

New-Onset Posttransplantation Diabetes Mellitus: Insulin Resistance or Insulinopenia?

Impact of Immunosuppressive Drugs, Cytomegalovirus and Hepatitis C Virus Infection

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Abstract: Restoration of renal function may ameliorate uremia induced insulin resistance. Therefore it seems a paradox that new-onset posttransplantation diabetes mellitus (PTDM) is a frequently observed complication after renal transplantation. The incidence varies between 2 and 50% depending on the population under study, criteria for the diagnosis of diabetes and the time of follow up.

This review addresses recent findings on transplant specific risk factors and pathogenesis of PTDM after solid organ transplantation, and we focus on the following issues:

1. The relative impact of insulin resistance and insulinopenia in the pathogenesis of PTDM.
2. The role of immunosuppressive drugs with special emphasis on calcineurin inhibitors (cyclosporine A, tacrolimus) and steroids.
3. The possible roles of cytomegalovirus and hepatitis C infections.

Conclusions: New-onset PTDM is characterized by a variety of clinical manifestations, ranging from predominantly insulin resistance which can be handled with lifestyle intervention, to β -cell failure requiring insulin treatment. The etiology is multi-factorial, but diabetogenic immunosuppressive drugs are of major importance. Future studies should therefore address the effects of different immunosuppressive regimens on the incidence of PTDM. In addition, the impact of cytomegalovirus infection and hepatitis C on PTDM needs further evaluation.

Keywords: Diabetes mellitus, transplantation, insulin, immunosuppression, steroids, virus infection.

Chronic Kidney Disease and Diabetes Mellitus

Diabetes accounts for about 40% of new cases of end-stage renal disease (ESRD) in the U.S. and is the most common single cause of ESRD in the U.S. and Europe [1]. Type 2 diabetic patients constitute over half of the diabetic subjects starting on dialysis [1].

Moreover, patients with chronic renal failure show reduced insulin secretion and degradation, gluconeogenesis and insulin sensitivity (IS), and end stage renal failure is probably an important risk factor for impaired glucose tolerance (IGT) [2].

There is some evidence that the normalization of renal function after renal transplantation is accompanied by improvement of IS and glucose tolerance in transplant recipients [3-4]. Unfortunately, despite this potential beneficial effect, new-onset posttransplantation diabetes

mellitus (PTDM) and IGT are still commonly observed complications after renal transplantation [4-7].

Accumulating evidence during the last decade demonstrates that PTDM increases the risk of all cause mortality and cardiovascular disease [7-11]. In addition, reduced graft survival has been reported to be associated with PTDM [7, 11], the latter possibly in part caused by allograft diabetic nephropathy [12].

Incidence of New-Onset PTDM

In the early years of transplantation high-dose glucocorticoid immunosuppressive regimens were used to prevent acute rejection episodes, and steroid induced diabetes was reported in up to 50% of recipients [13]. After the introduction of the steroid sparing calcineurin inhibitors two decades ago, the reported incidence of PTDM has shown great dispersion, ranging from 2 to 50% [reviewed in 14]. Different study designs and various definitions of PTDM may to some extent explain the difficulties in obtaining a reliable estimate of the true incidence. However, transplant physicians and endocrinologists have recently agreed that

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PTDM should be diagnosed according to current guidelines as suggested by the "Expert Committee on the Diagnosis and Classification of Diabetes Mellitus" [15-18]. Nonetheless, the prevalence of PTDM will probably increase in parallel with the growing number of overweight and older renal transplant recipients observed during the last decade [19].

A recent meta-analysis of 16 studies including a total of 3,043 patients receiving a calcineurin based immunosuppressive regimen, showed that 13.4% of the recipients developed PTDM during the first year after transplantation [20]. In this analysis, PTDM was defined as new-onset "insulin dependence", in other words treatment with insulin in previously non-diabetic individuals. A large-scale US-population study of self reported diabetes by Kasiske *et al.* demonstrated a cumulative incidence of PTDM increasing from 9% to 16% and 24% at 3, 12 and 36 months posttransplant respectively [7].

