelectrical impedance vector analysis; post-HD OH: post-dialysis overhydration.

| Table 4. Post-dialysis hydration status. Concordance between the definition criteria used by SF-BIVA and MF-BIS systems |
|-----------------------------------------------------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| SF-BIVA overhydration (+3 and +2 on ord. scale) | SF-BIVA normal hydration (+1, 0 and -1 on ord. scale) | SF-BIVA dehydration (-2 and -3 on ord. scale) | Total                                               |
| MF-BIS overhydration (post-HD OH>1.1l)              | 2                                               | 2                                               | 0                                               | 4                                                |
| MF-BIS normal hydration (post-HD OH between -1,1l and 1,1l) | 2                                               | 16                                              | 0                                               | 18                                               |
| MF-BIS dehydration (post-HD OH<1.1l)               | 0                                               | 5                                               | 11                                              | 16                                               |
| Total                                               | 4                                               | 23                                              | 11                                              | 38                                               |
| Kappa index                                        | 0.64                                            |                                                 |                                                   |

MF-BIS: multi-frequency bioelectrical impedance spectroscopy; SF-BIVA: single-frequency bioelectrical impedance vector analysis; ECW: extracellular water; OH: overhydration.
significance when analysing patient prognosis or nutrition status.

We conclude that the SF-BIVA and MF-BIS monitor systems produce comparable results for resistance and phase angle at a frequency of 50kHz. The measurement of body compartments does have a high inter-method variability that is probably due to the equations used. However, the different criteria used for defining hydration status by each device are comparable and classify patients quite consistently.

The choice of which bioelectrical impedance system to use in patients on dialysis has caused considerable controversy. With our results, we cannot conclusively say which one is more advisable. If phase angle and ICW are used as nutritional parameters and hydration status is measured following our method, the results from the two different systems are comparable, and in our opinion, both procedures are clinically useful.

Acknowledgements

We would like to thank Andrés Sánchez Iglesias, physics professor, for assistance in comprehending the functioning of bioelectrical impedance analysis.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

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Dear Editor,

We comment on a recent study on haemodialysis using high cut-off dialysers for treating acute renal failure in multiple myeloma, and we send our personal experience.

We read with interest the article of Dr. Martín-Reyes et al. We agree with the motivation of their study: 1. the survival of the patients suffering from Multiple Myeloma (MM) depend on whether or not they recover renal function, not only due to the complications derived from the renal failure itself, but also from the reduced possibility of access to more effective treatments; 2. the importance of rapid reduction of free light chains blood levels in order to facilitate the recovery of renal function. We wish to report our experience in this topic. In April 2011 a 43-year-old man, with a previously normal renal function, was admitted to our hospital for severe acute renal failure (ARF) of an unknown cause. The review of the clinical history didn’t reveal any previous disease. For 2 months he was suffering from lumbar pain. We started haemodialysis treatment three times a week. Laboratory investigations and bone marrow biopsy detected a lambda IgG MM. We performed kidney biopsy and we observed glomerular deposition of lambda chains, without histological signs of chronic renal damage, and a negative Congo red stain test. In 2 weeks the patient received 10 haemodialysis (HD) treatment with high cut-off (HCO) dialyzer (Theralite®, Gambro Henchingen, Germany). We performed on alternating days HCO HD sessions with standard monitors; they lasted for 5 hours, involved a blood flow of 300ml/min and had an ultrapure dialysate flow rate of 500ml/min. Sodium Reviparine (Clivarina®) was applied at 2400IU in single dose priming. The values of Platelets (60.000/mmc) motivated the prescription on the duration of HCO HD and on the dose of heparin. At the end of each session we didn’t administer albumin. Ultrafiltration was programmed according to the clinical need. Before and after each session, mean free light chain levels were measured in terms of mg/l using nephelometry (N latex test, Siemens). Initially λ-FLC concentration was 5500mg/L. At the end of HCO dialyzer HD end of HCO dialyzer HD cycle, the concentration was 94.80mg/L. The concentrations and ratios of light chain levels from the start to the end of treatment are summarised in Table 1.

We didn’t observe any adverse effects. We observed after the first HCO HD a percentage reduction in light chain levels of 74 with dialysis alone before the chemotherapy was initiated. After the third HCO HD the patient started PAD Orlowsky chemotherapy (Bortezomib-Doxorubicin-Dexamethasone) with successful haematological result, but with partial renal function recovery. At this moment (10 months after high cut-off dialyzer treatment) the patient is on maintenance HD two times a week. Some reports show a recovery of renal function after several months. We will continue the mixed therapy (HCO HD-chemotherapy according to the protocols of the haematology department) in patients with ARF and MM.

Conflict of interest
The authors declare that there is no conflict of interest associated with this manuscript.


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Table 1. FLC concentrations and ratios before and after HCO-dialyzer HD

<table>
<thead>
<tr>
<th>n° HD treatment</th>
<th>κ-FLC mg/L (normal value 6.70-2.40)</th>
<th>λ-FLC mg/L (normal value 8.30-27.00)</th>
<th>Ratio κ/λ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1°: Before/After</td>
<td>41.50 / 13.10</td>
<td>5500 / 1090</td>
<td>0.01 / 0.01</td>
</tr>
<tr>
<td>3°: Before/After</td>
<td>24.40 / 8.16</td>
<td>1410 / 301</td>
<td>0.02 / 0.03</td>
</tr>
<tr>
<td>6°: Before/After</td>
<td>28.00 / 8.65</td>
<td>743 / 203</td>
<td>0.04 / 0.04</td>
</tr>
<tr>
<td>10: Before/After</td>
<td>24.50 / 9.17</td>
<td>428 / 94.80</td>
<td>0.06 / 0.10</td>
</tr>
</tbody>
</table>

FLC: free light chain; HCO: high cut-off; HD: haemodialysis.
Progression of chronic kidney disease. 
Prevalence of anxiety and depression in autosomal dominant polycystic kidney disease

Nefrologia 2012;32(3):397-9

To the Editor,

Autosomal dominant polycystic kidney disease (ADPKD) affects the physical condition of the patients and has an impact on mental health.1 Anxiety and depression are the two most commonly associated psychological disorders with chronic kidney diseases (CKD).2

Depression is an affective disorder that is associated with a sense of loss that many patients experience when faced with renal failure, since they lose autonomy, their physical health deteriorates, and watch as their family and occupational roles are altered. Despite being the most common psychological problem among patients with CKD, depression has not been adequately studied in relation to the different stages of the disease.3

Anxiety, the second most commonly associated pathology with CKD, is a warning response produced by the body to situations of danger, threat, or change. However, when anxiety is maintained in the absence of danger, or cannot be coped with, it becomes pathological. This leads to behavioural changes4 in the patient that alter relationships with health professionals and the family, and can even lead to non-compliance with medical treatment.

In addition, suffering from one of these two psychological disorders in the initial stages of CKD is a predictor for elevated mortality in patients that reach later stages.1 Although technological advancements have enabled us to reduce the mortality of patients with CKD, depression and anxiety increase the risk of suicide.5

The high prevalence of depression in patients with CKD is mediated by the combination of the physical symptoms of depression and the symptoms experienced by dialysis patients, which are the consequence of nephrological diseases. Since this combination can lead to an over-estimation of the prevalence of this psychological problem in renal patients, we need to improve the precision and accuracy of the diagnostic process. One way to improve in this area is to use the Hospital Anxiety and Depression Scale (HADS),4 as we did in our study, as this does not take into account physical symptoms in the overall score for diagnosing depression, but only cognitive symptoms that are characteristic of this mood disorder.5

With this in mind, we examined the prevalence of anxiety and depression in patients with ADPKD. We also sought to determine whether clinical variables could be correlated with the specific symptoms characteristic of these two psychological disorders.6

The first objective of our study was to calculate the prevalence of anxiety and depression in patients with ADPKD (Table 1). The prevalence of these two psychological disorders in patients with ADPKD on haemodialysis (HD) was lower than in those without ADPKD that were undergoing the same treatment (55.9% of patients with depression and 46.72% of patients with anxiety). However, the estimated rates of depression in non-HD patients were similar to those observed by Hedayati et al.7 We are unable to establish comparisons with the prevalence of anxiety in non-HD patients, since no studies have been carried out in this field.

Our second objective was to establish which specific symptoms of these two psychological disorders were associated with two clinical variables (time on HD and time since diagnosis). Our predictions were less exact in this subject, since no studies have specifically examined this topic.

A detailed analysis of questionnaire items and clinical variables, which specifically examined the relationship between HADS and HD/non-HD, time on HD, and time since the diagnosis, revealed several significant differences.

We observed that HD/non-HD influenced the feeling of lethargy and unrest and it appears that the duration of dialysis treatment plays an important role in several items (Table 2). As Watnick et al.10 showed, symptoms of depression and anxiety are most common at the start of dialysis.

