Nephrol Dial Transplant (2005) 20: 2311–2315
doi:10.1093/ndt/gfi033
Advance Access publication 26 July 2005

Is there a link between cytomegalovirus infection and new-onset posttransplantation diabetes mellitus? Potential mechanisms of virus induced β-cell damage

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Keywords: cytomegalovirus infection; posttransplantation diabetes mellitus; risk factor

Introduction

Several types of viral infections have been associated with increased risk of diabetes mellitus [1,2]. Enteroviruses are among the most studied environmental triggers of type 1 diabetes, but also other viruses such as the rubella virus, mumps virus, Epstein–Barr virus, varicella zoster virus and cytomegalovirus (CMV) have been suggested to be associated with type 1 diabetes [1].

Recently, hepatitis C virus (HCV) has emerged as an important risk factor of type 2 diabetes and new-onset posttransplantation diabetes mellitus (PTDM) [2]. Insulin resistance secondary to hepatic steatosis, or elevated levels of pro-inflammatory cytokines such as TNF-α [2], may explain the latter relationship. Others have argued that both insulin resistance and insulinopaenia are involved in the pathogenesis of HCV-associated glucose intolerance [3].

In the present article we address a possible relation between CMV infection and new-onset PTDM in renal transplant recipients, and potential pathogenetic mechanisms will be discussed in detail.

This is not a systematic review of the literature. However, to secure the identification of publications addressing the hypothesis of a potential relationship between CMV infection and PTDM in kidney transplant recipients, we searched Medline (OVID Technologies and PubMed, 1966-present), EMBASE (OVID Technologies <1980–2005 Week 19) and the Cochrane Library (all limited to English language), using the combination of the following subject headings: 'diabetes mellitus' and 'cytomegalovirus infection' and 'kidney transplantation'. The majority of reports satisfying the search criteria did not address the hypothesis (eight out of nine reports from Medline, 37/41 from PubMed, 88/92 from EMBASE and 1/1 from Cochrane Library). Taken together, five reports, including three prospective observational cohort analyses [4–6], one retrospective cohort analysis [7] and one case report [8] did address the hypothesis, and these reports are discussed in the first part of this commentary. Literature supporting the second part of this commentary was provided from high quality reports and reviews discussing the potential relationship between virus infections and diabetes mellitus in general and CMV infection, hepatitis C and diabetes mellitus in particular.

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Association between CMV infection and new-onset PTDM

CMV is a β-herpes virus and was first isolated nearly 50 years ago [9]. The virus may infect several organs, and is transmitted through infected body secretions (saliva, cervical fluid, semen, urine, breast milk), blood and organ allografts.

CMV infection remains a major cause of morbidity and mortality after renal transplantation [10]. CMV infection is defined as isolation of the CMV virus or detection of viral proteins or nucleic acid in any blood or tissue specimen. Active systemic CMV infection may be diagnosed as CMV-DNA in plasma by polymerase chain reaction methods or by the detection of CMV-antigen in leukocytes (CMVpp65). At our centre patients with CMV pp65 antigenemia of $\geq$1 per 100 000 leukocytes or >400 CMV-DNA copies per ml plasma are classified as having systemic CMV infection or CMV disease depending on the absence or presence of clinical symptoms and signs of disease [11].

Association between CMV infection and PTDM

In 1985, a case report of CMV-induced diabetes in a renal transplant recipient was published [8]. Approximately a decade later, we suggested a possible association between ganciclovir treated CMV disease and new-onset PTDM [4,12]; {PTDM diagnosed if fasting plasma glucose $\geq$7.0 mmol/l or oral glucose tolerance test (OGTT) 2 h glucose $\geq$11.1 mmol/l}.

More recently, results from a prospective observational cohort study indicated that both asymptomatic CMV infection and CMV disease are independent risk factors for early developing new-onset PTDM (RR = 4, adjusted for rejection, age, family history of diabetes, body mass index and daily prednisolone dose) [5,13]. On average, patients with active CMV infection were characterized by a significantly lower insulin secretion than controls without infection [5,6,13].