Few studies have implemented OGTTs to diagnose posttransplant glucose intolerance. However, in a carefully conducted prospective observational study of 114 Korean living donor related kidney transplant recipients, glucose tolerance was assessed one week before and 9-12 months after transplantation [4]. All patients had normal glucose tolerance before transplantation, 24% developed PTDM and 46% IGT during the first year after transplantation [4]. Seven years ago, we found a high incidence of PTDM (18%) and IGT (31%) in a series of 167 consecutive previously nondiabetic patients, the majority Caucasian, 3 months after transplantation [6]. Taken together, the 1-year cumulative incidence of PTDM probably varies between 5 and 25% in different transplant populations.

How to Measure Insulin Sensitivity and Insulin Secretion In Solid Organ Transplant Recipients

The two gold standard methods to measure insulin action and secretion, hyperinsulinemic euglycemic glucose clamp and hyperglycemic glucose clamp respectively, are cumbersome and impractical to use in epidemiological studies. Therefore, in larger studies, different surrogate measures such as IS and insulin release indexes derived from fasting blood glucose, insulin, triglycerides, free fatty acid levels or an OGTT have been implemented [21-28]. The HOMA-IS index and QUICKI were reasonably well correlated with the clamp derived IS index in a study of kidney-pancreas transplanted patients ($r=0.47$ for both) [21]. We validated 8 surrogate measures of IS against the clamp method in renal transplant recipients [22, 23]. This study revealed a moderate correlation between both the HOMA-R [24], the index suggested by McAuley [25] and the clamp derived index ($r=-0.30$, $p<0.05$ and $r=0.43$, $P<0.01$ respectively). However, our own OGTT derived index modified from Stumvoll *et al.* [22, 26] correlated best with the gold standard method ($r=0.58$, $P<0.001$).

To date, several surrogate estimates (indexes) of insulin release have been validated in the general population. Some of these indexes have been documented to correlate well ($r=0.57-0.74$) with both β -cell function in general, and more specifically with first phase and second phase insulin release, as measured by hyperglycemic clamp studies in patients with varying degrees of glucose tolerance [26-28].

INSULIN RESISTANCE IN THE PATHOGENESIS OF PTDM

Although some reports indicate that IS improves after renal transplantation [3, 4], renal transplant recipients are on average more insulin resistant than healthy controls [29]. Ekstrand *et al.* demonstrated that the mean total glucose disposal during hyperinsulinemic euglycemic glucose clamp was 25% lower in normoglycemic kidney transplant recipients treated with 8 ± 2 mg methylprednisolone/day than in age and sex matched controls [29].

Possible Pathogenetic Mechanisms of Posttransplant Insulin Resistance

Glucocorticoids and Body Weight

The diabetogenic effect of glucocorticoids is primarily caused by insulin resistance followed by enhanced gluconeogenesis in the liver and decreased glucose uptake and glycogen synthesis in skeletal muscle cells [30, 31]. There is some evidence to support the notion that these side effects are dose dependent, and that lowering of steroid dose may be associated with improved insulin sensitivity [22, 32]. In addition, the common combination treatment of cyclosporine A (CsA) and prednisolone is accompanied by higher serum steroid concentration than treatment with prednisolone alone, due to mutual inhibition of metabolism [33]. However, more indirect adverse effects of steroids on weight change, deposition of intra-abdominal fat and appetite [34-36], may also contribute to posttransplant insulin resistance.

It is generally accepted that overweight causes insulin resistance, but IS after transplantation is also negatively influenced by other risk factors such as hypertension, antihypertensive therapy and plasma lipids [22]. A weight gain of 5-15% is common during the first posttransplant year [34, 35]. This may be partly related to alleviation of the pretransplant uremic catabolic state, but in fact very few patients are underweight before transplantation, and an increasing number of overweight transplant recipients has been recognized during the last years [19]. The prevalence of obese transplant patients ($BMI \geq 30 \text{ kg/m}^2$) at time of kidney transplantation in the United States doubled in the period 1987 to 2001, and is even higher than in the general population (2001; 25 vs 20%) [19].

