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Calcineurin inhibitors induced post-transplant diabetes mellitus: A risk worth taking

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Abstract

Discovering miraculous medicines for the treatment of protracted diseases have long been a principal objective of the pharmaceutical scientists. Calcineurin inhibitors that include tacrolimus and cyclosporine are widely utilized for the inhibition of post-transplant tissue rejection. However, practice of these drugs is associated with certain complications such as diabetes mellitus onset after transplantation or post-transplant diabetes mellitus (PTDM). This PTDM renders the patients with eminent endangerments of diabetes mellitus, cardiovascular complications and impairs the survival rate. This review focuses on the complications caused by calcineurin inhibitors, determines the risk-to-benefit ratio of using these immuno-suppressants and discusses the various treatment options to treat onset of diabetes. It was observed that the non-diabetic and dialysis patients administered with tacrolimus were witnessed with decreased insulin release without instigating insulin resistance. This investigation was found to be dose dependent. Previous reports also suggest that the withdrawal of corticosteroids from their combination with tacrolimus result a decrease in insulin resistance, however, had inadequate influence on insulin secretion. Furthermore, a decrease of 30% in tacrolimus serum concentrations demonstrated a 24 % increase in insulin and 36 % increase in secretion of C-peptide. On the basis of these studies, it is evident that the effect of cyclosporine and tacrolimus on the secretion of insulin is reversible and dose dependent.

Keywords

Diabetes mellitus
Calcineurin
Insulin resistance

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Introduction

The use of calcineurin inhibitors in transplant procedures causes pronounced reduction in tissue rejection. However, their widespread use in tissue rejection is complicated by certain side effects shared by both drugs (Ghisdal et al., 2008). One noteworthy newly discovered adverse effect is post-transplant onset of diabetes mellitus that is worsened by concomitant use of corticosteroids. Several *in-vitro* studies carried out on purified islets and beta-cells clearly demonstrated that both the tacrolimus and cyclosporine exert diabetogenic effects that manifests as impaired insulin secretion, decrease in insulin content of beta-cells and impaired insulin transcription (Hagen et al., 2003; Heisel et al., 2004; Kamar et al., 2007; Cole et al., 2008; Van Laecke et al., 2009; Kuo et al., 2010; Øzbay et al., 2011). However, the exact mechanism underlying this metabolic disturbance that worsens with the use of corticosteroids is unknown (Midtvedt et al., 2004; Van Hooff et al., 2004).

Diabetes mellitus: Diabetes mellitus (DM) is a metabolic disorder related with an increased level of glucose in blood that paves the way for other complications. Post-transplant diabetes mellitus (PTDM) is one of the types of DM that occurs due to

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decreased level of insulin leading to elevated insulin resistance or dysfunction in insulin secretion or may be a result of both. The risk to PTDM is greater in patients undergoing recent transplant primarily due to the use of immunosuppressive agents used after transplantation (Van Hooff et al., 2004).

Calcineurin: Calcineurin (CN) is calcium and calmodulin dependent "serine/threonine protein phosphatase" also termed as "protein phosphatase 3" and "calcium-dependent serine-threonine phosphatase". Calcineurin triggers insulin gene transcription within beta cells that produces insulin via activation of transcription nuclear factor of activated T-cells. Studies exhibits the calcineurin associated anti-apoptotic and pro-apoptotic events in the cell or some other functions in the cell subjected to tight regulation (Øzbay et al., 2011). Impact of calcineurin hindrance was studied using insulin secreting cells when exposed to tacrolimus and cyclopsporin. Changing concentrations of tacrolimus and cyclosporine were delivered to beta cells for a period of 6 to 24hrs to measure basal glucose concentrations. INS-1E cells were cultured and used to observe the regulatory effects calcineurin activity and insulin release (Øzbay et al., 2011).

