INFLAMMATION IN PERITONEAL DIALYSIS:
A LATIN-AMERICAN PERSPECTIVE

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Peritoneal dialysis (PD) patients present an extremely high mortality rate, but the mechanisms mediating the increased risk of mortality observed in this group of patients are still largely unknown, which limits the perspective of effective therapeutic strategies. The leading hypothesis that tries to explain this high mortality risk is that PD patients are exposed to a number of traditional risk factors for cardiovascular disease (CVD) already at the onset of their chronic kidney disease (CKD), since many of these risk factors are common to both CVD and CKD. Of particular importance, chronic inflammation recently emerged as an important novel risk factor related to multiple complications of CKD. There are many stimuli of the inflammatory response in CKD patients, such as fluid overload, decreased cytokine clearance, presence of uremia-modified proteins, presence of chronic infections, metabolic disturbances (including hyperglycemia), obesity. Many of these factors are related to PD. Latin America has made some progress in economic issues; however, a large portion of the population is still living in poverty, in poor sanitary conditions, and with many health-related issues, such as an increasing elderly population, low birth weights, and increasingly high energy intake in the adult population, which, in combination with changes in lifestyle, has provoked an increase in the prevalence of obesity, diabetes, and CVD. Therefore, in Latin America, there seems to be a peculiar situation combining high prevalence of low education level, poor sanitary conditions, and poverty with increases in obesity, diabetes, and sedentary lifestyle. Since inflammation and mortality risk are intimately related to both sides of those health issues, in this review we aim to analyze the peculiarities of inflammation and mortality risk in the Latin-American PD population.

KEY WORDS: Latin America; inflammation; cardiovascular risk.

Peritoneal dialysis (PD) patients present an extremely high mortality rate, but the mechanisms mediating the increased risk of mortality observed in this group of patients are still largely unknown, which limits the perspective of effective therapeutic strategies (1). The leading hypothesis that tries to explain the high mortality risk observed in PD patients is that they are exposed to a number of traditional risk factors to cardiovascular (CV) disease already at the onset of their chronic kidney disease (CKD), since many of these risk factors are common to both CV disease and CKD. In the progression of renal dysfunction, CKD-related risk factors are introduced, changing the profile of both the CV disease and markers of risk. In this phase, usually starting when the glomerular filtration rate is below 60 mL/minute, the list of risk factors is enriched with disturbances of mineral metabolism, anemia, fluid overload, and uremic toxicity. Of particular importance, chronic inflammation recently emerged as an important novel risk factor related to multiple complications of CKD. There are many stimuli of the inflammatory response in CKD patients, such as fluid overload, decreased cytokine clearance, presence of uremia-modified proteins, presence of chronic infections, metabolic disturbances (including hyperglycemia), obesity. Although many of the risk factors linked to high mortality burden are not related to the dialytic procedure, there is additional harm introduced after the initiation of PD, such as the presence of chronic infections and factors related to the PD fluids, particularly the reabsorption of glucose (1). Latin America is a region comprised of 20 countries, former colonies of European countries where Latin-derived languages are spoken. Latin America has made some progress in economic issues; however, a large
portion of the population is still living in poverty, in poor sanitary conditions, and with many health-related issues, such as an increasing elderly population, low birth weights, and increasingly high energy intake in the adult population (2), which in combination with the changes in lifestyle has provoked an increase in the prevalence of obesity, diabetes, and CV disease. Therefore, in Latin America, there seems to be a peculiar situation combining high prevalence of low education level, poor sanitary conditions, and poverty with increases in obesity, diabetes, and sedentary lifestyle. Since inflammation and mortality risk are intimately related to both sides of those health issues, in this review we aim to analyze the peculiarities of inflammation and mortality risk in the Latin-American PD population.