It has been shown that BMI "Fig. (1)", daily prednisolone dose "Fig. (2)", hypertension, number of antihypertensive agents and the use of diuretics or β -blockers, all were associated with insulin resistance 3 months after transplantation [22]. A trend towards lower IS was observed in patients with increasing levels of triglycerides ($P=0.050$), ganciclovir treated CMV infections ($P=0.067$) and in recipients using ACE inhibitors ($P = 0.077$). However, age, gender, a family history of diabetes, daily dose of CsA and CsA whole blood trough levels did not influence IS significantly. The multivariate analysis showed that increasing BMI, daily prednisolone dose and triglycerides are independent predictors of increasing insulin resistance.

Glucocorticoid treated renal transplant recipients seem to be particularly prone to develop cardiovascular metabolic syndrome. De Vries and co-workers documented that nearly

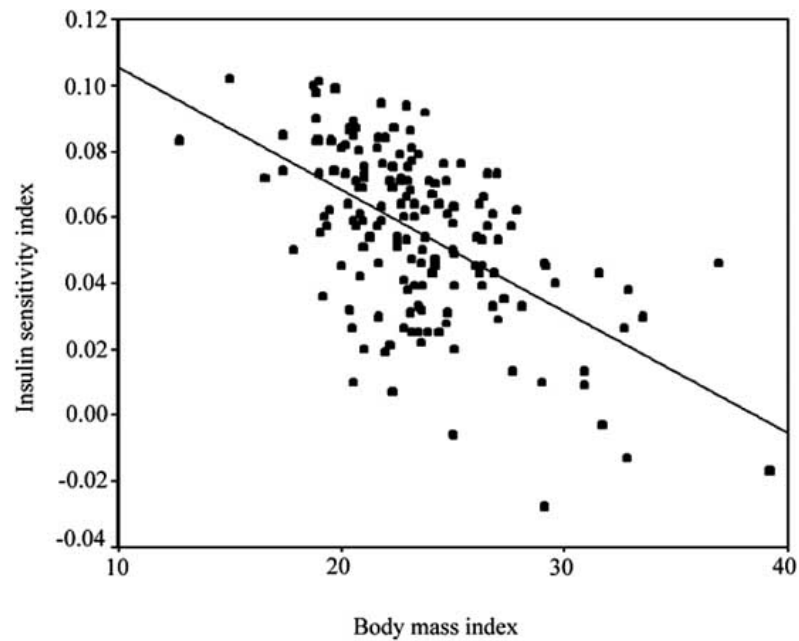


Fig. (1). Correlation between BMI (kg/m^2) and the OGTT derived insulin sensitivity index (ref 22), Linear regression; $r^2=0.31$, $P<0.001$.

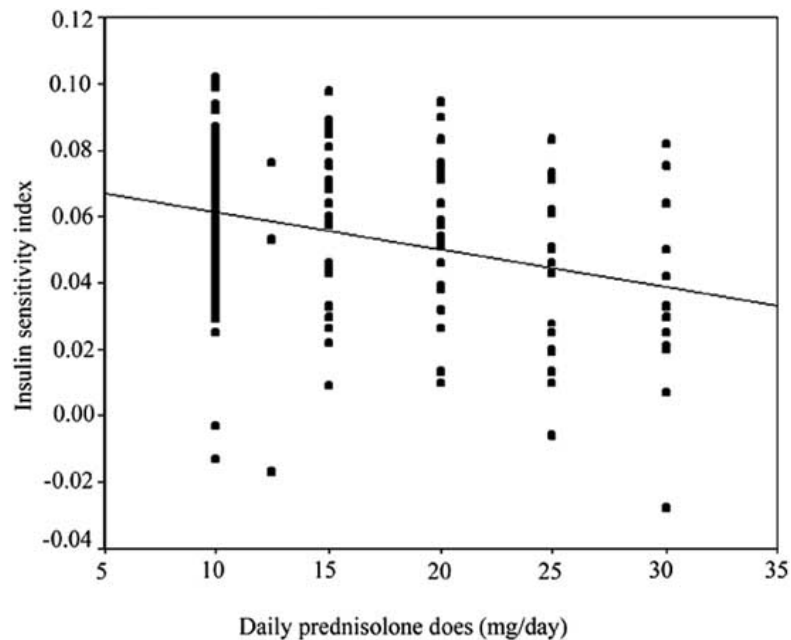


Fig. (2). Correlation between daily prednisolone dose and the OGTT derived insulin sensitivity index (ref 22), Linear regression; $r^2=0.09$, $P<0.001$.

two thirds of a large renal transplant population (383 out of 606 patients) suffered from metabolic syndrome at a median of 6 years after transplantation [37]. We have previously reported a high incidence of early (< 3 months) posttransplant glucose intolerance associated with a lower HDL cholesterol level, higher triglycerides and higher 2-hour insulin concentrations [38].

