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Post Transplant Diabetes Mellitus after Renal Transplantation: The Emerging Clinical Challenge

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INTRODUCTION

The incidence of type II diabetes mellitus is increasing in the general population and worldwide represents a major clinical and economic challenge. Similarly, the incidence of post transplant diabetes mellitus (PTDM) appears to be increasing and represents a real challenge to the success of transplantation, impacting heavily on graft function and survival and patient morbidity and mortality, as well as on quality of life and healthcare costs. Furthermore, development of diabetes after transplantation is a major determinant of the increased cardiovascular morbidity and mortality observed in transplant patients imposing a greater relative risk than hyperlipidaemia and hypertension in this patient population[1]. The additional risk for serious macrovascular and microvascular complications comparable to type I and type II diabetes mellitus compound the already complex matter to the transplant recipient, adding to the post transplant care requirements and imposing further significant economic burden on the healthcare systems.[2]

Renal transplantation has significantly improved the survival of patients with end stage renal disease (ESRF).[3] Despite consistent improvements in transplant graft survival with the advent of new immunosuppressive drugs, particularly the calcineurin inhibitors (CNIs), the graft half life has not increased as much as expected. The introduction of Cyclosporin (CSA) led to a significant improvement in patient morbidity and mortality.[4] However, death with a functioning graft has emerged as one of the major causes of graft loss amongst renal transplant recipients with a switch from infection as an important determinant of mortality[6] to cardiovascular disease.[5,7] The path of physiology of cardiovascular disease in renal transplant recipients is likely to be multi factorial and various metabolic and cardiovascular disturbances have been identified in association with immunosuppressive regimens which can contribute to cardiovascular risk. Nevertheless, it is clear that PTDM underlying associated disturbances of glucose metabolism such as insulin resistance present a significant risk factor for the patient mortality and graft loss.[8,9]

PTDM is diabetes mellitus which develops de novo after transplantation and is also known as new onset diabetes mellitus (NODM). PDTM is not unique to renal transplantation and is an important complication following other solid organ transplants.[10,11] The path of physiology has important similarities to type II DM in that there is co--existing insulin resistance and insulin hyposecretion.[12,13] This paper is a review of PTDM to include the incidence and prevalence, clinical diagnosis, pathophysiology including contribution of immunosuppressive agents and general management principles.

INCIDENCE AND PREVALENCE

The reported incidence of PTDM has ranged from 2.5%[14] to 57.6%.[15] This is attributable to a number of factors. Montori et al. analysed 12

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studies examining the incidence of PTDM and found that differences in immunosuppression regimen explained 74% of this variability.[16] Other factors include variations in the diagnostic criteria for PTDM, failure to identify pre-transplantation diabetes and differences in study follow up times.[17] In a large retrospective analysis of 11,659 patients on the USRDS database who had received their first transplant between 1996 and 2000, the cumulative incidence of PTDM was 9.1%, 16% and 24% at 3, 12 and 36 months following transplantation.[18] However it has been consistently demonstrated that the majority of cases of PTDM develop in the first year following transplantation.[14] Nevertheless there is also some evidence that the incidence of PTDM may be increasing.[8]

DIAGNOSING PTDM

Diagnosing PTDM can be difficult. Several patients develop a transient hyperglycaemia in the early days following transplantation, which is probably due to a combination of increased catabolism post-operatively, high dose corticosteroid and calcineurin therapy. Sometimes, this can be severe enough to warrant treatment with insulin. Hence, many studies in the past have defined PTDM on the basis of requiring an oral hypoglycaemic or insulin therapy.[8,19,20] In recent years, there has been a strong advocacy to use current WHO/ADA criteria for the diagnosis of diabetes mellitus to diagnose PTDM as well.[21] Whilst this may identify more patients with PTDM, it could have a positive influence on patient care and highlight cardiovascular risk factors. However, it is also important to recognise that in some patients disturbance in glucose tolerance may only be transient,[22] and the persistent label of PTDM, which probably carries additional stigma to that of being a renal transplant recipient may not be appropriate. Nevertheless, confirmation of a return to normal glucose tolerance requires long term surveillance.