INFLAMMATION AND INCREASED CV RISK IN CKD

The mechanisms underlying CV disease have shifted recently to include inflammation as a pivotal factor determining the initiation and progression of CV damage in CKD patients. The vascular endothelium, once considered a barrier between intravascular and interstitial compartments, is nowadays considered much more than an inert, cellular, single layer covering the internal surface of blood vessels. In normal conditions, the endothelium actively decreases vascular tone, inhibits cell adhesion and aggregation, limits activation of the coagulation system, and stimulates fibrinolysis. Another fundamental function of the healthy endothelium is to keep vascular permeability tightly controlled. Several factors induce vascular damage, which leads to a change in endothelial cell phenotype (characterized by impaired nitric oxide production), altered smooth muscle cell relaxation and proliferation, reduced angiogenesis, activation of coagulation, and increased cell adhesion to the vascular wall (3). Atherosclerotic CV disease is initiated and perpetuated by the interaction of immune cells with cells of the vessel wall, which is mediated by chemokines and adhesion molecules. There is increasing evidence generated from experimental and clinical studies that these early (inflammation mediated) stages of atherosclerosis are extremely important (4). In addition, prospective data strongly suggest that endothelial activation through inflammation occurs early in the atherosclerotic process and that high serum levels of inflammation markers, chemokines and adhesion molecules are predictors of future CV events in the general (5) and CKD (6) populations.

Since the first report by Bergström and his co-workers (7) of an association between elevated C-reactive protein (CRP) and increased mortality, several groups have reported almost identical findings in other series (and using other markers of inflammation), including patients on PD (8–10). Although the association between single or multiple measures of inflammation markers and an increased risk of mortality in CKD patients is a consistent finding, the triggers of the inflammatory response are still only superficially understood. In addition, whether inflammation is a direct causative factor determining target organ damage or whether it represents an epiphenomenon is still an unanswered question. Since efficient therapeutic strategies may have to be directed toward reducing the causative factors of the inflammatory response, a more in-depth analysis of those factors associated with inflammation and oxidative stress is necessary to define targets for intervention.

Many causes present even before the initiation of PD can be considered potential triggers of the inflammatory response. Uremic toxicity, accumulation of modified proteins (such as advanced glycation end products), retention of cytokines, mechanical stress of the vascular wall as a result of hypertension, comorbidities such as advanced age and diabetes, and extraosseous calcification are examples of factors potentially triggering the inflammatory response and that are unrelated to dialysis treatment. Upon the introduction of PD, some other inflammation and oxidative stress-inducing factors are added to that list. Therefore, chronic infections related to PD, reabsorption of glucose degradation products present in the dialysate, transient intraperitoneal acidosis and intraperitoneal inflammation, and oxidative stress (with potential impact on the systemic side) have to be considered potential additional causes of systemic inflammation. Finally, the presence of glucose as an osmotic agent in the PD fluid is also a potential villain inducing systemic complications. In the following section, we will review the potential causes of inflammatory activation, particularly those peculiar to Latin-American patients.

CAUSES OF SYSTEMIC INFLAMMATION IN PD PATIENTS

Causes of inflammation in PD patients are multiple and include bioincompatibility of conventional PD solutions (11–13), fluid overload (14), and reduction in residual renal function (15). In addition, genetic factors may be implicated in the pathogenesis of inflammation influencing the expression and production of both pro-inflammatory and anti-inflammatory mediators (15,16). Unfortunately, not much information in this regard has come from our Latin-American patients; however, some data suggest that fluid overload (17,18) and increased intraperitoneal dialysate volume (19) are also implicated
in the genesis of inflammation in PD. Late referral to the nephrologist (20) and late initiation of dialysis (with reduced residual renal function) (21,22), and the high prevalence of comorbidities at initiation of dialysis (21,23–28) may also influence the presence of inflammation, which in turn may be amplified in countries with poor economic conditions combined with unhealthy lifestyles.

Well-accepted risk factors for mortality identified in the PD population include age, diabetes mellitus, CV disease, malnutrition–hypoalbuminemia, peritonitis, and cancer (29–31), and many of these have also been identified in our setting (21,24–26). The ADEMEX study (27) definitely discarded the notion that higher peritoneal clearances determine patient outcomes (as previously considered), and it also established that the survival benefit of PD is obtained within a range of clearances achievable in usual practice.