We also observed that scores for a feeling of lethargy (Table 2) were higher in patients that had spent 2.2–22 years on HD, as compared to those with only 0–4 months of treatment. Contrary to the aforementioned results regarding anxiety, the latter finding is supported by several studies that affirm those patients that have been on dialysis for more than one year have a greater tendency for depression.11

Our results also suggest that the time since the patient was diagnosed with:

Table 1. Scores for the hospital anxiety and depression questionnaire

<table>
<thead>
<tr>
<th>Possible depression</th>
<th>Depression</th>
<th>Possible anxiety</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-haemodialysis (%)</td>
<td>5 (14.3%)</td>
<td>1 (2.9%)</td>
<td>6 (17.1%)</td>
</tr>
<tr>
<td>Haemodialysis (%)</td>
<td>6 (25%)</td>
<td>1 (4.2%)</td>
<td>5 (20.8%)</td>
</tr>
</tbody>
</table>
kidney disease is significantly correlated with feelings of concern and sudden panic (Table 2). In this manner, scores were higher among patients that had been diagnosed with ADPKD for 0-12 months than in those who had been diagnosed with ADPKD for 14-25 months. We believe that this finding confirms that concern regarding this disease is strongest immediately following diagnosis.

In conclusion, our study shows that patients with ADPKD have a higher prevalence of symptoms of anxiety and depression than in the general population, regardless of whether or not they are undergoing dialysis treatment. More studies that examine psychological aspects of patients with ADPKD are necessary, in order to attend to their biopsychosocial needs in the best possible manner. An early identification of psychological problems along with a study of the context in which they have arisen allows us to reduce the disparity between long-term and short-term progression and development of kidney disease, as well as to improve patients’ quality of life.

Acknowledgments

This article was made possible by funding from the Canary Islands Savings Bank (Caja de Canarias) and the Mapfre Guanarteme Foundation for the genetic and psychosocial study of patients with autosomal dominant polycystic kidney disease in the province of Las Palmas (Análisis Genético y Evaluación Psicosocial de pacientes con Poliquistosis Renal Autosómica Dominante en la Provincia de Las Palmas).

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.


Table 2. Mean score for each item on the hospital anxiety and depression questionnaire

<table>
<thead>
<tr>
<th>Anxiety items</th>
<th>HD</th>
<th>Non-HD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervousness</td>
<td>1.125±0.899</td>
<td>1.086±0.853</td>
<td>.788</td>
</tr>
<tr>
<td>Fear</td>
<td>0.875±1.116</td>
<td>0.543±0.8168</td>
<td>.058</td>
</tr>
<tr>
<td>Concern</td>
<td>1.123±1.116</td>
<td>1.029±1.071</td>
<td>.811</td>
</tr>
<tr>
<td>Ability to feel relaxed</td>
<td>0.96±0.999</td>
<td>1±0.804</td>
<td>.135</td>
</tr>
<tr>
<td>Strange feeling in the pit of</td>
<td>0.5±0.722</td>
<td>0.6±0.736</td>
<td>.478</td>
</tr>
<tr>
<td>the stomach</td>
<td>1.125±1.154</td>
<td>0688±0.758</td>
<td>.006*</td>
</tr>
<tr>
<td>Unrest</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Depression items</th>
<th>HD</th>
<th>Non-HD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capacity for enjoyment</td>
<td>0.63±0.647</td>
<td>0.4±0.553</td>
<td>.276</td>
</tr>
<tr>
<td>Capacity for laughing</td>
<td>0.25±0.505</td>
<td>0.26±0.442</td>
<td>.766</td>
</tr>
<tr>
<td>Happiness</td>
<td>0.67±0.868</td>
<td>0.46±0.561</td>
<td>.304</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1.208±1.285</td>
<td>0.314±0.676</td>
<td>.004*</td>
</tr>
<tr>
<td>Lost interest in appearance</td>
<td>0.625±0.924</td>
<td>0.429±0.778</td>
<td>.381</td>
</tr>
<tr>
<td>Optimism for the future</td>
<td>0.67±0.816</td>
<td>0.60±0.775</td>
<td>.892</td>
</tr>
<tr>
<td>Capacity for fun</td>
<td>0.58±1.018</td>
<td>0.49±0.853</td>
<td>.463</td>
</tr>
</tbody>
</table>

HD: haemodialysis patients; Non-HD: non-haemodialysis patients
* P<.05
Diabetic foot and renal failure. Theoretical and practical considerations

Nefrologia 2012;32(3):399


To the Editor,

Diabetic patients with diabetic foot have high mortality rates and it has been suggested that aggressive cardiovascular treatment decreases morbidity and mortality in these patients.1,2 As such, we decided to perform a retrospective review of the level of compliance with consensus documents on secondary prevention in patients with diabetic foot at their first hospital examination. We assessed a total of 129 patients, collecting clinical information, haemogram and biochemical test results, and treatments administered. We performed all statistical analyses using SPSS statistical software version 15.0. Of the 129 patients studied, 80 were male and 49 were female, with a mean age of 63.02±13.49 years. The clinical parameters measured revealed arterial hypertension in 71.3% of patients, 23.3% were active smokers, mean HbA1c was 8.74±2.23%, mean LDL cholesterol was 90.06±35.58mg/dl, and mean triglycerides were 151.84±82.49mg/dl. As regards treatment, 64.3% received insulin and 43.4% oral anti-diabetic drugs. In addition, 52.7% of patients received statins, 1.6% fibrates, 13.2% allopurinol, 21.7% calcium antagonists, 38.8% diuretics, 14.7% beta blockers, 24.8% angiotensin-converting enzyme (ACE) inhibitors, 30.2% angiotensin receptor blockers (ARB), and 55.8% anti-platelet drugs. Thirty-one patients (24%) had a MDRD-4<60ml/min. As compared to patients with an MDRD-4<60ml/min, this group was older (70.52±10.87 years vs 60.04±12.64 years; P=.000), had lower levels of Hb (10.62±1.79g/dl vs 12.33±1.96g/dl; P=.000) and haematocrit (31.71±5.77% vs 36.04±5.46%; P=.001), and had higher levels of K+ (4.77±0.56mmol/l vs 4.52±0.39mmol/l; P=.027), uric acid (6.86±2.16mg/dl vs 4.67±1.18mg/dl; P=.000), and red blood cell distribution width (RDW) (16.93±3.75% vs 14.16±2.53%; P=.000), with no differences based on the treatments administered. Based on these results, we can conclude that patients with diabetic foot that seek their first hospital evaluation have hypertension, poorly controlled high glucose levels, and are receiving treatments that are quite different from those recommended for secondary prevention. We must point out that approximately 20% of patients in our study also had chronic renal failure, and there were no significant differences in terms of treatment administered between this sub-group and all other patients. Furthermore, these patients with diabetic foot and chronic renal failure had a higher percentage of RDW, which has been associated with increased mortality.3

In order to achieve treatment targets and a change in mentality, it is important to know the present situation and prioritise the goals accordingly. The fact that 44.2% of these patients go without anti-platelet treatment, 35% without ACE inhibitors or ARBs, and 47.3% without statin treatment should lead us to reflect upon the current reality and how to bring our clinical action more in line with theoretical recommendations on a long-term basis.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.


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Effects of suspending ACE inhibitors and ARBs in advanced chronic kidney disease
Nefrologia 2012;32(3):400-1

To the Editor,
Renin-angiotensin system inhibition is a commonly used therapeutic measure for slowing the progression of kidney disease in diabetic nephropathy and nephropathies with proteinuria. It has also been established that activation of this system is necessary for maintaining glomerular filtration when renal perfusion is severely impaired, as occurs in ischaemic nephropathy and cases of hypotension and dehydration. In these situations, the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) can deteriorate renal function.

In a recent and very shocking study carried out in patients with advanced chronic renal failure, Ahmed et al showed that halting renin-angiotensin system inhibitor treatment was associated with a relevant and persistent improvement in renal function, with an increase in glomerular filtration rate >25% in 61.5% of cases.1 These results led us to question the adequacy of using these drugs in advanced chronic kidney disease, and we decided to confirm these findings in our own patients.

Between January and June 2011, ACE inhibitors and ARBs were suspended in patients with stage 5 chronic kidney disease that were undergoing predialysis programmes at the Hospital Ramón y Cajal in Madrid. The study included a total of 14 patients (5 women and 9 men) with a mean age of 68±12 years (range: 42-88 years). The aetiologies of the different cases were diabetic nephropathy (5 cases), nephroangiosclerosis (3 cases) polycystic kidney disease (2 cases), and other (4 cases). Eleven patients were receiving ARBs, one received ACE inhibitors, and the other two received both ARBs and ACE inhibitors. These drugs were replaced with calcium channel blockers or beta blockers. When the renin-angiotensin system inhibitor was suspended, all patients were clinically stable, with no signs or symptoms of heart failure, with blood pressure values under control and fractional sodium excretion ranging between 2% and 5.6%.