Does Steroid Dose Reduction or Withdrawal Improve Insulin Sensitivity?

Steroid tapering or withdrawal has been reported to improve IS in some studies [32, 39, 40]. In a Canadian study including 26 renal transplant recipients [39], a significant reduction in fasting insulin was observed after withdrawal of

prednisolone (10 mg/day). In contrast, most metabolic benefits of prednisolone dose reduction were seen during tapering down to 5 mg/day, whereas no significant further benefits were observed after steroid withdrawal in a recent report [41].

A recently published prospective study of 46 Norwegian renal transplant recipients assessed changes in insulin resistance with the hyperinsulinemic euglycemic glucose clamp method at 3 and 12 months after transplantation [42]. This study showed that lowering the daily prednisolone by an average of 7 mg (mean change from 16 to 9 mg, corresponding to 0.22 – 0.12 mg/kg) was associated with improved insulin action. In contrast, withdrawal of 5 mg prednisolone in a smaller group of stable renal transplant recipients (n=11) did not improve IS significantly [42].

Possible Mechanisms for Improved Insulin Sensitivity After Tapering of Steroids

In 1995, Steiger *et al.* [43] addressed the effects of posttransplant prednisolone dose reduction on protein, glucose and fat metabolism. In a prospective observational longitudinal study it was demonstrated that oxidation of fatty acids was significantly lower in renal transplant recipients six weeks after transplantation than in controls. However, fatty acid oxidation in transplant recipients increased to values similar to controls 14 months later. A linear relationship was found between reduction in daily prednisolone dose (0.45 to 0.15 mg/kg; 30 – 10 mg/day) and enhanced fatty acid oxidation.

Interestingly, several recently published studies add support to the hypothesis that impaired fatty acid oxidation, enhanced intracellular lipid accumulation and mitochondrial dysfunction in muscle cells, represent important pathogenic mechanisms for both inherited and acquired insulin resistance and diabetes [44-46]. Similar mechanisms may explain the association between hepatic steatosis and insulin resistance [47, 48], and it has been shown that dexamethasone inhibits hepatic fatty acid -oxidation in mice [49].

In view of these findings, one may speculate that inhibition of fatty acid oxidation is involved in the pathogenesis of steroid induced insulin resistance after solid organ transplantation.

Calcineurin Inhibitors

The steroid sparing calcineurin inhibitor CsA was introduced in the early eighties, and a second calcineurin inhibitor, tacrolimus, was launched a decade later. The addition of calcineurin inhibitors to immunosuppressive protocols has resulted in major improvements of short-term graft survival during the last two decades [reviewed in 50].

The literature is sparse, but some studies have suggested that calcineurin inhibitors impair peripheral IS [51-54]. One study showed that *in vitro* addition of CsA to skeletal muscle cells from mice, resulted in a significantly lower insulin induced glucose uptake as compared with controls [53]. Interestingly, blockade of calcineurin activity promoted the transformation from type I slow-twitch skeletal muscle fibers

to the less insulin sensitive type II fast-twitch skeletal muscle fibers in rat soleus muscle [55]. Conversely, calcineurin activation in transgenic mice has been shown to be associated with increased insulin sensitivity, glucose uptake, amino acid uptake and fatty acid oxidation [56]. These findings may have relevance for future treatment of both type 2 diabetes and PTDM, but further studies are needed to address this issue in more detail.

Wahlstrom *et al.* demonstrated a dose dependent inhibition of insulin release and clamp derived insulin resistance in dogs treated with CsA [57], and withdrawal resulted in reversal of these changes. However, we could not confirm any dose dependent adverse effect of CsA on IS or insulin release in renal transplant recipients [22, 58].