On the other hand, high peritoneal transport type is implicated in the higher mortality of PD patients (32,33), which has also been shown in patients of Latin-American origin (23). Subjects with fast peritoneal transport develop the lowest serum albumin levels (34), which in turn may be partially explained by a greater protein loss in dialysate (35) and which consequently may influence nutritional status. A direct correlation between peritoneal transport rate and malnutrition, however, has not been demonstrated (36). Alternatively, a higher inflammatory status present in those patients with high peritoneal transport rate (37–39) may explain their higher mortality, as markers of inflammation such as CRP and interleukin (IL)-6 have been clearly demonstrated as predictors of higher mortality in PD (8,40). Inflammation, which seems to be as highly prevalent in our setting (28,41) as in other countries, could also influence the development of malnutrition and atherosclerosis, worsening again the outcome of PD subjects (28,42).

The “Westernization” of life habits is a global trend and it is likely that these habits may lead to changes in diets, tobacco smoking, and decreases in physical activity that will contribute to increasing CV disease in developing countries (43). However, underdeveloped and developing countries still face the problem of inadequate diet and inappropriate sanitary infrastructure, leading to higher prevalence of chronic infectious diseases such as Chlamydia pneumoniae, Helicobacter pylori, HIV, and periodontal pathogens, all of which may represent significant etiological factors linking inflammation to atherogenesis. For example, whereas the prevalence of antibodies to Chlamydia pneumoniae is approximately 40% in the northern hemisphere, it is over 60% in underdeveloped countries (44). Helicobacter pylori is another infectious agent causing a chronic, often silent infection inducing overproduction of cytokines in non-renal patients (45) that may be a significant contributor to the malnutrition–inflammation–atherosclerosis (MIA) syndrome. The prevalence rate of Helicobacter pylori in the developing world is very high; in an African study, the prevalence of this pathogen was found to be 96% (46). In a recent report, Aguilera et al. indicated the association of Helicobacter pylori infection with anorexia, inflammation, and malnutrition in PD patients (47). Moreover, chronic periodontal disease provides a rich source of subgingival microbial and host-response products and may exert its effect over a long period. Other chronic infections that are highly prevalent in developing countries are tuberculosis, HIV, hepatitis B and C, and malaria. The systemic impact of these infections on malnutrition, inflammation, and atherosclerosis needs further study.

TREATMENT PERSPECTIVES

As in the rest of the world, specific anti-inflammatory treatment is not currently available or employed in Latin America. Future availability of more biocompatible PD is expected in our region, and will probably improve the problem significantly. Meanwhile, other treatments have been experimented with. The use of nocturnal intermittent PD was associated with decreases in serum CRP and IL-6 in high transport patients compared to CAPD, due probably to better fluid control, as a decrease in inflammation marker concentration in dialysate was not shown; however, this measure seems to be only temporal as long as residual renal function allows the use of nocturnal intermittent PD (17). Recently, the use of statins was probed as an effective measure to reduce CRP in hemodialysis patients (48), but no information is available in PD. Our group found in a controlled crossover clinical trial (unpublished data) that pravastatin, at a dose of 20 mg/day, significantly decreased CRP compared to placebo in CAPD patients. The use of other measures such as angiotensin–converting enzyme inhibitors, angiotensin receptor antagonists, aspirin, or antioxidants as anti-inflammatory therapy has not been reported in our setting.

INFLAMMATION IN LATIN–AMERICAN PD PATIENTS: AN INTEGRATED VIEW

Finally, countries in Latin America are in epidemiological transition, displaying features of developed and developing countries in many aspects, including health.
Therefore, the immunity alterations already present in uremia (49) may have superimposed some environmental factors (as proposed by the hygiene hypothesis) that could result in a particular inflammatory status different from that observed in developed countries. This latter feature may deserve further investigation.

Latin America, as a region of epidemiological transition, shares those characteristics that complicate health-related issues in the developed and developing world.

**SUMMARY AND CONCLUSIONS**

The use of PD in Latin America in general is low, but some countries employ this therapy in a large proportion of end-stage renal disease patients. Outcomes on PD and the presence of risk factors for morbidity/mortality in PD seem to be similar to those reported in other countries, but the presence of inflammation deserves further research. Apart from the inflammation-associated factors found worldwide in PD patients, the possibility that environmental factors linked to the epidemiological transition characteristic of our countries may superimpose on the already altered immunity of uremia is intriguing and deserves further investigation.

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