Calcineurin and NFAT signaling pathway: The common name "Nuclear factor of activated T-cells" (NFAT) is assigned to a group of transcription factors that are proved vital in the immune responses of the body. It comprises of 5 entities $NFATc_1$, $NFATc_2$, $NFATc_3$, $NFATc_4$, and $NFATc_5$. $NFATc_1$ and $NFATc_4$ follow Calcium signalling pathway. Calmodulin is a prominent calcium sensor protein, initiates the serine-threonine phosphatase calcineurin (CN). Another review suggested that NFAT regulates insulin gene promoter activity specifically due to synergistic pathways initiated by glucose and glucagon like peptide. The process indicates a direct relation between the rate of insulin gene transcription in the β-cells of pancreas with the activation of NFAT. The process is mediated by calcium-calmodulin dependent protein phosphate 2B (Calicineurin) due to elevated levels of calcium. The study was supported by researchers of the Harvard medical school who demonstrated similar pattern and substantiated calcineurin is crucial for the activation of NFAT signalling pathway (Hogan et al., 2003; Lawrence et al., 2001).

Cell death and resistance induced by calcineurin inhibitor: SREBP-1c is a lipogenic factor and is known to be vital in the functioning of Beta-cells by suppressing genes. The regulation of this factor is studied to observe the cellular dysfunction caused by calcineurin inhibitors. The results exhibited that cyclosporine considerably elevates the expression levels of SREBP-1c whereas prolonged treatment with tacrolimus reduced the expression level in glucose stimulated cells. This interesting finding suggests tacrolimus as a suitable substitute with lesser side effects but recent studies proved it wrong because tacrolimus and cyclosporine both have a potential to induce side effects of similar magnitude. High doses of tacrolimus (200 $nmol/L^{-1}$) and cyclosporine (10 $micromol/L^{-1}$) were also found to be cytotoxic after 24hrs of exposure (Øzbay et al., 2011).

Risk factors linked to diabetes in transplant individuals: supportive factor in the diagnosis, prevention and treatment of NODAT is to anticipate specific patient's ability to develop diabetes followed by transplantation (Davidson and Wilkinson, 2004). There are no clearly characterized elements helpful for the diagnosis of NODAT, even though some common factors are considered helpful in the prevention of diabetes after transplant (Reisaeter and Hartmann, 2001). Risk factors involved in the induction of NODAT can be helpful in the management of disease (Kasiske et al., 2003).

a. Age of patient: The incidence of diabetes after transplant is greater in old age patients. NODAT occurrence is common in patients above 40 years (BOUDREAUX et al., 1987; David et al., 1980; Reisaeter and Hartmann, 2001; Sumrani et al., 1991). However some studies repo age isnot considered an important hazard in the progression of diabetes after liver transplantation certain studies suggested But in certain reviews age does not seem, by all accounts, to be an important hazard in the progression of diabetes after liver transplantation (Sarno et al., 2012; Steinmüller et al., 1999).

b. Ethnicity: There is a very firm evidence that ethnicity is a standout amongst the most vital hazard elements in diabetes development after transplantation e.g. Hispanic and African American populations are at a more serious danger of the progression of diabetes after transplant as compared to white population (Kasiske et al., 2003; Sumrani et al., 1991). This elevated danger of diabetes might be expected due to the difference in the pharmacokinetic and diabetogenic effects of immunosuppressant (Montori et al., 2002). If we look at the comparison between the dose required by the white and African American, the African American require 37% more dose of tacrolimus to achieve desired plasma level hence such a high concentration is up to 5 times more diabetogenic as compared to cyclosporine and it has a particular potent diabetogenic effect in African Americans (Kasiske et al., 2003; Neylan, 1998).

c. Familial history: Several reviews reflect that there are many factors playing a role in the progression of type II diabetes mellitus including both genetic and environmental causes (Ghisdal et al., 2009; McIntyre and Walker, 2002). One study indicates that familial background of diabetes elevates the risk of NODAT up to 7 folds (Arner et al., 1983; Sumrani et al., 1991). All these findings suggest that it is important to distinguish

specific patients with history of diabetes among primary relatives in the early option of therapy in order to tailor the immunosuppressive therapy accordingly. It has been accounted for that the danger of creating diabetes is advanced in people with definite kind of histocompatibility leukocyte antigen (HLA) phenotypes yet the result behind these assumptions are opposing and encompass minor number of patients (David et al., 1980; Hjelmesæth et al., 1997; Sarno et al., 2012; Sumrani et al., 1991).