Table 1 summarises the progression of glomerular filtration rate (MDRD-4), proteinuria (proteinuria:creatinine ratio) and serum potassium concentration since the renin-angiotensin system inhibitors were suspended (baseline values) to three months later.

We only observed an increase in glomerular filtration rate >25% in one patient, and this increase was temporary. Overall, the removal of ACE inhibitor and ARB treatment was associated with an almost statistically significant increase in proteinuria. However, in 5 patients, the increase in proteinuria:creatinine ratio in urine samples was greater than 1mg/mg. There were no changes in serum potassium concentrations. We did not find an increase in blood pressure in any patient following the suspension of renin-angiotensin system inhibitors; however, two patients requested reinstatement of treatment, attesting to a better clinical tolerance. No patients suffered cardiovascular events during the follow-up period.

Our results in patients with stage 5 chronic kidney disease differ from those published by Ahmed et al. Although these drugs may worsen renal function in cases of compromised renal perfusion, the removal of renin-angiotensin system inhibitors failed to provide any relevant benefits in clinically stable patients without signs of dehydration. Even in these advanced phases of renal failure, ACE inhibitors and ARBs have an antiproteinuric effect. We believe that larger studies are needed in order to clarify whether suspending treatment with ACE inhibitors or ARBs in advanced chronic kidney disease impacts glomerular filtration rate, and if so, which patients would benefit from this protocol.

Conflicts of interest
The authors affirm that they have no conflicts of interest related to the content of this article.


Table 1. Evolution of glomerular filtration rate and proteinuria following suspension of ACE inhibitors and ARBs

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular filtration rate (ml/min/1.73m²)</td>
<td>11.3±2.7</td>
<td>11.4±3.7</td>
<td>.982</td>
</tr>
<tr>
<td>Proteinuria:creatinine (mg/mg)</td>
<td>2.03±1.64</td>
<td>2.90±2.4</td>
<td>.09</td>
</tr>
<tr>
<td>Serum potassium (mEq/l)</td>
<td>4.7±0.5</td>
<td>4.6±0.6</td>
<td>.3795</td>
</tr>
</tbody>
</table>

ARB: angiotensin receptor blockers; ACE: angiotensin-converting enzyme.
To the Editor,

Albuminuria increases the risk of progression of renal failure (RF), even in advanced stages.\(^1\) Renin-angiotensin-aldosterone system (RAAS) inhibitors are the main tool used for reducing albuminuria and slowing the progression of RF, although this treatment is often insufficient.\(^2\) Recently, paricalcitol has been proven effective in reducing albuminuria in certain patients.\(^3\)

The aim of our study was to assess the usefulness of paricalcitol to reduce albuminuria in patients with stage 4-5 RF.

Method: We included all patients referred to the predialysis unit. Patients were administered paricalcitol at an initial mean dose of 1±0.3 \(\mu\)g/day orally, adjusted for calcium/phosphorous metabolic parameters. Follow-up continued for at least 6 months, with three visits every 2 months, in which albuminuria, MDRD, and calcium/phosphorous metabolism parameters were registered. Treatment with RAAS inhibitors and hidroferol continued without change. Statistical analysis: we used analysis of variance for comparing the means of quantitative variables, Wilcoxon tests for comparing medians, and chi-square tests to compare percentages.

Results: Our study included a total of 40 patients, 67% males, with a follow-up period of 135-235 days. Baseline MDRD was 19.5±3ml/min, 97.5% of patients had hypertension, and 35% were diabetic. Mean urine albumin-to-creatinine ratio (UACR) was 1932±1641mg/g. Initial calcium-phosphorous metabolism parameters were: calcium: 8.8±0.5mg/dl; phosphorous: 4.5±0.5mg/dl; intact parathyroid hormone (iPTH): 473±143pg/ml. At the start of the follow-up period, 25% of patients received angiotensin-converting enzyme inhibitors, 42.5% angiotensin receptor blockers, 55% hidroferol, and 12.5% calcitriol. During the follow-up period, we observed a significant decrease in MDRD (19.5±3ml/min vs 17.3±3.4ml/min; \(P=0.003\)). There was also a decrease in iPTH and an increase in calcium, both significant results (473±143pg/ml vs 197±88pg/ml, and 8.84±0.5mg/dl vs 9±0.4mg/dl; \(P=0.00\) and \(P=0.01\), respectively). We also observed an increase in phosphorous, although this was not significant (4.5±0.5mg/dl vs 4.8±0.6mg/dl; \(P=1\)). UACR decreased over the course of the study from an initial mean value of 1932±1641mg/g to the final mean value of 1417±1284mg/g, a 27% decrease \((P=0.1)\). In the group of patients with higher initial UACR values (>3000mg/g), the decrease was significant (4258±944mg/g vs 2786±1630mg/g; \(P=0.03\)). We observed an increase in patients with normalised albuminuria and a decrease in those with albuminuria >3000mg/g. UACR was not associated with treatment with RAAS inhibitors, hidroferol, or calcitriol. In no cases was suspension of treatment necessary due to altered calcium/phosphorous metabolism or secondary side effects, although 17% of patients required dosage adjustments.

Our study shows that treatment with paricalcitol in this group of patients is associated with a significant decrease in UACR, leading to a higher proportion of patients with normal excretion of albumin, in addition to providing better control of bone metabolism. The effect was greatest and most significant in patients with higher initial albumin excretion levels, which is the group with the highest risk for progression of RF.\(^4\)

It may be that the small sample in our study was insufficient to demonstrate the antiproteinuric effects of this treatment with a greater level of significance. We may not have observed significant results in the control of renal function deterioration because of this same reason. Although it was not an objective of this study, we should also keep in mind the decreased cardiovascular risk associated with reduced UACR.

Conclusion: Paricalcitol can be effective in halting proteinuria in patients with stage 4-5 chronic renal failure disease and controlling secondary hyperparathyroidism. Its efficacy in preventing the progression of IR must be verified in future studies.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.


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Microalbuminuria, another use for paricalcitol? Our experience in advanced chronic kidney disease
Nefrología 2012;32(3):401-2

Letters to the editor
Monitoring haemodialysis in the Cabueñes Hospital
Nefrologia 2012;32(3):402-3

To the Editor,

In 2007, the Quality Management Group from the Spanish Society of Nephrology proposed a system for monitoring haemodialysis with the objective of establishing a standardised protocol for implementation, in accordance with the KDOQI guidelines from previous years. In this context, we registered the data for our unit, which treats approximately 300,000 inhabitants, subtracting the 50% that undergo dialysis from the Spanish Red Cross, approximately 150,000 patients.

We included the information for all patients on dialysis in our hospital during 2011 in our analysis. This produced a total of 77 patients; of them, 31 were included in the study over the course of the year, yielding a final prevalence of 47 patients. The mean age was 68.07 years, 69% were male, and the treatment administered was primarily conventional haemodialysis with biocompatible filters. The distribution of renal diseases was similar to rates in previous studies, with a higher frequency of nephroangiosclerosis, diabetic nephropathy, and of an unknown aetiology, with similar percentages. We analysed the standard demographic and biological indicators related to dialysis treatment, anaemia, iron parameters, renal osteodystrophy, etc. We would also like to highlight certain characteristics of the patients who passed away, given their homogeneity.

The prevalence during 2011 is summarised in Table 1.

Some 30% of both prevalent and incident patients were diabetic, and 36% had a Charlson index >7. Only 3 patients underwent dialysis treatment more than 3 days per week, and none underwent less than 3 sessions per week. Gross mortality was 11.68%, with normal hospitalisation rates and duration of hospital stay. We observed positive results with permanent catheters: Kt/V (1.37) was similar to rates with fistulas. Furthermore, there was a very low rate of infections (1 bacteremia in 22 permanent catheters in place for at least 3 months). Values for renal osteodystrophy were acceptable, with P<55 in 70%, Ca×P<55 in 73%, and parathyroid hormone (PTH) <300 in 70%. There were no cases of PTH>800 + Ca×P>55, thus no need for parathyroidectomy. All parameters for treated water and vaccinations were fulfilled without exception. We were satisfied that 80% of the patients starting dialysis treatment were referred from specialists and only 20% from emergency departments (pericarditis, uraemic coma, etc., and some patients that abandoned regular visits). However, we were unable to reach adequate Hb levels (11-13g/dl) in 90% of patients, as is suggested by standard guidelines. We only reached adequate Hb levels in 55% of cases. Furthermore, despite having a predialysis unit for patients with renal failure, a catheter was needed in the first session in approximately 50% of patients, not always due to the lack of an established vascular access, but rather inadequate performance by the already created vascular access in elderly patients. We also failed to comply with the recommended fistula:catheter ratio, resulting in a 3:1 value.

