Immunosuppressive Drugs and Kidney Post-transplant Diabetes Mellitus

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1. Background

Decreased uremic toxin and improved glucose tolerance have been reported as the results of successful renal transplantation. However, the consumption of immunosuppressive drugs following renal transplantation can, to a large extent, lead to glucose intolerance, finally resulting in the development of post-transplant diabetes mellitus (PTDM) which can cause death.

Different research studies have reported that patients who have undergone renal transplantation and 30 healthy individuals. A questionnaire was utilized to gather their demographic information, and direct interviews were conducted with the subjects. To examine random blood sugar (RBS), white blood cell (WBC) count, creatinine level, and blood urea nitrogen (BUN), blood samples were obtained from the subjects. The mentioned parameters were analyzed using SPSS 22.0.

Results: According to the results, the groups were homogenous in age, body mass index (BMI), and male-to-female ratio. However, there were significant differences between the two groups in RBS (P=0.011), WBC count (P=0.031), creatinine level (P=0.001), and BUN (P=0.001).

Conclusion: Failure of allograft survival of renal transplantation was found to be a leading cause of death, which has been reportedly been treated by the consumption of immunosuppressive drugs such as CsA. However, this drug can increase the patient’s chances of developing PTDM. PTDM development can be reduced by applying a dosage of 10 mg/kg/d during the first week and 8-9 mg/kg/day during weeks 2-5 following transplantation.

Keywords: Immunosuppressive Agents, Cyclosporine A (CsA), Chronic kidney Disease, Renal Transplantation, Diabetes Mellitus

1. Background

Decreased uremic toxin and improved glucose tolerance have been reported as the results of successful renal transplantation. However, the consumption of immunosuppressive drugs following renal transplantation can, to a large extent, lead to glucose intolerance, finally resulting in the development of post-transplant diabetes mellitus (PTDM). Different research studies have reported that patients who have undergone renal transplantation are likely to experience PTDM during the first 3 months after transplantation and that there will be an increase in the risk of transplantation failure, mortality, and infectious and cardiovascular diseases as a result of PTDM.

It has also been demonstrated that PTDM developed in 40% of patients as a result of employing high-dose corticosteroid therapy in the early period after renal transplantation. However, once better immunosuppressive drugs like tacrolimus and cyclosporine A (CsA) were introduced, a significant decrease in corticosteroid consumption was observed, which then led to significant improvements in transplantation survival. Although PTDM incidence has remarkably decreased as a result of introducing and employing immunosuppressive drugs to enhance allograft survival renal transplantation, PTDM has been reported to be experienced by 20% of transplant patients; therefore, the diabetogenic feature of these drugs have been pinpointed.

As indicated by experimental studies, immunosuppressive drugs like CsA and tacrolimus can lead to diabetes by decreasing insulin production and release, reducing peripheral insulin sensitivity, and being β-cell toxic. These 2 immunosuppressive drugs have also been the focus in various comparative studies which have revealed
a significantly higher incidence of PTDM as a result of tacrolimus therapy compared to CsA therapy.\textsuperscript{14,15} Other risk factors including a history of diabetes in the family, obesity, human leukocyte antigen type, race, and age have also been reported to be involved with the incidence of PTDM.\textsuperscript{16,17} It should be noted that because PTDM has not uniformly been defined, classifying patients with varying degrees of glucose tolerance is difficult, which, in turn, complicates evaluating the importance of different risk factors affecting long-term outcomes.\textsuperscript{18}

As suggested by research studies, different protocols of immunosuppressive drugs need to be employed for different patients. For example, patients with delayed graft function, a higher level of preformed antibodies, and previous transplants, or young patients should be given higher doses of immunosuppression. In addition, patients receiving kidneys from older donors are likely to be less tolerant to immunological assault and other aggression, while those with kidneys received from well-matched donors may need fewer immunosuppressive drugs.\textsuperscript{19} It has also been shown that acute rejection may happen during the first months after transplantation (induction phase) and decline later on (maintenance phase). As a result, the highest level of immunosuppressive drugs should be administered during the early period followed by decreased levels for long-term therapy.\textsuperscript{20}

Although controlling immunologic phenomena after transplantation and allograft survival have improved greatly,\textsuperscript{21} mortality among transplant recipients has been frequently referred to as a threat to the success of renal transplantation.\textsuperscript{22,23} Cardiovascular causes are responsible for a high mortality rate among renal transplant recipients;\textsuperscript{24} therefore, identifying the variables relevant to cardiovascular risks is highly significant. According to research, there is a relationship between post-transplant insulin resistance in patients consuming immunosuppressive drugs (such as CsA and tacrolimus) and cardiovascular risk.\textsuperscript{25,26}

2. Objective

Since renal transplantation is quite prevalent, and the high mortality rate caused by transplant failure has been reported to be correlated with cardiovascular risks associated with the consumption of immunosuppressive drugs, the current study examined the role CsA plays in causing PTDM among patients with chronic kidney disease (CKD) who have undergone renal replacement therapy. Other aims of the present study were to determine the different factors involved with PTDM, estimate the proper dose of CsA to prevent PTDM incidence, and determine the side effects of the drug.