RISK FACTORS FOR PTDM

Various risk factors for PTDM have been identified. Non-modifiable risk factors include increasing age (> 45 years), Afro-Caribbean or Hispanic ethnicity and a family history of Type II diabetes.[18] Modifiable risk factors include corticosteroid therapy,[23] obesity[18] and calcineurin inhibitor therapy.[19] Several studies have demonstrated a higher incidence of PTDM in patients treated with Tacrolimus based regimens compared to Cyclosporin.[18,20,24,25] Recent studies have shown that a lower insulin secretory capacity before transplantation may be predictive without developing PTDM.[26,27] Moreover, Hepatitis C infection has also been identified as a risk factor for PTDM particularly in Tacrolimus treated patients.[28]

PATHOPHYSIOLOGY OF PTDM

It is well established that, like patients with Type II diabetes, renal transplant recipients with PTDM exhibit insulin resistance and insulin hyposecretion.[13] It is also important to recognise that not all renal transplant recipients have normal glucose metabolism prior to transplantation. Insulin resistance is common place in uraemic subjects through the combined effects of anaemia, acidosis and uraemic toxins.[29] The effect of uraemia on insulin secretion is less well defined. Whilst these deleterious influences should be ameliorated by successful renal transplantation, other factors can then impinge on glucose metabolism. For example, the association between high dose corticosteroid therapy and insulin resistance is well established in renal transplant recipients.[23] This is also supported by the finding that corticosteroid dose reduction improves glucose tolerance status in recipients.[22] Following renal transplantation, nutritional status improves and weight gain can influence insulin sensitivity. Visceral obesity in particular is an important determinant of insulin resistance in the non-transplant population.[30,31] Whilst this has not been clearly demonstrated in renal transplant recipients the same principles are likely to apply. The role of calcineurin inhibitors in the pathophysiology of PTDM is not as clear cut as with corticosteroids. There is evidence that calcineurin inhibitor therapy can decrease pancreatic β islet cell function

in vitro.[32-34] Evidence for β islet cell toxicity *in vivo* is variably reported in recipients of kidney or orthotopic liver transplants.[10,35] Tacrolimus-based regimes may have a higher incidence of PTDM than cyclosporine as a complication, but this information has to be interpreted with caution when considering changing imunosuppression regimens in favour of metabolic disturbances, and balancing the relative risks of rejection. This is an important issue to clarify as there is some evidence that the principle determinant of glucose tolerance status in these patients may be insulin hyposecretion rather than insulin resistance.[26,27] Thus pathogenitus of PTDM appears to be multifactorial due to a combination of background previous opposing factors determined by age, ethnicity, genetic and lifestyle compounded by pre existing factors due to chronic kidney disease such as insulin resistance and beta cell dysfunction. The transplant operation represents a "glucose stress test" due to the operative procedure, corticosteroids and immunosuppressive agents. The resulting emergence and abnormalities of glucose metabolism being a result of the balance between beta cell dysfunction and insulin resistence.

THE CLINICAL IMPACT OF PTDM

When reviewing the literature on the clinical impact of PTDM, it is important to differentiate mortality/morbidity data for patients who developed end stage renal failure with pre-existing diabetes from those with true PTDM.

Patient survival

Most studies report worse patient survival in patients with PTDM than in normoglycaemic recipients, but not as poor as in subjects with pre-transplantation diabetes. For example, in a single centre study of 1811 adults transplanted between 1983 and 1998, 293(20%) developed PTDM. 18% of all recipients had diabetes prior to transplantation. After 8.3 years of follow-up, 22% of patients with PTDM had died, compared to 31% of patient with pre-transplant diabetes and 16% of normoglycaemic recipients.[36] The cause of death depends on the era of transplantation. Cosio et al. examined patients transplanted after calcineurin inhibitors came in to use and found cardiovascular disease to be commoner.[36] Friedman examined patients receiving azathioprine-based therapy and found infection as the main cause of death.[37]

Graft survival

The majority of studies report poorer graft survival with PTDM. However, the difference compared to non-diabetic recipients is seldom statistically significant or the studies are small. Miles et al. found that after 12 year follow-up of 40 subjects with PTDM was graft survival, even when censured for death with a functioning graft, because of small numbers, it was not possible to establish statistical significance.[6] However, recent USRDS data demonstrates a significant impact of PTDM on graft failure.[18] The mechanism for graft loss is unknown. Diabetic nephropathy takes several years to develop amongst subjects with Type II diabetes mellitus, and nephropathy in subjects with PTDM would have to evolve at a much greater rate to account for the excess of graft loss. It is possible that hypertension and reduced immunosuppression may make a contribution.