The most interesting results were those aspects that deviated from guideline objectives: the only patients that died were older than 80 years (mean: 85 years); except for one case, none responded to vaccination; and in more than half of all deaths, the patient left treatment several days or weeks before dying, rather than prolonging regressive situations without recourse. However, the mean duration on haemodialysis in these patients that died was 21 months, which should be taken into account when evaluating patient age upon inclusion in the programme.

No patients included in the treatment programme produced unexpected emergencies, although 2 cases occurred in patients in predialysis (pulmonary oedema) and 4 life-threatening situations were produced in previously unknown patients.

Table 1. Prevalence during 2011

<table>
<thead>
<tr>
<th>Category</th>
<th>Prevalent on 31-12-2011</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referred to Spanish Red Cross</td>
<td>11</td>
<td>14.3%</td>
</tr>
<tr>
<td>Referred to CAPD</td>
<td>3</td>
<td>3.9%</td>
</tr>
<tr>
<td>Transplant recipients</td>
<td>7</td>
<td>9.1%</td>
</tr>
<tr>
<td>Deaths</td>
<td>9</td>
<td>11.7%</td>
</tr>
<tr>
<td>No. prevalent</td>
<td>77</td>
<td>100%</td>
</tr>
</tbody>
</table>

CAPD: continuous ambulatory peritoneal dialysis.
To the Editor,

We present the case of a 75 year-old male with hypertension and chronic obstructive pulmonary disease who was diagnosed with chronic delusional disorder and mixed personality disorder, along with partial epilepsy due to a left parietal haematoma from several years prior. The patient was under treatment with topiramate, levetiracetam, quetiapine, sertraline, clobazam, and bronchodilators. He sought treatment for a respiratory infection and functional deterioration consisting of apathy, drowsiness, and periods of aggressive behaviour. A physical examination revealed that the patient had no fever, although he did suffer from disorientation and slurred speech, and would drift off to sleep, but with no apparent focal loss of motor function. The patient also had shallow tachypnoea, widespread rhonchi, and crackles in the left base, with radiological images indicative of superinfection of the abnormally widened bronchial tubes. We performed a laboratory analysis, revealing mildly elevated chlorine (114mEq/l), with nor-

Table 2. Vascular access and Kt/V

<table>
<thead>
<tr>
<th>Vascular access</th>
<th>No.</th>
<th>Percentage</th>
<th>Kt/V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriovenous fistula</td>
<td>52</td>
<td>67.53%</td>
<td>1.37</td>
</tr>
<tr>
<td>Catheter</td>
<td>25</td>
<td>32.46%</td>
<td>1.38</td>
</tr>
</tbody>
</table>

To conclude: in our experience, the positive results in permanent catheters are due to the total freedom in our unit for inserting, removing, replacing, and choosing catheters, for which we owe eternal thanks to Dr Forascepi; there is nothing like working closely with the patient to improve our results. Secondly, the few emergencies that were produced in prevalent dialysis patients were closely related to the referral of cardiologically unstable patients to peritoneal dialysis (essential collaboration from the Hospital Central de Asturias), and in some cases due to administering extra scheduled dialysis. Finally, avoiding unnecessarily prolonged treatment in certain patients with very low life expectancy and poor quality of life is an obvious goal, and we are focused on avoiding unnecessary suffering and ethical issues, etc., for heavily burdened families. In our opinion, senile patients with an acceptable quality of life should be included in this treatment programme. We need to improve many aspects of the treatment that we provide, but always with the patient’s needs in mind.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

5. Torregrosa JV, Bover Sanjuán J, Cannata Andía J. Recomendaciones de la Sociedad Española de Nefrología para el manejo de las alteraciones del metabolismo óseo-mineral en los pacientes con enfermedad renal crónica. Nefrologia 2011;31 Supl 1:3-32.

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C) BRIEF CASE REPORTS

Topiramate-induced metabolic acidosis: a case study
Nefrologia 2012;32(3):403-4

To the Editor,

We present the case of a 75 year-old male with hypertension and chronic obstructive pulmonary disease who was...
Topiramate is a sulphamate with anti-epileptic effects, and is indicated in preventative treatment of migraine, the treatment of neuropathic pain, bipolar disorder, tobacco dependence, and bulimia nervosa, among other pathologies. Its most common secondary side effects are asthenia, dizziness, drowsiness, emotional lability, and weight loss. The development of urolithiasis and hyperchloremic metabolic acidosis with a normal anion GAP is much less common, but has been reported. Topiramate has a molecular structure very similar to acetazolamide and inhibits the carbonic anhydrase enzyme, especially the type II isoenzyme that predominates in human kidneys. This can lead to mixed renal tubular acidosis (type 3) as a result of ultrafiltration of bicarbonate in both proximal and distal tubules, thus altering urine acidification and provoking a decrease in serum bicarbonate and CO₂ concentrations, which is usually mild and asymptomatic, although can produce hyperventilation, neurological symptoms, nephrolithiasis, osteoporosis, and osteomalacia in the long term. The circumstances that predispose patients to developing this complication are not well established, but patients are more likely to develop it if they have other conditions that cause acidosis, such as infections, diabetic ketoacidosis, chronic renal failure, or surgery. Certain genetic polymorphisms in the involved carbonic anhydrase isoenzymes may explain a greater or lesser susceptibility of certain patients to develop this complication. Some authors have suggested the possibility of monitoring bicarbonate or CO₂ levels to predict these cases, although this is not a completely validated method. The development of metabolic acidosis during chronic treatment with topiramate is a reversible condition, regardless of the dosage and duration of treatment. The only treatment is to suspend the use of the drug (there is no antidote) and replace it with a substitute. When the withdrawal of the drug is not possible, and the patient maintains acceptable levels of pH and serum bicarbonate, with no symptoms, indefinite treatment with oral alkaline supplements can be administered (sodium citrate or citric acid).

Conflicts of interest
The authors affirm that they have no conflicts of interest related to the content of this article.


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Giant true aneurysm of the radial artery following ligation of an arteriovenous fistula for haemodialysis
Nefrologia 2012;32(3):404-6

To the Editor,
Aneurysms and pseudoaneurysms develop in approximately 8% of arteriovenous fistulas (AVF) created for haemodialysis. They are potential sources of embolisation and thrombosis, and can occasionally erode the skin, giving rise to infection and local bleeding, and can even deform the af-
fected limb. True aneurysms in AVF are dilations in which the structure of the vein or artery wall remains intact. They frequently consist of venous aneurysms in long-term autologous fistulas associated with venous stenosis. True arterial aneurysms are less common and frequently occur in the axillary or humeral arteries following ligation of an AVF in the elbow.\(^1\) The increase in arterial flow and wall vibration are believed to be involved in the pathogenesis of this condition. On the other hand, pseudoaneurysms or fake aneurysms are expandable dilations caused by persistent subcutaneous bleeding through a continuous deterioration of the fistula or prosthesi-\(^2\)

**CLINICAL CASE**

A 65 year-old male was referred from the nephrology department to the vascular surgery unit due to a large pulsatile mass in the left forearm that has been present for several years, undergoing an accelerated and progressive growth in recent months. The patient had a background of arterial hypertension, dyslipidaemia, and a left radiocephalic fistula created 20 years earlier for haemodialysis due to terminal chronic renal failure. Six years after having received a transplant, this fistula was ligated.

The physical examination revealed an enormous pulsatile mass in the anterior side of the left forearm, with no signs of thrill or murmur (Figure 1). The hands were well perfused, with both radial and ulnar pulses present. We first performed a Doppler ultrasound analysis, which revealed intense blood flow within the mass, although we were unable to determine whether this was an aneurysm or pseudoaneurysm. We proceeded with an axial computed angiotomography angiography (CTA), and we were able to observe an enlarged and elongated humeral artery, an aneurysm or pseudoaneurysm of 62 millimetres in diameter in the radial area, permeable ulnar and interosseous arteries, and an obstructed distal radial artery.

The suspected diagnosis of aneurysm or pseudoaneurysm of the radial artery secondary to a ligated radiocephalic AVF in the transplant recipient led to the indication of surgical treatment.