Contrasting our findings, a retrospective analysis of Indian patients transplanted between 1989 and 2000 did not reveal any significant association between CMV infection and PTDM [7]. However, this study had some limitations. First, no information on diagnostic methods for CMV was given, and the question whether seropositive, asymptomatic or symptomatic patients were included was not addressed. Moreover, the diagnosis of PTDM was retrospective, and no OGTT was performed.

Importantly, the use of different diagnostic criteria both for PTDM and CMV infection may obscure a possible relationship between these complications. Therefore, implementation of generally accepted guidelines for diagnosis of both conditions is recommended [11,12].

Immunosuppressive drugs

Calcineurin inhibitors and steroids are important risk factors for new-onset PTDM [12]. These drugs, however, also increase the risk of CMV infection, which may in turn cause rejection and subsequent higher doses of diabetogenic immunosuppressive agents. Thus, immunosuppressive therapy makes it difficult to discern any potential independent relationship between CMV infection and PTDM.

Hepatitis C and CMV

Recent clinical reports suggest that CMV infection may be an independent risk factor of graft failure [14] and cirrhosis [15] in HCV seropositive liver transplant recipients. In addition, HCV-RNA may contribute to CMV infection in HCV seropositive renal transplant recipients [16]. Whether the risk of PTDM is potentiated by co-infections with CMV and HCV is at present unknown.

Possible pathogenetic mechanisms of CMV induced β-cell damage

In PTDM, CMV may damage the β-cell in various ways, either (i) directly by viral infection of β-cells with cytopathic effects and induction of apoptosis, (ii) by cytotoxic effects by infiltrating leukocytes, or (iii) by induction of proinflammatory cytokines caused by infection of β-cells, neighbouring pancreatic cells or infiltrating leukocytes leading to altered β-cell function or apoptosis. Possible mechanisms for CMV-induced β-cell damage are illustrated in Figure 1 and discussed below.

CMV infection of β-cells

Case reports from fatal CMV infections in children have shown that the pancreas may be a major target organ as CMV has been discovered in various types of pancreas cells [17], and characteristic inclusion bodies and virus antigen/DNA/RNA have been detected in the β-cells [1]. The virus has also been found in islet cells from both type 1 [18] and type 2 diabetic patients [19]. Contrasting these findings, CMV-DNA could not be detected in pancreas sections from 43 type 2 diabetic patients [20].

Although several CMV gene products have anti-apoptotic effects [21], CMV has also been shown to promote apoptosis in various cells [22,23]. Thus, viral induction of apoptosis may be a possible mechanism leading to β-cell destruction.

Cytotoxic effects by infiltrating leukocytes

Natural killer cells or CMV-specific cytotoxic T-cells may kill virus-infected β-cells. Furthermore, autoreactive T-cells may kill β-cells, e.g. by recognition of the autoantigen GAD 65, which has sequence similarity to the CMV DNA-binding protein pUL57 (molecular mimicry) [24]. Interestingly, a biopsy from a patient with recurrent diabetes after receiving an HLA-identical pancreas graft showed CMV specific T-cells together with insulitis and autoimmune β-cell destruction [25].

Also, activated monocytes, macrophages and granulocytes attracted to CMV-infected pancreatic cells may be cytotoxic by secretion of reactive oxygen or nitrogen intermediates or other toxic compounds.