Sirolimus and Mycophenolate

To our knowledge, no clinical study has addressed IS in individuals treated with the mammalian target of rapamycin (mTOR)-inhibitor sirolimus or the IMPdh-inhibitor mycophenolate. However, the results of two recent studies on insulin action in cell cultures of 3T3-L1 adipocytes indicate that rapamycin (sirolimus) partly prevents insulin resistance induced by chronic insulin treatment [59], and mTOR itself may play a central role in the development of insulin resistance by phosphorylating serine 307 of the insulin receptor substrate (IRS)-1 [60].

INSULINOPENIA IN THE PATHOGENESIS OF PTDM

The results from a hyperglycemic clamp study of 24 renal transplant recipients, of whom 14 had PTDM and 10 normal glucose tolerance (NGT), indicate that both inadequate insulin secretion and insulin resistance are necessary for the development of PTDM in Caucasian transplant recipients [29]. Similar findings were reported in the Korean study mentioned previously: The group of patients who developed PTDM had a significantly lower AUC-insulin and a higher proinsulin/insulin ratio than the NGT-group both before and after transplantation [4]. In a subgroup of patients gaining > 3% weight (n=68, 60%), posttransplant IS was significantly lower in the PTDM- than the NGT-group, whereas no significant difference in insulin action was found between PTDM- and NGT-patients in the “non-weight gain” group.

We addressed the relative importance of defects in OGTT derived I_{Sec} and insulin action in the pathogenesis of PTDM and IGT/impaired fasting glucose (IFG) in a Caucasian renal transplant population of 167 consecutive previous non-diabetic recipients at 3 months after renal transplantation [61]. In addition, the prognostic impact of impaired I_{Sec} and IS on glucose tolerance one year later was evaluated. The median I_{Sec} and IS was significantly higher in patients with NGT compared with IGT-patients, and the patients with IGT had higher IS and I_{Sec} than those with PTDM (Table 1). The results were essentially unaltered after adjustments for confounding factors and assessment of insulin release as disposition index (product of first phase I_{Sec} and IS). Most patients who had NGT at baseline, stayed normoglycemic one year later. Half of those with PTDM at baseline improved to IGT/IFG or NGT, and half of those with

Table 1. (modified from ref 61)

Insulin secretion and insulin sensitivity in the three groups of patients with varying degrees of glucose tolerance at ten weeks after renal transplantation (n=167).

Values are given as medians. Kruskal-Wallis test.

	PTDM (n=29; 17%)	IGT/IFG (n=55; 33%)	NGT (n=83; 50%)	P
First phase insulin release (Secr _{1,phase})	475	983	1350	<0.001
Second phase insulin release (Secr _{2,phase})	164	276	353	<0.001
Insulin sensitivity (ISI _{TX} *10 ⁻²)	4.8	6.5	9.0	<0.001

Table 2. (modified from ref 61)

Baseline insulin secretion and insulin sensitivity in glucose intolerant patients categorized according to changes in glucose tolerance during the first year after transplantation.

Secr_{1,phase} = First phase insulin release

Secr_{2,phase} = Second phase insulin release

Group 1; Patients with PTDM at baseline who improved to NGT or IGT at follow up.

Group 2; PTDM at baseline and unchanged at follow up.

Group 3; IGT/IFG at baseline improved to NGT at follow up.

Group 4; IGT/IFG at baseline and IGT/IFG or PTDM at follow up.

Values are given as medians. Mann-Whitney test.

	PTDM at baseline		P	IGT/IFG at baseline		P
	Group 1 (Improved; n=12)	Group 2 (Unchanged; n=9)		Group 3 (Improved; n=16)	Group 4 (Unchanged / worsened; n=13)	
Secr _{1,phase}	674	143	< 0.001	1279	727	0.004
Secr _{2,phase}	209	75	< 0.001	344	211	0.005
ISI _{TX} (*10 ⁻²)	4.8	4.5	0.831	5.4	7.2	0.023

IGT/IFG improved to NGT during the observation time (Table 2). PTDM-patients who improved their glucose tolerance during the first year after transplantation, had a significantly higher baseline median first phase insulin release, disposition index and second phase insulin release than the patients who remained diabetic (Table 2). Moreover, the recipients with IGT/IFG at baseline who improved to NGT during the first year after transplantation, had a significantly higher baseline median first phase and second phase insulin release than patients remaining glucose intolerant at follow up.