We performed incisions in the elbow joint and distally along the radius, and then isolated the humeral, radial, and ulnar arteries, observing a giant true aneurysm along the entire radial artery. We completely resected the aneurysm and performed a proximal and distal ligation of the radial artery, since it was chronically thrombosed (Figure 2) and the vaso-\(^2\)

**DISCUSSION**

True arterial aneurysms must be quickly treated due to the risk of local and systemic complications, including embolisation, thrombosis, skin erosion and infection, bleeding, and compression of adjacent nervous structures, producing paraesthesia, pain, and reduced mobility.\(^4\) The treatment of choice is a resection of the aneurysm and arterial recon-

---

**Figure 1. Physical examination.**

Clinical appearance of the tumoral mass.
conclusion, we suturing the graft defect or by graft infection, a local repair can ensue by each case. Appropriate treatment varies with proper treatment planning, since the nervous) and pseudoaneurysms for between aneurysms (arterial and venous) dilations are complications that would like to point out that aneurysms primarily in puncture sites. Pseudoaneurysms are ruptures contained by the soft tissue that occur primarily in puncture sites. Pseudoaneurysms of PTFE (polytetrafluoroethylene) prostheses can also be treated using percutaneous or surgical approaches. In the absence of infection, a local repair can ensue by suturing the graft defect or by graft interposition. To conclude, we would like to point out that aneurysmal dilations are complications that can jeopardize both the viability of the vascular access and the life of the patient. As such, it is essential to make a correct differential diagnosis between aneurysms (arterial and venous) and pseudoaneurysms for proper treatment planning, since the appropriate treatment varies with each case.

**Conflicts of interest**
The authors affirm that they have no conflicts of interest related to the content of this article.


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**Nephrogenic ascites: a thing of the past?**


To the Editor,

Nephrogenic ascites is a refractory type of ascites that affects patients with chronic kidney disease on haemodialysis. Although the pathogenesis of this condition is not completely clear, it appears that these patients with hypoalbuminemia could have altered permeability of the peritoneal membrane and deficient lymph drainage. The diagnosis is made by exclusion, after ruling out other causes such as infection, liver disease, and heart failure. The best available option for treatment is daily haemodialysis treatment, the best alternatives for which are peritoneal dialysis and kidney transplantation. There have been documented cases of complete remission of ascites following kidney transplantation. Without treatment, the prognosis for nephrogenic ascites is very poor.

Here we present the case of a 66-year-old patient with no toxic habits and a history of arterial hypertension, atrial fibrillation, stroke in the left middle cerebral artery with residual right hemiparesis, aphasia, and dysarthria along with acute myocardial infarction. The patient started haemodialysis treatment in January 2005 due to renal failure secondary to post-streptococal glomerulonephritis. The patient sought treatment in November 2010 with a progressive increase of the abdominal perimeter, with a physical examination indicative of ascites. We performed an
ease demonstrated by the imaging tests. However, both conditions were ruled out and the patient was discharged.

Over a 6-month period, we administered 4 paracentesis sessions and sent samples for microbiological, histological, and laboratory analyses, with no changes from the aforementioned results. Considering the possibility of a tumour-based ascites, we decided to hospitalise the patient for analysis. We removed 5 litres of serosanguineous fluid by paracentesis and sent samples for testing. Given the cell counts (Table 1) and biochemical properties of the peritoneal fluid, we ruled out the possibility of infection; cultures also resulted sterile. A histological analysis ruled out the possibility of malignant tumour cells. We also confirmed negative serology tests for hepatitis C and B and HIV.

Blood analyses (Table 2) did not reveal any significant abnormalities. We performed an abdominal axial computed tomography and magnetic resonance cholangiography, in which we observed a slightly over-sized liver, and the head of the pancreas was not visible. We asked the gastrointestinal department to perform an endoscopy in order to confirm the existence of a lesion on the pancreas as well as to look for evidence of possible oesophageal varices that would indicate portal hypertension from cirrhosis, in light of the liver disease demonstrated by the imaging tests. However, both conditions were ruled out and the patient was discharged.

Over a 6-month period, we administered 4 paracentesis sessions and sent samples for microbiological, histological, and laboratory analyses, with no changes from the aforementioned results. Considering the possibility of a cardiological origin for the ascites, we performed an echocardiogram, observing severe biventricular dysfunction with an ejection fraction of 22% and degenerative mitral and aortic disease with no haemodynamic repercussions. Despite a pathological echocardiogram, the patient never showed signs of heart failure, with no oedema or dyspnoea. Since a serum albumin-ascites gradient

| Table 1. Characteristics of the ascites fluid |
| Glucose | 103mg/dl |
| Triglycerides | 42mg/dl |
| Total protein | 4.1g/dl |
| Albumin | 3.4g/dl |
| LDH | 121IU/l |
| Amylase | 43IU/l |
| Adenosine deaminase | 23.6IU/l |
| Cell count |
| - Leukocytes | 100/mm³ |
| PMN | 2% |
| MN | 98% |
| - Blood cells | Abundant |
| Culture | Sterile |
| Histology | Cytology negative for tumour cells |
| LDH: lactate dehydrogenase; MN: mononuclear; PMN: polymorphonuclear neutrophils. |

| Table 2. Blood test results |
| Leukocytes | 2.68x10⁹/ml |
| - Neutrophils | 65.0 |
| - Lymphocytes | 20.3 |
| - Monocytes | 7.9 |
| - Eosinophils | 3.7 |
| - Basophils | 0.8 |
| Blood cells | 3.56x10⁹/ml |
| Haemoglobin | 11.3g/dl |
| Haematocrit | 37.0% |
| - MCV | 103.9fl |
| - MCH | 31.8pg |
| - MCHC | 30.6g/dl |
| - RDW | 14.7% |
| Platelets | 100x10⁶/ml |
| Iron | 38g/dl |
| Transferrin | 169mg/dl |
| Iron transfer capacity | 215g/dl |
| Transferrin saturation index | 18% |
| Ferritin | 589ng/ml |
| Sodium | 135mmol/l |
| Potassium | 4.9mmol/l |
| Chlorine | 99mmol/l |
| Glucose | 75mg/dl |
| Total cholesterol | 98mg/dl |
| Total protein | 5.2g/dl |
| Albumin | 3.9g/dl |
| Total calcium | 10.6mg/dl |
| Phosphate | 4.3mg/dl |
| LDH | 163IU/l |
| GOT | 13IU/l |
| GPT | 100IU/l |
| GGT | 35IU/l |
| Alkaline phosphatase | 90IU/l |
| Cholinesterase | 4726IU/l |
| Amylase | 81 IU/l |
| Lipase | 30IU/l |
| Total bilirubin | 0.85mg/dl |
| Creatinine | 4.5mg/dl |
| Urea | 84mg/dl |
| Uric acid | 3.6mg/dl |

MCHC: mean corpuscular haemoglobin concentration; GGT: gamma-glutamyl transferase; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; MCH: mean corpuscular haemoglobin; LDH: lactate dehydrogenase; RDW: red blood cell distribution width; MCV: mean corpuscular volume.
greater than 1.1 g/dL is indicative of portal hypertension with a 97% accuracy, we performed 2 tests, which resulted in values <1.1% and ruled out both liver disease and heart failure. Even so, we continued screening for a liver disease, ruling out viral, alcoholic, and other possible causes of an autoimmune liver disease. We also ruled out infections and peritoneal carcinomatosis.

Given the findings from numerous tests, the diagnosis appears to be compatible with nephrogenic ascites. Given the patient’s situation and inability for self-care, peritoneal dialysis is not an option. Kidney transplant is not an option either due to the associated comorbidities and the patient’s important bilateral iliac atherosclerosis. As recommended by the gastrointestinal department, evacuation paracentesis continues to be administered upon demand. We intensified the dialysis treatment and added intra-dialysis parenteral nutrition, with progressive improvements in the patient’s nutrition, with progressive improvements in the patient’s nutritional parameters and a complete disappearance of ascites. Currently the patient is asymptomatic.

Conflicts of interest
The authors affirm that they have no conflicts of interest related to the content of this article.


Postpartum hemolytic uremic syndrome with multiple organ involvement in a severe case

Nefrologia 2012;32(3):408-10

To the Editor,
Postpartum hemolytic uremic syndrome (PHUS), first described in 1968, is defined as a thrombotic microangiopathy (TMA) typically following a normal delivery after a symptom-free interval (mean 26.6±35 days). It usually occurs in primigravida with the mean age of 27.0±6 years and preeclampsia is historically associated with the disease. The involvement of extrarenal vascular beds in PHUS has been less reported. Here we report for the first time a severe case of PHUS complicated by pancreatic necrosis, bilateral visual loss due to central retinal artery occlusion (CRAO) and disseminated intravascular coagulation (DIC).

A 20-year-old primigravid was admitted for edema and headache when she was 34 weeks pregnant. On presentation her blood pressure (BP) was 180/115 mmHg and moderate edema on face was noted. Initial investigations showed 3+ proteinuria and normal serum creatinine (Scr) concentration. The diagnosis of preeclampsia was established and a cesarean section was performed in the 35th week of gestation. Nine days later, the patient complained of oliguria, nausea with BP of 175/105 mmHg. Laboratory tests revealed hemolytic anemia, with hemoglobin of 81 g/L, serum haptoglobin <0.2 g/L, and schistocytes shown in peripheral blood smear. Platelets (Plt) were markedly reduced at 41×10^9/L and an acute rise of Scr to 463.2 µmol/L showed acute renal failure. The immunologic studies revealed negative anti nuclear antibody and Coomb’s tests. Under suspicion of PHUS, antihypertensives, aspirin and furosemide were commenced on the 1st day of presentation and renal biopsy was performed on day 2.