Cytokines

Proinflammatory cytokines may have a pivotal role in the pathogenesis of both type 1 [26] and type 2 diabetes [27]. Tumour necrosis factor (TNF)-α, interferon (IFN)-γ and interleukin (IL)-1 have deleterious effects on pancreatic beta cells, and TNF-α and IL-6 also induce insulin resistance. The detrimental effect of cytokines on β-cell function may be explained by induction of apoptosis [28], or toxic effects caused

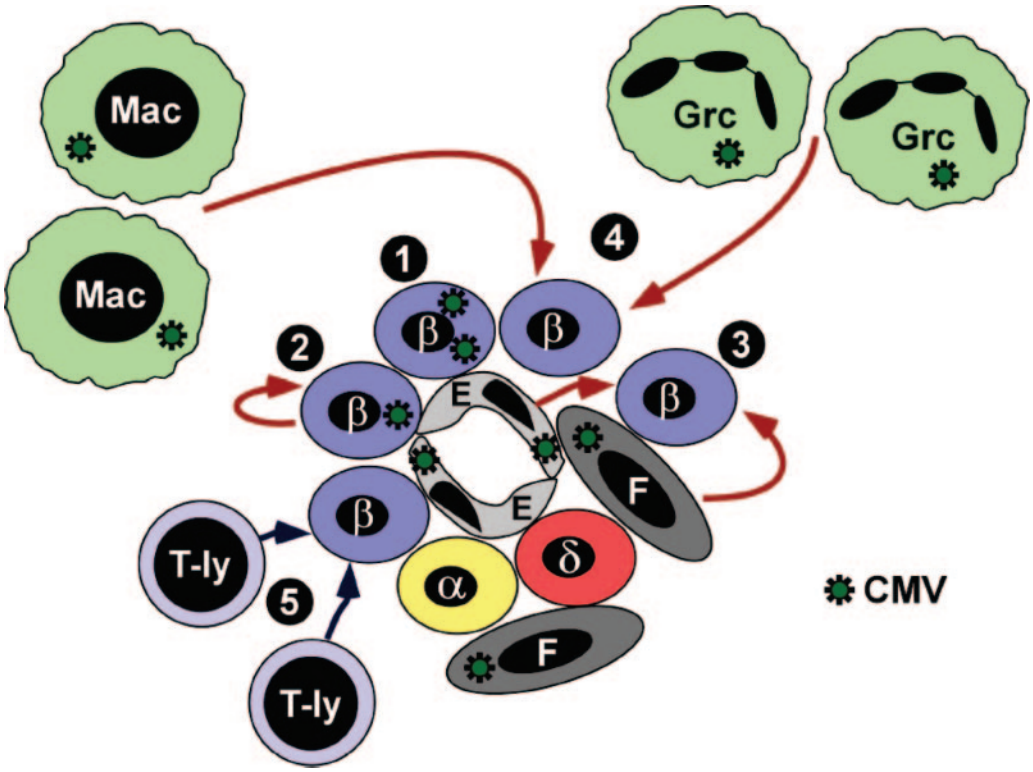

Fig. 1. Possible mechanisms of β-cell damage after CMV infection. 1. CMV-induced cytopathic effects and apoptosis in β-cells due to CMV infection. 2. CMV-infection of β-cells leading to cellular production of proinflammatory cytokines causing apoptosis of the cells. 3. Production of proinflammatory cytokines in other islet cells (e.g. fibroblasts and endothelial cells) due to CMV-infection with subsequent induction of apoptosis in β-cells. 4. Production of proinflammatory cytokines in infiltrating macrophages and granulocytes due to CMV-infection or other activating signals, with subsequent induction of apoptosis in β-cells. 5. CMV-specific T-cells cross-reacting with the β-cell auto-antigens such as GAD-65 (molecular mimicry) with killing of β-cells. Abbreviations: α, α-cell; β, β-cell; δ, δ-cell; E, endothelial cell; F, fibroblast; Mac, macrophage; T-ly, T-lymphocyte; Grc, granulocyte. Red arrows represent proinflammatory cytokines, black arrows represent cytolysis of β-cells by cytotoxic T-cells.

by reactive oxygen or nitrogen species, or elevated free fatty acids and by insulin resistance in the β-cell itself [27].