Kidney transplant recipients who developed new-onset PTDM during a 6-years prospective observational study, were characterized by a significant decline in the OGTT derived first phase and second phase insulin release (58% and 47% respectively, p=0.005 for both) [32]. On the other hand, patients who normalized their glucose tolerance from PTDM or IGT at baseline to NGT at follow-up, increased their IS significantly (68%, p=0.002) without significant alterations in ISec.

Thus, β -cell dysfunction seems to be of major importance in the pathogenesis of new-onset PTDM [4, 29, 32, 61], although insulin resistance is also involved. Importantly, this hypothesis is in line with the generally accepted

understanding of the pathogenesis of type 2 diabetes [62, 63].

DETERMINANTS OF INSULIN RELEASE

Calcineurin Inhibitors

Several lines of evidence from in vitro studies in human and animal models indicate that both CsA and tacrolimus may impair pancreatic β -cell function [5, 20, 40, 51, 57, 64, 65]. This adverse effect may be mediated through diminished pancreatic β -cell volume, reduced insulin synthesis or impaired insulin release.

The majority of published studies supports the hypothesis that tacrolimus has a greater diabetogenic propensity than CsA [7, 20, 66, 67]. A recently published meta-analysis of 16 prospective randomized comparative studies of solid organ transplant recipients (n=3,043), concluded that the incidence of "insulin dependent" PTDM was higher in patients receiving tacrolimus than CsA (16.6% vs 9.8%) [20]. This trend was similar in renal, liver, heart and lung transplant recipients.

There is also some evidence supporting the notion that the detrimental effect of calcineurin inhibitors on pancreatic β -cell function is dose dependent [5, 40, 64, 65]. However,

we are not aware of any clinical study documenting any correlation between CsA dose or CsA blood trough concentration and impaired insulin secretion. It has been argued that the inhibitory effect of tacrolimus on insulin secretion may be caused by high blood trough levels, and that lowering of trough level is associated with improved pancreatic β -cell function [40]. However, larger epidemiological studies do not support this theory [66, 67]. In a Canadian study of nearly 400 kidney transplant recipients tacrolimus and CsA trough level were not associated with PTDM [66]. Further, a recent epidemiological study using data from the United States Renal Data System, did not support the hypothesis that tacrolimus dose reduction lessens the risk of developing PTDM [67].

African Americans may be particularly susceptible to the diabetogenic effects of tacrolimus. In a study by Neylan, more than one third (37%) of African American renal transplant recipients developed PTDM at one year after tacrolimus treatment, as compared with a PTDM incidence of 12% in Caucasian patients [68]. African Americans also required a higher dose of tacrolimus to achieve comparable plasma concentrations of the drug.

Further studies are needed to give a definite answer to the diabetogenic potential of tacrolimus vs CsA. A randomized head to head comparison study between the two calcineurin inhibitors including OGTTs at 3 and 6 months is currently ongoing [69], and the results are expected to be published in 2006.

Other Risk Factors of Impaired Insulin Release

Recently, we addressed the impact of several candidate risk factors for impaired β -cell function such as age, family history of diabetes, cytomegalovirus (CMV)-disease, whole blood CsA and different antihypertensive drugs [58]. Increasing age was strongly and independently associated with impaired insulin secretion even after adjustment for IS ($P=0.001$). Insulin release, as assessed in the linear regression model, declined about 50 % from the age of 20 to 80. CMV-disease and treatment with furosemide were also both independently associated with β -cell dysfunction. However, neither dose nor trough level of CsA was associated with impaired insulin release. This does not necessarily imply that pancreatic β -cell function is unaffected by CsA, but indicates that any such adverse effect is not altered in the normal dose range following renal transplantation.

DIFFERENT CLINICAL PATTERNS OF PTDM

In view of recent findings from studies addressing the pathogenesis of PTDM [4, 6, 29, 32, 42, 58, 70], one may argue that at least three different clinical patterns of PTDM can be observed.