The patient complained of left-upper abdominal pain after renal biopsy and developed a sudden bilateral painless visual loss. The subcutaneous bleeding over her upper arms was noted and she rapidly developed anuria, dyspnea, confusion, hypotension with BP of 70/50 mmHg. The ultrasound scan excluded the existence of perinephric / subcapsular hematoma caused by renal biopsy. The fundus exam revealed bilateral CRAO. Laboratory tests on day 3 showed elevated serum amylase, lipase and Scr up to 625 µmol/L, Plt down to 12.2×10^9/L. The level of fibrinogen decreased to 3.82 µmol/L with delaying activated partial thromboplastin time and positive D-dimer. Computed tomography scan confirmed pancreatic necrosis. Renal pathology showed thickened glomerular capillary walls with subendothelial edematous expansion that forming double contouring and renal arteriolar intimal expansion with fibrin exudation on the arteriolar wall (Figure 1). Based on these findings, the diagnosis of PHUS complicated by pancreatic necrosis, CRAO and DIC was established.

She was treated with pulse methylprednisolone 500 mg/d and intravenous immunoglobulin (IVIG) 20 g/d for 3 days. Meanwhile, plasma exchange (PE) with fresh frozen plasma (FFP) infusion and CRRT were initiated. Anticoagulant therapy for DIC and CRAO were also carried out. On day 15, she was improved significantly and the uri-
HUS and thrombotic thrombocytopenic purpura (TTP), collectively referred to as TMAs, occur with increased frequency during pregnancy or the postpartum period. These two disorders are considered by many to be manifestations of the same disease process; however, others consider HUS and TTP to be distinct entities. Since TTP and HUS share many overlapping features, distinguishing the two disorders may be difficult. As in the case we showed, the patient developed TMA with disturbance of consciousness that seemed to suggest TTP; however, the prominent renal insufficiency and the lack of diffused thrombi in renal tissue might support PHUS rather than TTP. Another differential diagnosis should be included in this case is hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP syndrome). HELLP, usually associated with preeclampsia is more common in multiparous women and approximately 70% of HELLP occur prior to term, with the remainder usually occurring within 48 hours after delivery. Patients with HELLP frequently present with severe right upper quadrant pain. Based on these characteristics of HELLP, we prefer to diagnose our case as PHUS. Although the pathogenesis of PHUS is unknown, the previous cases reported and the case presented here demonstrated preeclampsia could possibly trigger PHUS by causing platelet aggregation, deposition of microthrombi and occlusions in the microvasculature of the kidney, resulting in acute renal failure. The deficiency of ADAMTS-13, a metalloprotease that cleaves ultra-large von Willebrand factor (VWF) multimers observed in PHUS which suggest PHUS may be also associated with ADAMTS-13 deficiency. Recent studies revealed alternative complement 3 convertase dysregulation were detected in most PHUS patients suggesting PHUS was probably associated with complement gene mutation.

Multiple organ involvement such as pancreas and ocular structures were reported in non-pregnancy-related HSP, where PHUS involving extrarenal vascular beds has been less reported so far except central nervous system and liver damage. Does this mean PHUS have a better prognosis than non-pregnancy HUS? The case we described here developed multiple organ damage such as pancreatic necrosis, CRAO, DIC and progressed to secondary diabetes mellitus, bilateral visual loss and CRF eventually. The severe complications of pancreatic necrosis and CRAO might be the manifestations of TMA in PHUS, but might be more likely induced by DIC in this patient. Anyway, this case suggests PHUS could also involve multiple organ dysfunctions and result in bad outcomes even if the appropriate treatments have been given without delay.

The renal pathology in HUS is characterized by glomerular capillary subendothelial expansion, arteriolar fibrinoid necrosis, arterial edematous intimal expansion and vascular thrombosis. The preceding etiologic conditions of HUS and the histological findings appeared not to be related to each other. Our case showed typical subendothelial edematous expansion and renal arteriolar intimal expansion with fibrin exudation which supported renal microangiopathy, but without diffused thrombi and fibrinoid necrosis in renal tissue which seemed to be inconsistent with the following development of multiple organ complications and the progression to CRF. This was considered to be due to the early performance of renal biopsy after the attack and the early pathological findings in PHUS presented here may be difficult to predict the disease development and poor prognosis.

In conclusion, pancreatic necrosis, CRAO and DIC were observed in PHUS. Although renal replacement therapy and PE with FFP infusion have improved the survival of PHUS significantly, multiple organ complications such as pancreatic necrosis, CRAO and DIC may cause severe sequelae and lead to a poor prognosis of PHUS.

**Conflict of interest**

The authors declare that there is no conflict of interest associated with this manuscript.

Good results can be achieved. Nefrologia 2010;30:593-4.


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**Primary sclerosing cholangitis and interstitial nephropathy: an emerging association?**

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**To the Editor,**

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterised by inflammation and fibrosis in the intrahepatic and extrahepatic bile ducts, which primarily affects middle-age males.1 It can occur as an isolated entity or in association with inflammatory bowel disease. The aetopathogenesis of PSC has not been established, although growing evidence points towards genetic and immunological causes.1

Associated interstitial nephropathy in patients with chronic cholestatic liver disease was first described in the medical literature during the 1990s in paediatric patients, and it was suggested that this association might represent a new syndrome.2 4

Recently, the existence of a new disease, called “IgG4-related sclerosing disease” has been proposed.5 6

Here, we describe the case of a female patient diagnosed with PSC with severe interstitial nephropathy.

**CASE REPORT**

A 77 year-old female was referred to the nephrology department due to plasma creatinine values of 2.4mg/dl. The patient’s history included several surgical procedures: meniscus in 1985, thymoma with benign histology in 1999, nasal sinus polyps more than 20 years ago and again in 2008, varicose veins in 2006, cystocele in 2008, and hip fracture in July 2010. She was diagnosed with primary sclerosing cholangitis in 2003, and was under treatment with ursodeoxycholic acid. On several occasions, the patient had been placed retrograde biliary catheters and undergone sphincterotomy and dilation of the areas of stenosis. Inflammatory bowel disease had also been diagnosed around the same time. In later follow-up sessions, she underwent several colonoscopies, which occasionally produced normal results, and at other times revealed small ileocecal and colonic ulcers. The patient also suffered an episode of pericarditis of unknown cause in January 2010, and had bilateral gonarthrosis. The patient was intolerant to oral iron supplements, and had no toxic habits.

At the first visit, the patient was taking zolpidem 10mg/day, ursodeoxycholic acid 1250mg/day, pantoprazole 40mg/day, miratapine 15mg/day, and occasional paracetamol and dextropropoxyphene.

The patient complained of intense fatigue, dyspnoea after moderate exercise, reduced appetite, occasional nausea associated with coughing, periodical constipation lasting 48 hours and alternating with diarrhoea that produced 3 or 4 evacuations per day, but with no pathological signs, nocturia twice per day for several months, diurnal urination every 3-4 hours, and no history of reno-ureteral lithiasis or haematuria.

As regards family background, the patient’s parents both died at an elderly age, and three brothers had died as a result of tumours.

The physical examination revealed the following values for standard parameters: height: 159cm; weight: 53kg; blood pressure: 137/72mm Hg; heart rate: 95bpm. We did not observe jugular vein engorgement, carotid pulses were rhythmic and symmetrical, cardiopulmonary auscultation normal, and we observed hepatomegaly of approximately 4 finger-widths in
globulins in a blood sample, and non-se-
Electrophoresis revealed decreased immu-
rathyroid hormone was 149pg/ml.

dies were within normal levels. Intact pa-
Thyroid hormones and anti-thyroid antibo-
were all negative.

Serology for hepatitis B and C and HIV
plasmin were all within normal ranges.

factor, C-reactive protein, and cerulo-
82-453mg/dl). Complement, rheumatoid
304mg/dl); IgA: 81mg/dl (normal: 1560mg/dl); IgM: 10mg/dl (normal: 46-
bulins: IgG: 253mg/dl (normal: 751-
also detected a decrease in immunoglo-
and anti-mitochondrial antibodies. We
nuclear antibodies (ANA), anti-DNA an-
for anti-neutrophil cytoplasmic antibo-
An immunological analysis was positive
for anti-cardiolipin IgM po-

The results of a 24-hour urine test were: pro-
teinuria: 0.53g/24h; creatinine clearance:
17ml/min. The urine resulted negative.