d. Body weight: Obesity often develops in transplant patients and is accompanied with lessened graft and patient survival (Bumgardner et al., 1995; Cosio et al., 2002). Many studies suggest that body weight is linked with the diabetes progression subsequently after transplantation (Arner et al., 1983; BOUDREAUX et al., 1987; David et al., 1980; Kasiske et al., 2003; Miles et al., 1998) on the contrary some studies show that the link between body weight and BMI with post-transplant diabetes is weak (Montori et al., 2002), nevertheless obesity is one of the significant causative element in the progression of diabetes and it elevates the risk of diabetes development in transplant patients aswell.

e. Immunosuppressive therapy: There are many studies that indicate that immunosuppressive therapy increases the chances of NODAT. Corticosteroids increase the incidences of diabetes and glucose tolerance after transplant (Arner et al., 1983; Friedman et al., 1985; Midtvedt et al., 2004; Starzl et al., 1964).

Etiology of nodat: Recipients of organ transplant can stay predisposed to the progression of diabetes after transplantation due to multiple factors such as advancing age, nonwhite ethnicity, central obesity, an individual history pertaining to glucose intolerance or a familial background of diabetes (Øzbay et al., 2011). A research carried out on Korean renal allograft recipients showed that non-Caucasian patients and african-americans experienced a greater risk of NODAT despite receiving the similar doses of immuno-suppressants and corticosteroids while this particular research pointed toward the fact that may be concomitant use of corticosteroids along with immunosuppressants can also be a cause of NODAT, but other causes for onset of diabetes after transplantation were similar such as old age, high blood pressure, high triglyceride value, insulin resistance and family history of diabetes. One interesting aspect of NODAT is that HCV can potentiate the diabetogenic effect of tacrolimus but due to lack of sufficient data to support this hypothesis it was not proved (Cho et al., 2003). Exact etiology still remains unclear, the clinical presentations may resemble either to type-I diabetes mellitus with serious onset requiring rapid insulin treatment or type-II diabetes which is more insidious often asymptomatic. The research carried out on Korean patients reflects that tracrolimus caused insulin deficiency by inhibition of transcription of insulin gene that is associated with of calcineurin-linked inhibition of FK506-binding protein-12 (FKBP-12), rather than that sirolimus which likewise associates with FKBP-12 interacts with mTOR a mammalian target of rapamycin leading to hyperlipidemia by inhibiting insulin action (Cho et al., 2003). The presence of asymptomatic cytomegalovirus infection may also increase the threat of NODAT in kidney transplant individuals. (Hjelmesaeth et al., 2004; Lowance et al., 1999) by inducing insulin resistance through the stimulation of cytokines and tumor necrosis factor alpha.

Diagnosis of nodat: The incidences of NODAT in adult kidney, liver and heart recipients is <5% to >50% (Montori et al., 2002). This wide variation is a result of inconsistent diagnostic criteria and because data is insufficient and there is no definite criteria for diagnosis of NODAT best choice for now is to link the current diagnostic criteria of diabetes on general public with the recommendations of WHO (Consultation, 1999; Krentz et al., 1995), the international diabetes federation (IDF), and American diabetes association (ADA). The constant monitoring of impaired fasting glucose (IFG) and impaired glucose tolerance (IDT) is vital in organ transplant individuals who are non-diabetic. These conditions have been connected with elevated risk of cardio-vascular disease and since most of the cases the condition is asymptomatic it is only detected through biochemical tests. This is of significant importance as the treatment that targets post-prandial hyperglycemia might increase vascular safety but this is still undergoing extensive research and the results are satisfying but only in non-transplant patients (Wheeler and Krentz, 2007).

It is prescribed that irregular glucose regulation ought to be monitored at least once annually in listed individuals with IGF before transplantation. This yearly screening has the benefit of being simple. It is very essential to observe the blood glucose level immediately after transplantation as well as at 3, 6 and 12 months after transplant subsequently, yearly monitoring must also be implemented in all individuals. Patients who were observed to have temporary hyperglycemia in a short period after transplantation must be monitored every 3-6 months as they are at a greater danger of progression of irreversible hyperglycemia later onwards.