The predominant characteristic of the first pattern of early developing (< 3-6 months after transplantation) PTDM is a pronounced insulin resistance induced by high dose glucocorticoid therapy. These patients seldom need hypoglycemic drugs, and an OGTT may be necessary for the diagnosis. Although many of these patients normalize their

glucose tolerance after tapering of steroids, they may be at increased risk for later recurrence of PTDM as described below.

Both insulin resistance and insulinopenia characterize the second manifestation of early developing PTDM. Treatment with insulin or oral hypoglycemic drugs is indicated in the majority of patients, and glucose tolerance does not improve significantly even after tapering of immunosuppressive therapy.

A third pattern of later developing (>6 months) PTDM appears despite a stable low-dose immunosuppressive therapy (including steroids or not). This pattern of PTDM may develop in predisposed patients, for example individuals with IGT/IFG, increasing body weight, or family history of diabetes. This group of patients is characterized by varying degrees of insulin resistance and impaired insulin secretion, and hypoglycemic drug therapy is often indicated.

POSSIBLE ROLE OF CMV INFECTION IN THE PATHOGENESIS OF PTDM

Recurrent CMV infection is highly prevalent after solid organ transplantation and remains an important cause of patient morbidity and mortality [71, 72]. If no anti-CMV prophylaxis is given, approximately two thirds of renal transplant recipients develop active systemic CMV infection [73]. To diagnose CMV infection, isolation of the CMV virus or detection of viral proteins or nucleic acid in any blood or tissue specimen is necessary [72]. From a clinical point of view it is relevant to distinguish between two patterns of active systemic CMV infection, either symptomatic CMV disease or asymptomatic CMV infection [73].

We have previously suggested that ganciclovir treated CMV disease may be an independent risk factor for PTDM [6], and that CMV disease may be associated with insulin resistance [22] and impaired insulin release [58]. In a recent publication, we demonstrate that patients with asymptomatic CMV infection have a four-fold increased risk of PTDM, and that asymptomatic CMV infection is associated with impaired insulin secretion as compared to patients without CMV infection [74]. Different pathogenic mechanisms may explain the potentially detrimental effect of CMV on pancreatic β -cells. First, CMV infection of the β -cell may lead to apoptosis induced by viral proteins. Second, apoptosis in β -cells may be triggered by pro-inflammatory cytokines derived from the β -cell itself, from other infected islet cells or from infiltrating leukocytes [75, 76]. Third, CMV has been suggested to be involved in the pathogenesis of type 1 diabetes through T-cell crossreactivity with the β -cell autoantigen glutamic acid decarboxylase (GAD65) [77, 78]. However, no PTDM patients in our material were anti-GAD positive [74], which may reflect different pathogeneses of PTDM and type 1 diabetes.

Prophylactic treatment with oral valganciclovir during the first 3 months after transplantation significantly reduced the incidence of both CMV viremia and disease in a large placebo-controlled study including about 600 renal transplant recipients [79]. A strategy of pre-emptive treatment of patients with asymptomatic CMV infection with

intravenous [80] or oral ganciclovir [81] has also shown to be effective in reducing the incidence of CMV disease. However, whether treatment of CMV infection reduces the incidence of new onset PTDM is unknown. Also, altered immunosuppressive regimens with reduced use of steroids and calcineurin inhibitors may affect the incidence of CMV infection and PTDM, as suggested in a recent study [82]. Further studies are however mandatory to test the hypothesis of a potentially causal relationship between CMV infection and new-onset PTDM.

POSSIBLE ROLE OF HEPATITIS C IN THE PATHOGENESIS OF PTDM

During the last decade a strong and consistent association between chronic HCV infection and type 2 diabetes has been unraveled [83-89, reviewed in 90]. Recently published data from the Third National Health and Nutrition Examination Survey showed that persons with hepatitis C (HCV) infection, were more than three times more likely to have type 2 diabetes mellitus than those without infection [83]. Also, classical autoimmune type 1 diabetes has been reported after treatment of hepatitis C with interferon (IFN)- α [91]. In addition, HCV seropositive liver and kidney transplant recipients seem to be at increased risk for developing new-onset PTDM [92-95].