An immunological analysis was positive
for anti-neutrophil cytoplasmic antibodies
(ANCA) (anti-MPO and anti-PR3
negative); the test was negative for anti-
nuclear antibodies (ANA), anti-DNA an-
tibodies, anti-smooth muscle antibodies,
and anti-mitochondrial antibodies. We
also detected a decrease in immunoglob-
ulins: IgG: 253mg/dl (normal: 751-
1560mg/dl); IgM: 10mg/dl (normal: 46-
304mg/dl); IgA: 81mg/dl (normal:
82-453mg/dl). Complement, rheumatoid
factor, C-reactive protein, and cerulo-
plasmin were all within normal ranges.

Serology for hepatitis B and C and HIV
were all negative.

Thyroid hormones and anti-thyroid antibo-
dies were within normal levels. Intact pa-

Electrophoresis revealed decreased immu-
oglobulins in a blood sample, and non-se-

tective proteinuria in a urine sample. A
Bence-Jones proteinuria test was negative.

In imaging tests (renal ultrasound), we ob-
served kidneys with normal size, morpho-
logy, and echogenicity, with no lithiasis or
dilation.

Given the deteriorated renal function of
unknown cause (we had no previous re-
ference values to compare with), we per-
formed a percutaneous renal biopsy with
the following findings: 4 glomeruli, 2 of
which were completely sclerosed, and
the other 2 progressing towards sclerosis. An
immunofluorescence study was nega-
tive for IgG, IgA, IgM, and C3. We ob-
served dense lymphocyte infiltration ex-
anding throughout the interstitial tissue,
destroying the normal architecture of the
renal parenchyma (Figure 1A and Figure
1B). We could not properly assess fibro-
sis due to the high level of infiltration. Fi-
gure 2A displays the immunohistochemi-
cal results using CD3 (monoclonal
 antibody that marks all T-lymphocytes),
demonstrating that the majority of the in-
filtration is due to T-lymphocytes, and Fi-
gure 2B shows the results of the immu-
nohistochemical analysis using CD4.
The final histological diagnosis was se-
vere tubulointerstitial nephropathy (in-
terstitial infiltration was predominantly
by CD4-positive T-lymphocytes).

The biopsy findings indicated treatment
with prednisone 50mg/day in a progress-
vically decreasing prescription.

Eight months later, the patient has stable
renal function (plasma creatinine:
2.2mg/dl; creatinine clearance: 20ml/min;
proteinuria: 0.49g/24h). Current liver func-
tion values are: GOT: 24U/l; GPT: 18U/l;
GGT: 172U/l; alkaline phosphatase:
342U/l.


discussion
PSC is a disease of an unknown aetiology,
with a progressive clinical presentation
that affects the bile ducts and causes cir-
rhosis. Patients with PSC can have a num-er of serological findings, including
hyper-gamma-globulinaemia and positive
tests for atypical ANCA and other auto-an-
tibodies such as anti-nuclear, anti-smooth
muscle, anti-thyroid, anti-cardiolipin, and
rheumatoid factor antibodies. Elevated
IgG4 levels (a characteristic marker of au-
toimmune pancreatitis) have also been
described in some patients with PSC. In
fact, IgG4-related sclerosing cholangitis is
also included in the group of idiopathic
sclerosing cholangitis.

Recently, “IgG4-related sclerosing di-
sease” has been classified as a new pa-
thological/clinical entity. It is a syste-
mic disease characterised by infiltration
of plasma IgG4-positive and T-
lymphocyte cells into several different
organisms: pancreas, bile ducts, salivary
glands, retroperitoneum, kidneys lungs,
and prostate. The histological findings
in affected organs include fibrosis, scle-
rosis, destroyed glandular architecture,
and lymphoplasmacytic infiltration.

Tubulointerstitial nephropathy is also re-
lated to certain medications, infections, and
autoimmune processes. Several cases of
interstitial nephropathy have been associa-
months progressed before the biopsy, with severe histological damage), we did manage to stabilise renal function.

In conclusion, we have described the case of severe interstitial nephritis in a woman with primary sclerosing cholangitis: in these patients, we should examine whether this association could be referred to as an emerging pathology: “IgG4-related systemic disease.”

Conflicts of interest
The authors affirm that they have no conflicts of interest related to the content of this article.

mal haemoglobin, leukocyte, and platelet values; creatinine: 0.75mg/dl; urea: 31mg/dl; total cholesterol: 241mg/dl; albumin: 3.2g/dl; ANA+: 1/640 (several years earlier: +1/320); anti-Ro: 127.9U/ml; normal/negative results for lupus anti-coagulants, anti-cardiolipin antibodies, anti-DNA, ENA, anti-La, and C3-C4; proteinogram without a monoclonal peak; proteinuria: 6.2g/24 hours (high-resolution electrophoresis [HRE]: selective glomerular pattern); urinary sediment: 12-20 red blood cells/field; negative urine culture. Serology for hepatitis B and C, HIV, and Epstein-Barr was negative; cytomegalovirus: previous exposure, negative RPR. Chest x-ray, echocardiogram, renal ultrasound, mammography, thoracic/abdominal/pelvic tomography, and gastroscopy were without relevant abnormalities.

The percutaneous renal biopsy (13 glomeruli) showed 2/3 normal glomeruli and 1/3 with mesangial widening, with no thickening of the capillary walls or other lesions (Figure 1); the immunofluorescence analysis revealed IgM mesangial deposits in less than 1 third of the glomeruli, with no IgG or complement; the electron microscope analysis found diffuse effacement of pedicels and an absence of electron-dense deposits, all of which was compatible with MCN.

We administered prednisone 50mg/day for 8 weeks in a progressively decreasing pattern. Proteinuria decreased progressively, with partial/complete remission 14 months after the diagnosis (proteinuria: 480mg/24h).

MCN is uncommon in SLE, with a prevalence <2% in adults.2,3

MCN can appear in SLE along with the initial diagnosis or during a flare, but can also occur several years after the onset of SLE and without any apparent lupus activity.2 It is still under debate whether this is a causal relationship or some sort of histological sub-class of lupus nephritis. In principle, the appearance of two autoimmune diseases in the same patient suggests linked pathogenesis. On the other hand, some authors estimate that the prevalence of MCN in SLE is much higher than in the general population, and that

In the current classification system for lupus nephritis (ISN/RPS, 2004), minimal mesangial lupus nephritis is established as class I, characterised by normal glomeruli in optical microscopy analysis and mesangial deposits in immunofluorescence tests and/or electron microscopy analysis.4 Cases of MCN in SLE have been described such as ours in which no significant deposits are observed in immunofluorescence or electron microscopy analyses,5,6 and that do not fit the current classification for lupus nephritis. However, according to the WHO classification system, they could be categorised as class Ia.

In this patient, we observed no temporal relationship with NSAID treatment.

To conclude, SLE appears to be a precipitating factor for MCN. However, in certain cases such as ours, in which MCN appears several years after SLE onset, with little or no lupus activity and no deposits observed in the renal biopsy samples, the pathogenic relationship is more debatable.

Acknowledgements

We would like to thank Professor Jerónimo Forteza, head of the histopathology department at the Hospital Clínico Universitario de Santiago de Compostela, for his invaluable assistance with the electron microscopy analysis.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.


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Minimal change disease following influenza vaccination and acute renal failure: just a coincidence?
Nefrologia 2012;32(3):414-5

To the Editor,
Since, 1966 different reports have associated minimal change disease (MCD) with different immunogens as well as the presence of acute renal failure (ARF) in the MCD, which pathogenic mechanisms are being debated up to the present.

A 44-year old man was admitted to our hospital with edema in his face and legs and cervical lymphadenopathy which occurred 18 days after influenza vaccine (Agrippal, Novartis). The laboratory showed: creatinine 44mg/l, urea 106mg/dl. In the urinalysis was evident: proteinuria 4g/24h and hyaline casts. Serological test (ANA, DNA, ANCAp, ANCAc, C3, C4, HBsAg, HCV and HIV) were negative. Renal biopsy was performed. Light microscopy showed evidence of severe acute tubular injury (Figure 1 A) and a moderate, diffuse interstitial inflammatory infiltrate consisting of mononuclear cells and severe edema. The immunofluorescence did not show deposits of IgG, IgA, IgM, C3 and C1q. Ultrastructural examination showed diffuse foot-process effacement, microvillous transformation and cytoplasmic vesicularization (*) (x 2479).

Figure 1. (A) Dilated renal proximal tubule-like distalization (*) and disappearance of the brush border (arrowhead). Note the normal optical appearance glomerular segment present in the figure (PAS x 400). (B) Electron micrograph of part of a glomerulus which has extensive fusion pedicel (arrowheads) and podocyte cytoplasm vesiculatization (*) (x 2479).