3. Methods

3.1. Study Design and Setting

Using a quantitative method and following a case-control design, the present study was conducted in Zheen International hospital located in Erbil, the Kurdistan region of Iraq, over a 6-month period from October 2016 to March 2017.

3.2. Participants and Intervention

The study sample in the present case-control study consisted of 30 patients with renal transplantation and 30 healthy individuals without renal transplantation who had referred to Zheen International hospital located in Erbil, the Kurdistan region of Iraq. CKD patients, ≥18 years of age, who had undergone renal transplantation were included in the study. Patients with significant coronary artery disease (CAD), who were awaiting a repeat transplant, or had an unwillingness to participate in the study were excluded. A convenience purposive sampling method was utilized to select the subjects. who were then assigned into a patient group (case) and a healthy group (control). There were 30 individuals in each group who were homogenous in terms of their body mass index (BMI) (25.33 ± 2.2 kg/m\(^2\) in the case group and 24.88 ± 1.35 kg/m\(^2\) in the control group) and mean age (33.8 ± 3.9 and 35.3 ± 2.2, respectively, in case and control groups). CsA at doses of 10 mg/kg/d for 1-6 days following transplantation and 8-9 mg/kg/d for 2-5 weeks following transplantation was administered to the patients during the maintenance phase, while the control group was not given anything. To complete the questionnaire consisting of questions regarding the subjects’ family history of diabetes, gender, and age, each individual was interviewed face to face. For the purpose of biochemical examinations, blood samples (5 mL) were taken from the individuals of both groups.

3.3. Data Collection and Instruments

A self-designed questionnaire was used to gather the participants’ demographic data which included gender, age, and history of smoking, pre- and post-transplant diabetes, and family history of diabetes under the supervision of specialists in the fields. The questionnaire was valid (overall alpha value of 0.89) and reliable (\(r = 0.85\), ranging from 0.79-0.90). Before and 4 to 6 weeks following renal transplantation, the case group’s data was collected through face-to-face interviews with the subjects. Blood samples were also obtained on which biochemical examinations were conducted so as to collect the required data on the subjects’ random blood sugar (RBS), white blood cell count (WBC), creatinine level, and blood urea nitrogen (BUN).

3.4. Data Analysis

Quantitative data was given as mean ± standard deviation (SD). The independent sample \(t\) test was employed to compare the parameter means (age, BMI, BUN, creatinine, WBC, RBC, cholesterol, triglyceride, K\(^+\), Na\(^+\), and Ca\(^+\)) between the two studied groups (case and control). A \(P\) value of <0.05 was considered as the statistically significant level. SPSS 22.0 was used to analyze the data.

4. Results

Analysis of the data collected from the questionnaire
demonstrated that the case and control subjects’ mean age was 33.8 ± 3.9 and 35.3 ± 2.2 years, respectively. The results also indicated that 55.6% of the case subjects (n = 17) were males and 44.4% (n = 13) were females. In the control group, half of the subjects (50%) were women and half (50%) were men. In addition, it was observed that the case group had an average BMI of 25.33 ± 2.2, and the control group’s average BMI was 24.88 ± 1.35. It was concluded that the two groups were not significantly different in terms of the above-mentioned variables (Table 1).

Data analysis also revealed that 20.4% of the case patients (n = 8) smoked, while none of the control subjects smoked. It was also observed that 9 (24.1%) case patients had a family history of diabetes, 7 (16.7%) had hypertension, 8 (26%) had post-transplant diabetes, 4 (11%) had pre-transplant diabetes, and 10 patients (13%) had diabetes, while none of the control subjects had these variables. Thus, the difference between the two groups in terms of these variables was significant (Table 1).

The data related to the CsA dosage that was administered during the maintenance phase is presented in Table 2. As indicated, the patients in the case group were given 10 mg/kg/d for a period of 1 to 6 days following renal transplantation and 8-9 mg/kg/d for a period of 2-5 weeks after renal transplantation (Table 2).

Based on the results of ANOVA indicated in Table 3, it was concluded that there was a significant difference between the two groups in terms of their BUN (P = 0.001), creatinine level (P = 0.001), WBC counts (P = 0.031), and RBS (P = 0.011).

According to the results of the present study, the 2 groups were significantly different in terms of their blood and serum parameters. A significant increase was observed in cholesterol and triglyceride levels, and serum ions (particularly potassium ions) underwent a drastic rise; the difference was significant. Moreover, the same condition was observed for calcium, while changes in the sodium ion was not significant (Table 4).

5. Discussion

Based on the results of the present study, it was concluded that the patients and the healthy individuals were not significantly different in terms of their BMI. However, research has indicated a higher risk of developing new onset diabetes mellitus after transplant (NODAT) among patients who have a BMI of equal to or greater than 30 kg/m², which cannot be compared with the current results, because none of the subjects had a BMI of equal to or greater than 30 kg/m². Diabetes mellitus has been cited as one of the most frequent causes of CKD. Moreover, about 30% of non-diabetic patients with renal transplantation experience NODAT, also referred to as PTDM. This finding is in line with that of the current study, where diabetes mellitus (DM) developed after renal transplantation in 8 out of 30 patients (26%) (Table 1). Depending on the type of transplantation, i.e. renal, liver, or heart transplantation, the definition of NODAT, and the study design, a range of 4% to 40% of NODAT development has been reported by other studies.