The underlying mechanisms for the relation between HCV and diabetes mellitus have not been established, but insulin resistance is probably of major importance [84-86, 96], either due to hepatic steatosis or the adverse effect of elevated levels of pro-inflammatory cytokines such as TNF- α on insulin signaling activity. In a recent report, patients with hepatitis C and diabetes had a marked activation of the TNF- α system, significantly higher than a control group with HCV infection and no diabetes [86]. Moreover, administration of anti-TNF- α restored insulin sensitivity in a mouse model transgenic for the HCV core gene [84]. Interestingly, the clamp studies of the transgenic mice revealed hepatic insulin resistance, whereas the glucose uptake in muscle was normal [84]. In contrast, the authors of a recently published study argue that both insulin resistance and β -cell dysfunction seem to be involved in the pathogenesis of HCV associated glucose intolerance [97].

Association Between Hepatitis C and Diabetes in Patients with Liver Disease

The first publication indicating a possible relation between HCV infection and diabetes in patients with liver cirrhosis was published in 1994 [88]. Four years later, Knobler *et al.* demonstrated a significantly higher prevalence of PTDM in HCV (+) liver transplant recipients than in recipients with other types of liver disease (62 vs 9%, $P < 0.001$) [92].

Recently, a high prevalence (38%) of new-onset PTDM, defined as treatment with oral hypoglycemic agents and/or insulin, was reported in a series of 136 previously non-diabetic patients receiving a liver transplant between 1991 and 1998 with a mean follow up of about 4 years [93]. A total of 25 out of 39 (64%) HCV (+) patients as compared to 27 of 97 (28%) HCV (-) patients developed PTDM ($P = 0.0001$). The authors identified two groups of HCV (+)

PTDM-patients with different clinical courses; the first group developed diabetes at the time of or after the diagnosis of recurrent allograft hepatitis, whereas the other developed PTDM in the absence of or before recurrent hepatitis. Interestingly, the majority of the patients in the former group (11/12) received antiviral therapy (IFN- α +/- ribavirin), and the four patients who responded adequately to therapy were either withdrawn from insulin ($n = 2$) or had their insulin doses reduced to less than half. In contrast, no significant improvement of glucose tolerance was observed in the "non-responder" group [93]. In line with these findings, treatment with IFN- α was associated with improved glucose tolerance in a report of non-diabetic patients with HCV-induced liver disease [89].

Association Between Hepatitis C and PTDM in Kidney Transplant Recipients

In a recent large retrospective series of 427 kidney transplant recipients, including 71 HCV (+) patients, a 5-fold increased risk of PTDM was documented in HCV (+) recipients as compared to HCV (-) patients [94]. Interestingly, the incidence of PTDM was nearly 60% in tacrolimus treated HCV (+) recipients, as compared to 8% in CsA treated HCV (+) recipients. In contrast, the incidence of PTDM did not differ significantly between CsA and tacrolimus treated HCV (-) recipients (9% vs 10%, $P = 0.521$). Although two recent reports could not verify any significant association between HCV-infection and PTDM in kidney transplant recipients [98, 99]; a trend towards a relationship between HCV and PTDM was observed in both.

Finally, results from recent clinical trials indicate that CMV infection may be an independent risk factor for graft failure [100] and allograft cirrhosis [101] in HCV seropositive liver transplant recipients. In addition, HCV-RNA may also contribute to CMV infection as suggested by the authors of a recent study of HCV seropositive renal transplant recipients [102]. In this study HCV-RNA was correlated with CMV-Ag, and the former was detected earlier than the latter (1 v 2 months after transplantation) [102].

CONCLUSIONS

New-onset PTDM is characterized by a variety of clinical manifestations, ranging from predominantly insulin resistance that can be handled with lifestyle intervention, to β -cell failure requiring insulin treatment. Thus, PTDM and type 2 diabetes possess similar clinical and pathogenetic features. The major difference between these two types of diabetes is the transplant specific risk factors characterizing the former, namely immunosuppressive drugs and viral infections as discussed in this review.

Thus, the effects of changes in immunosuppressive regimens or prophylactic treatment of virus infections [103] on the incidence of PTDM should be addressed in future studies.

ACKNOWLEDGEMENTS

Thanks to Bartłomiej Jozef Witczak and Ida Hjelmæsæth for valuable comments after reviewing the manuscript. Jøran

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

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