On the other hand, it is unclear because patients with MCD may be more sensitive to develop ARF, compared to other nephrotic glomerulopathies. The mechanism underlying to this clinical-pathological entity has not been fully clarified. Several mechanisms attempt to explain the ARF in the nephrotic syndrome. The extensive interstitial edema observed in the present case, could lead to an increased intrarenal pressure and consequently explains the sharp drop in GFR observed in our patient. This finding is supported by one of the stronger hypothesis that explains this situation: nefrosarca hypothesis. Nevertheless, the hypothesis that links the ARF of nephrotic syndrome with changes in the coefficient of ultrafiltration should be considered. Finally, Chen et al. have hypothesized that cytokines secreted induce the production of endothelin-1, which generate contraction of mesangial cells resulting in a decrease of the filtration area.

In summary, in the present case the immune response after influenza vaccination generated the podocitopathy known as minimal change disease possibly due to hypersensitivity syndrome. In this clinical-pathological context the patient developed acute renal failure which pathogenic bases are still controversial and debated in the biomedical area.

Acknowledgements
The authors wish to thank Mrs Elena Pereyra and Mrs Lucía Artino for their excellent technical assistance.

Conflict of interest
The authors declare that there is no conflict of interest associated with this manuscript.


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Lanthanum carbonate and peritoneal catheter dysfunction
Nefrologia 2012;32(3):415-6

To the Editor,
Clinicians are frequently faced with relatively banal issues that become factors of diagnostic confusion or can even trigger more severe complications.

In patients treated with peritoneal dialysis, constipation can become a very difficult problem, and can even reach the point of completely impeding the drainage function of the peritoneal catheter. This is the result of displacement of the catheter towards the upper abdomen and the fact that, even with a properly positioned catheter, a rigid intestine hinders the recovery of infused peritoneal fluid. Over 50% of catheter dysfunctions are related to constipation, and at times this necessitates intensive laxative treatment. Constipation is also an issue in the development of hernias and complications from pressure on the abdominal wall, and can even facilitate the passage of bacteria from the intestinal lumen, leading to peritonitis.

Constipation can be associated with several different factors, such as a certain degree of intestinal paresis, insufficient mobility, and a diet low in fibre, which is often the result of diets that restrict the intake of fruits, and frequently is a result of the medications administered for concomitant problems. Several treatments administered to dialysis patients can generate or aggravate this situation, such as the resins used for hypercalcaemia and phosphate binders. Lanthanum carbonate is a phosphate binder, without calcium or aluminium, which is effective in controlling hyperphosphataemia. Due to several failed vascular accesses, it was suggested that the patient be transferred to peritoneal dialysis, and a straight, double-cuff Tenckhoff catheter was implanted. During training, we detected catheter malfunction with incomplete drainage, so we performed abdominal x-rays (Figure 1) and peritoneography (Figure 2). In addition to the remnants of the radio-opaque material from the graft embolisation, we observed a large quantity of faecal matter throughout the large intestine, with radiolucent images indicating the presence of lanthanum carbonate. The peritoneal catheter was poorly positioned towards the hepatic flexure of the colon, and the peritoneography dye was completely restricted between the transverse colon and the lower edge of the liver, which was clearly outlined, without disseminating into the rest of the abdominal cavity. Suspension of the lanthanum and intensive laxative treatment progressively resolved the constipation and dye restriction, although it did

Figure 1. Simple abdominal x-ray
Remnants of graft embolisation. Poorly positioned catheter and severe constipation caused by lanthanum carbonate use in radiolucent images.
To the Editor,

Here we present the case of a 64 year-old male with a history of obesity, arterial hypertension, diabetes mellitus, and chronic atrial fibrillation, under treatment with oral anti-platelet drugs, who had had pain in the right lumbar fossa radiating to the groin for more than 24 hours, nausea and vomiting. The patient was without fever and had a blood pressure of 140/90mm Hg. Heart auscultation revealed systolic murmur. The patient’s abdomen was soft and depressible, with pain in the left flank and hypochondrium and no succussion splash. The rest of the physical examination did not reveal any relevant findings.

Complementary tests also produced notable results including atrial fibrillation in the electrocardiogram, leukocytosis, elevated plasma creatinine, a marked increase in lactate-dehydrogenase (LDH) with normal transaminase levels, and microhaematuria. The urine culture test was negative, as well as parameters for autoimmune disease, immunoglobulins, and complement.

Due to the persistent abdominal pain and lack of concordance with digestive diseases, we performed an abdominal axial computed tomography that revealed segmental bilateral hypodense areas (Figure 1) with no lithiasis or dilatation of the urinary tract. Together with the rest of the findings from examining the patient, this was suggestive of multiple renal infarctions, probably of an embolic origin. We then performed an echocardiogram that revealed dilated cardiomyopathy of an unknown cause and aortic stenosis.

After the evaluation, we started the patient on conservative treatment, maintaining therapeutic anti-coagulation, statins, and blood pressure control. The patient’s clinical and biochemical progression was favourable. Our final diagnosis was of cardio-embolic renal ischaemia in a patient with previous anti-coagulation treatment.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

Severe hypertriglyceridaemia. Treatment with plasmapheresis

Nefrologia 2012;32(3):417-8

To the To the Editor,

The application of apheresis treatments is gaining more importance in nephrological practice. In patients with metabolic diseases, clear indications exist for apheresis procedures, such as in familial hypercholesterolaemia. However, in other diseases, this type of treatment is applied only as an alternative when normal therapies fail to garner a response, such as in primary hypertriglyceridaemia (HTG).

Very little experience has been gained in the treatment of HTG with apheresis, although the few studies in the medical literature describing the treatment of this pathology with apheresis have obtained very positive results.1,2

The current guidelines of the American Society for Apheresis (ASFA) consider this a category III practice, and have approved its use in the case of HTG and in the presence or possibility of severe pancreatitis, which is quite probable when triglyceride (TG) levels exceed 2000mg/dl, and always when the patient does not respond to normal medical treatment. There are few comparative studies, but they have shown that 1-3 sessions of plasmapheresis in patients with pancreatitis and HTG can reduce symptoms by 46%-80%, the same results as for drug treatment.3 In a study of 8 patients with recurring pancreatitis undergoing chronic treatment with plasmapheresis, the frequency of pancreatitis was reduced by 67% when TG levels were maintained below 150mg/dl, thus preventing patient hospitalisations and reducing health costs.

For filtration techniques, we can use double filtration or cascade filtration, where one filter separates blood from the plasma, which is then passed through a second filter with a smaller pore size that does not allow the passage of molecules with a larger molecular weight; in this case, TG.5 In the DALI (Direct Absorption of Lipoproteins) system, the TG are directly absorbed from the blood using a filter that consists of modified polyacrylate ligands immobilized on a polycrylamide matrix.

Here we discuss the case of a 45 year-old male with no relevant medical history and no symptoms, but whose laboratory tests revealed a TG value of 7916mg/dl. The patient was admitted to our department for therapeutic and preventative plasmapheresis against pancreatitis. Only two sessions were administered. We used an apheresis monitor that first passed the blood through a plasma separating filter, and then the plasma was passed through another filter that trapped TG from plasma using hydrophobic interactions, finally returning the treated plasma to the patient. This procedure does not require plasma or albumin supplements. The plasma volume treated was 2.5 litres, calculated by patient weight and haematocrit values, with a mean time per session of approximately 1 hour and 45 minutes. After the first session, TG levels decreased to 1500mg/dl. After the second session, the value was 476 (Table 1 and Table 2). The patient was then discharged with prescriptions for rosvastatin at 10mg/24h and fenofibrate at 145mg/24h. Currently, the patient is asymptomatic, with good lipid control under medical treatment, and does not require hospitalisation despite such high levels of TG.

With this case, we wish to awaken interest amongst nephrologists in understanding and implementing apheresis techniques. This is another type of extracorporeal purification that can obtain positive clinical results, avoiding unnecessary health costs and hospitalisations, as in our case.

Table 1. Total cholesterol, triglycerides, HDL, and LDL levels after the first apheresis session

<table>
<thead>
<tr>
<th></th>
<th>Start</th>
<th>1 hour</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>1104</td>
<td>980</td>
<td>675</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>7916</td>
<td>2940</td>
<td>1500</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>63</td>
<td>57</td>
<td>50</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>447</td>
<td>347</td>
<td>327</td>
</tr>
</tbody>
</table>

HDL: high-density lipoprotein; LDL: low-density lipoprotein.
Table 2. Total cholesterol, triglycerides, HDL, and LDL levels after the second apheresis session

<table>
<thead>
<tr>
<th></th>
<th>Start</th>
<th>1 hour</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>602</td>
<td>337</td>
<td>267</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>1270</td>
<td>512</td>
<td>476</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>35</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>307</td>
<td>231</td>
<td>162</td>
</tr>
</tbody>
</table>

HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Conflicts of interest
The authors affirm that they have no conflicts of interest related to the content of this article.

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