Blood plasma glucose have to be measured after 8-12hour overnight fasting taken by a repeated fasting or non-planned measuring of glucose if there are chances of diabetes. The most sensitive test for diagnosing diabetes is 75g glucose tolerance test but it is not useful in this case. However, in order to measure IGT, glucose tolerance test is necessary. Tubes should contain fluoride oxalate in which the blood is collected. Urine tests will determine whether ketones are present which

are associated with hyperglycemia which is a strong marker of insulin deficiency and it requires insulin treatment. One study shows that pre-transplant obesity and adiponectin also expect NODAT, and individuals with decreased levels of adiponectin and elevated BMI are at a higher danger of developing NODAT (Bayés et al., 2007).

Evaluating risk of nodat: Health professionals responsible for the care of the reciepients undergoing organ transplant and should be well informed of the risks linked with NODAT and they should be well aware of patient condition which might become a cause in the progression of NODAT. The primary goal in this case is to reduce the severity of immunosuppressants, specifically the complications that are metabolic in nature. It is quite clear that both cyclosporine and tacrolimus cause NODAT and the risk is greater with the concomitant use of corticosteroids, but since immunosuppressants are necessary for organ transplant recipients NODAT is unavoidable but what the health care professionals can do is to reduce the severity and complications associated with this condition. Ideally it is best to assess each patient's potential of developing NODAT prior to the transplantation but since there is no definite protocols for such procedure the best option in this case is to obtain patient's previous history such as diabetes, episodes of glucose intolerance, age, ethnicity, physical activity, hepatitis C infections, smoking or premature background of Cardiovascular Disease. Patient must be informed to avoid Post-transplant weight gain, healthy life style and a strict dietary regime is important to decrease the problems linked with NODAT. A proper dietary plan and exercise plan should be tailored according to the needs of individual patients. Selecting immunosuppressive therapy is also crucial in evaluating the risk of NODAT although the progress of NODAT comes second to preventing acute graft rejection and maintaining a good graft function still it is necessary to consider development of NODAT while selecting immuno-suppressive therapy. One suggested strategy is to reduce the dose of corticosteroids in patients who have a greater risk of developing NODAT and this strategy has shown some promising results but an abrupt and complete withdrawal of corticosteroids which is more common in everyday practice has not been satisfactory. Both tacrolimus and cyclosporine cause NODAT and the risk is increased with the use of corticosteroids but different researches show that risk of NODAT is higher with tacrolimus in comparison to cyclosporine in both adults and children. The national institute of clinical excellence recommends that choice between both drugs should be grounded on the individual side effect profile of each drug in individual patient and recognition of NODAT and hyperlipidemia as side-effects.

Managing nodat: Basic management of NODAT is analogous to that of diabetes management in non-transplant patients which includes:

- Treating acute osmotic symptoms and metabolic decompensation
- Developing long term glycaemia control
- Identifying and treating other major complications associated with diabetes such as hypertension, dyslipidemia
- Monitoring patient for development of microvascular complications

Reducing corticosteroids one year after transplantation is also beneficial, careful reduction in the dose of calcineurin inhibitors is also an option but such decision should be made by transplant specialists after careful assessment of the patient's current condition. A more abrupt change in the immunosuppressive therapy is also considered an option only if it is difficult to control diabetes. Some researches show that the reduction of dose did not prove to be effective although switching the patient from tacrolimus to cyclosporine reduced the side effects to a greater extent.

Patients who progress NODAT with symptomatic hyperglycemia which is also attended by impending or actual metabolic decompensation should receive quick treatment with insulin. It is recommended to slowly shift from insulin to oral antidiabetic agent for out-patient treatment but this should be done after consulting with local diabetes team. Withdrawal of antidiabetics is necessary after hyperglycemia is controlled but the health care providers must be ready to reinstate the therapy if diabetes recur. If irreversible diabetes develop after organ transplant the guidelines dictate that the patient should be treated according to the guidelines provided for type-II diabetes mellitus. Care should be taken while using oral anti-diabetics in transplant patients as there are more contraindications and more chance of adverse drug reactions as compared to non-transplant patients. Life style modification includes weight control, diet modification and exercise, patient should be monitored for signs of hyperglycemia and glycaemia control should be evaluated by determination of Hemoglobin $A1_c$ after every 3 months. An increase in level above 6.5% is an indicator for intervention. Having sufficient information relevant to patient's condition is helpful in treating NODAT and it reduces the risk of developing long-term microvascular complications.