PTDM and cardiovascular disease

Patients with pre-transplant diabetes carry a high risk of cardiovascular disease. In a 7 year follow up of 706 renal transplant recipients, pre-transplant diabetes carried independent relative risks of 3.25 for ischaemic heart disease, 3.21 for cerebrovascular disease and 28.18 for peripheral vascular disease.[38] In the same study, 7.1% of recipients developed PTDM and carried a relative risk of 2.22 for IHD, but was not independent of other cardiovascular risk factors such as such as serum cholesterol and triglyceride. Therefore it was not possible to conclude if PTDM was directly contributing to cardiovascular risk or merely confounding the effects of dyslipidaemia. However, the study did not examine diet-controlled diabetics, subjects with impaired glucose tolerance or normoglycaemic insulin resistant recipients.

The classical triad of insulin resistance, dyslipidaemia and hypertension known as the metabolic syndrome X is considered an important phenotype for the development of atherosclerosis in the general population.[39] Features of the metabolic syndrome have been identified in renal transplant recipients.[40,41] Even in the presence of normoglycaemia, insulin resistance may be an important risk factor for CVD in renal transplant recipients, but the size of this risk needs evaluation.

SCREENING, PREVENTION AND MANAGEMENT OF PTDM

In 2003, Canadian and International Consensus Guidelines on new onset diabetes after transplantation were published.[21,42] These recommend the diagnosis of PTDM should be based on WHO/ADA criteria.[43]

Recommendations for identifying risk factors for PTDM, CVD and screening for Hepatitis C infection were made to identify those on the transplant waiting list at risk. Targeting such a population should then be accompanied with counselling, dietary and life style advice.

Individuals who are predicted to be at high risk of developing PTDM (age, ethnicity, obesity, family history) consideration of base line immunosuppression with Cyclosporin rather than Tacrolimus should be balanced against the risk of other factors such as rejection. However, if an individual develops PTDM, a switch from Tacrolimus to Cyclosporin or alternatively Sirolimus may be considered. Steriod dose reduction and the use of steroid sparing regimens are endorsed and may be considered as the first option.

Following transplantation, fasting glucose should be examined weekly for 4 weeks, and then 3, 6 and 12 months after transplantation. Thereafter annual fasting glucose is suggested. In addition, random glucose testing can accompany every visit to check immunosuppression levels. Oral glucose tolerance testing should also be considered if there is any doubt.

However, the relative merits of different oral hypoglycaemic agents or the timing of insulin therapy is less clear in patients with PTDM, and this necessitates a better understanding of the pathophysiology of the disease.

Once PTDM has developed, the principles of treatment are extrapolated from recommendations for patient with Type II diabetes. There are no studies which examine treatment options in PTDM. In addition, deteriorating graft function could limit treatment options, as there is increased risk of lactic acidosis with biguanides and impaired renal sulphonylurea clearance could precipitate hypoglycaemia.

CONCLUSION

Post-transplantation diabetes mellitus is a well recognised complication of solid organ transplantation associated with higher patient mortality and graft loss. In addition, it appears to be a risk factor for cardiovascular disease. The majority of cases are diagnosed within the first year of transplantation, but thereafter the cumulative incidence still continues to rise about that observed in the general population for type II diabetes. The pathophysiology and risk factors for PTDM have important similarities to type II diabetes. Indeed, iatrogenic factors such as corticosteroids and calcineurin inhibitors which impair insulin sensitivity, and more importantly insulin secretion, may be serving to accelerate glucose intolerance in individuals who may have propensity for developing type II diabetes. Tailoring immunosuppressive therapy in accordance with the risk of developing PTDM should be considered. When PTDM develops, glycaemic control can be achieved with a similar approach to type II diabetes, but altering calcineurin inhibitor therapy and tailing off steroid therapy remains an option. The role of measures such as weight loss and exercise to reduce insulin resistance in this cohort of patients requires further evaluation. PTDM can exist as a state of transient glucose intolerance in some patients. However, one must not be lulled into a false sense of security, as persistent insulin resistance even in the presence of normoglycaemia may be a potent risk for cardiovascular disease in conjunction with other features of the metabolic syndrome.

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