During CMV infection, various cell types may produce proinflammatory cytokines. (i) First, β-cells may produce low levels of cytokines. Recently, it has been shown that β-cells express toll-like receptors (TLR) 2 and 4 [29]. Furthermore, TLR2 has been implicated in binding of CMV to target cells [30]. Activation of TLR2 in β-cells has been shown to activate NF-κB with subsequent production of low levels of proinflammatory cytokines [29]. (ii) Secondly, CMV infection may also infect neighbouring pancreatic cells, such as endothelial cells and fibroblasts, leading to cytokine production with paracrine effects on β-cells. For example, in endothelial cells, CMV infection leads to increased secretion of IL-1β [31]. (iii) Thirdly, the immune response to pancreatic CMV infection, with infiltration of T-cells, monocytes, macrophages and granulocytes inside the islets, may lead to local production of proinflammatory cytokines contributing to pancreatic β-cell dysfunction [32]. Binding of CMV to monocytes has been shown to induce IL-1β production and release [33]. This is particularly interesting, as it has recently been shown that IL-1β induces TNF-α production in human pancreatic duct cells, which in turn causes apoptosis of β-cells [34].

During the immune response to CMV infection after renal transplantation, the effect on β-cells may depend on the balance between T helper 1 (Th1) and Th2 lymphocytes with a predominant Th1 response leading to β-cell destruction [28]. Among Th1 cytokines, IL-2 stimulates cytotoxic T lymphocytes while IFN-γ activates macrophages to produce proinflammatory cytokines like IL-1β, IL-6 and TNF-α. In renal transplant patients, there are discrepant data regarding the strength of the Th1 response to CMV infection [35,36].

Implications for therapy and/or prophylaxis?

A large placebo-controlled study showed a lower incidence of CMV viremia and disease in renal transplant recipients receiving prophylactic treatment with oral valacyclovir during the first 3 months after

transplantation than in controls [37]. Pre-emptive treatment with intravenous [38] or oral ganciclovir [39] may also impair development of CMV disease in patients with asymptomatic CMV infection.

However, the question of whether a strategy of prophylactic or pre-emptive drug treatment of CMV infection will result in a lower incidence of new onset PTDM remains unanswered. In addition, avoidance of over-immunosuppression and reduced doses of steroids and tacrolimus may lower the incidence of both CMV infection and PTDM [40].

Finally, since antiviral drug treatment may only postpone the occurrence of future CMV infections, blood samples for analysis of CMV may be warranted several months after transplantation. However, the potential relationship between CMV infection and PTDM at this point of time has not been evaluated.

Conclusions

Limited available data indicate that active CMV infection increases the risk of PTDM by inhibiting pancreatic β-cell insulin release. This may be explained by CMV-induced proinflammatory cytokines leading to apoptosis or functional disturbances of the β-cell.

Importantly, further study on the potential causal relationship between active CMV infection and PTDM is needed.

Acknowledgements. Jøran Hjelmesæth received an educational grant from the Norwegian Foundation for Health and Rehabilitation.

Conflict of interest statement. None declared.

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Nephrol Dial Transplant (2005) 20: 2315–2317
doi:10.1093/ndt/gfi046
Advance Access publication 2 August 2005

The predictable effect that renal failure has on H2 receptor antagonists—increasing the half-life along with increasing prescribing errors

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Keywords: histamine H2 antagonists; kidney failure; kidney failure, acute; kidney failure, chronic; medication errors; pharmocokinetics

In this edition of NDT, Manlucu *et al*. [1] present results from a systematic review they performed on dose reducing of histamine 2 receptor antagonists (H2RA) in the presence of renal failure. Fundamentally, they demonstrate that H2RA should be given in lower doses as renal function deteriorates. These results in themselves are not surprising as H2RA are primarily excreted in the urine unchanged, and there is substantial evidence that clearance is reduced with renal failure [2–4]. The more surprising result is that these authors managed to identify 16 published clinical studies investigating an entirely predictable pharmacokinetic occurrence, including one published as recently as 2003. The implication of this is that despite the expected effect renal failure would have on the half-life of these drugs, this class of medication continues to be prescribed at inappropriately high doses or frequency.

The inappropriate prescribing of H2RA has been demonstrated in a study performed in 1996 on 100 consecutive patients receiving the drug intravenously

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