Patients should be encourage to measure their capillary blood glucose level at home, today due to great advancement in the field of medicine there are many treatment options available such as use of insulin along with an oral antidiabetic agent. Current research also dictates that patients should also take treatment for

suboptimal blood pressure and dyslipidemia. Dyslipidemia also contributes to the development of atherothrombotic vascular disease. Cigarette smoking should be strongly discouraged, regular monitoring of blood pressure and blood lipid measurement every 6months is of prime importance. It should be noted that transplant recipient patients require anti-hypertensive agents, lipid lowering drugs along with the usual immunosuppressants and antidiabetics in which case the side effect profile is much greater due to more chances of drug interactions however the frequency and severity of these side effects varies for example hypertension is more common with cyclosporine furthermore the use of corticosteroids worsen hypertension and dyslipidemia more.

To treat these problems the treatment regimen should be personalised according to the individual needs of patients. Fluvastatin and pravastatin are the safest of statins with minimum side effects which can be used in treatment of dyslipidemia in transplant patients but the risk is always there so close monitoring of patients in necessary. If the patient is allergic or resistant to statins then the situation is more complicated, combination use of statins and fibrates can be effective but it requires hospital supervision as side effects risk is far greater. Many patients with hypertension require combination therapy angiotensin receptor blockers and angiotensin converting enzyme inhibitors are most commonly used. Antiplatelet therapy is recommended with aspirin as the first line if patient has a history of cardiovascular complications (Krentz and Wheeler, 2006).

Normally the danger of diabetes mellitus onset after transplantation increases in a progressive manner after the transplantation, it may take months or even years before the symptoms start to appear and in some cases the condition is asymptomatic. Management of NODAT is multifactorial which is tailored according to each individual's conditions such as dietary modification, exercise and use of certain antidiabetics. All these management options depend upon the patient condition and severity of disease. In the early post-transplant period corticosteroids are administered along with immunosuppressants to reduce the chances of tissue rejection but there is a great risk that the patient may develop severe and symptomatic hyperglycemia with a risk of metabolic decompensation. These risk were discovered since the earliest days of organ transplant and such medical emergencies require immediate medical attention. In the beginning corticosteroids were considered to be a crucial part of immunosuppression therapy but later on it was proved that corticosteroids were potent insulin resistance and few researchers consider corticosteroids to be the main reason for NODAT. Hyperosmolar non-ketotic hyperglycemia and diabetic ketoacidosis have been described and these are serious medical conditions which require immediate intravenous insulin and fluids. Once patient condition is stable he/she can be relocated to subcutaneous insulin prior to release. As corticosteroids are withdrawn insulin should also be stopped as in non-diabetic patients the diabetes induced by immunosuppression therapy is usually reversible (Shapiro et al., 2000). In some cases blood glucose level return to normal without any significant use of insulin, however in patients with prolonged diabetes microvascular complications are also common such as nephropathy, retinopathy and neuropathy. In patients with kidney transplants cardiovascular disease was also reported and the frequency was twice as high as non-transplant population (Wheeler and Krentz, 2007).

Conclusion: After this discussion, it is quite clear that chronic treatment with anti-calcineurinic immuno-suppressant in transplant recipient patients induces diabetes mellitus with many complications which can ultimately lead to organ failure or even death. Evidences provided in the above discussion point to one inescapable fact that calcineurin is crucial for functioning and survival of beta-cells. However, the diabetogenic effect of calcineurin inhibitors and its molecular basis has not been understood properly. First of all, both the medications collectively weaken basal insulin secretion along with this glucose stimulated insulin secretion by inhibiting calcineurin activity in beta-cells. Secondly cyclosporine also increases the expression level of SREBP-1c lipogenic transcription factor that becomes a cause in promoting insulin resistance and effects the functioning of β-cells. Both tacrolimus and cyclosporine primarily impair basal insulin secretion and insulin released in response to glucose while content of insulin and mRNA remain unaltered. But an important aspect of this research shows that both tacrolimus and cyclosporine exert their effects in a different manner for example tacrolimus alone cause acute inhibition of basal insulin secretion whereas cyclosporine paradoxically increase glucose stimulated insulin secretion after short term exposure. The development of NODAT can lead to the progression of other difficulties such as macrovascular complications and increased mortality.

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