According to the results of the present study, a family history of diabetes mellitus, hypertension, and smoking with frequencies of 24.1%, 16.7%, and 20.4%, respectively, were among other effective risk factors in the development of PTDM. This finding is in agreement with those of the studies carried out by Rodrigo et al and Kaposztas et al. Rodrigo et al also reported age as one of the effective factors in NODAT; however, age was not found to be an effective factor in NODAT in the present study. This difference can be related to the fact that both groups in the present study

Table 1. Characteristics of Subjects in the Case and Control Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Groups</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ±SD)</td>
<td>Case n=30</td>
<td>Control n=30</td>
</tr>
<tr>
<td></td>
<td>33.8±3.9</td>
<td>35.3±2.2</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17/30 (55.6%)</td>
<td>15/30 (50%)</td>
</tr>
<tr>
<td>Female</td>
<td>13/30 (44.4%)</td>
<td>15/30 (50%)</td>
</tr>
<tr>
<td>BMI (Mean ±SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25.3±2.2</td>
<td>24.88±1.35</td>
</tr>
<tr>
<td>Smokers</td>
<td>8/30 (20.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10/30 (13%)</td>
<td>-</td>
</tr>
<tr>
<td>Pre-transplantation</td>
<td>4/30 (11%)</td>
<td>-</td>
</tr>
<tr>
<td>Post-transplantation</td>
<td>8/30 (26%)</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7/30 (16.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Family history</td>
<td>9/30 (24.1%)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2. Cyclosporine A (CsA) Dosage Given to Patients With Renal Transplantation

<table>
<thead>
<tr>
<th>Immunosuppressive Drug</th>
<th>Maintenance Phase</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA dosage</td>
<td>10 mg/kg/day</td>
<td>1-6 days</td>
</tr>
<tr>
<td>CsA dosage</td>
<td>8-9 mg/kg/day</td>
<td>2-5 weeks</td>
</tr>
</tbody>
</table>

Table 3. BUN Urea, Creatinine, and WBC Counts of the Case and Control Groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Case Mean ± SD</th>
<th>Control Mean ± SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (mg/dL)</td>
<td>132.1±12.53</td>
<td>45.1±3.87</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>6.14±0.88</td>
<td>1.04±0.09</td>
<td>0.001</td>
</tr>
<tr>
<td>WBC (10⁹/mL)</td>
<td>6.33±1.21</td>
<td>7.56±0.19</td>
<td>0.031</td>
</tr>
<tr>
<td>RBS (mg/dL)</td>
<td>128.8±6.560</td>
<td>95.36±2.260</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Table 4. Comparison of Patients and Control Group Regarding Blood Glucose, Cholesterol, Triglyceride, and Serum Ion Levels

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RT (Mean ± SD)</th>
<th>Control (Mean ± SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>200.8±12.093</td>
<td>171.1±9.111</td>
<td>0.025</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>174.4±12.45</td>
<td>102.3±6.436</td>
<td>0.001</td>
</tr>
<tr>
<td>K⁺</td>
<td>8.981±0.2310</td>
<td>4.832±0.1791</td>
<td>0.021</td>
</tr>
<tr>
<td>Ca⁺</td>
<td>8.613±0.4193</td>
<td>1.180±0.0264</td>
<td>0.001</td>
</tr>
<tr>
<td>Na⁺</td>
<td>132.2±1.484</td>
<td>136.1±1.797</td>
<td>0.117</td>
</tr>
</tbody>
</table>

* The independent sample t test was used to analyze the mean differences of parameters between case and control groups.
were homogenous in terms of age. It has also been reported that patients with previous type-2 diabetes are more prone to develop PTDM, which is also supported by the results of the present study (Table 1).

According to the research, immunosuppressive drugs like cyclosporine and tacrolimus can help with PTDM prevention and prolonged graft survival. There is research-based evidence showing that the transplanted organ might be rejected during the first months following transplantation (induction phase) and decrease later on (maintenance phase). As a result, patients need to be given immunosuppressive drugs at the highest level during the early period, and the dose should be reduced for long-term therapy. Accordingly, the patients in the present study were given 10 mg/kg of CsA per day during the first 6 days following the transplantation, and 8-9 mg/kg/d during the subsequent 2-5 weeks.

Moreover, a significant difference was found between the two groups regarding their BUN; therefore, BUN was found to be a PTDM risk factor; however, the development of diabetes mellitus following transplantation, as indicated by research, cannot be predicted through BUN.

In the present study, the case group patients with renal transplantation and a history of PTDM had a significantly higher level of serum creatinine; therefore, creatinine level was regarded as a risk factor for PTDM. Contradictory results have been reported with regard to the effect of serum creatinine level on PTDM development. For example, Sumrani et al reported that creatinine level does not influence the rate of PTD, while Choi and Kwon demonstrated that PTDM incidence can be predicted through creatinine level. This contradiction in research findings can be attributed to discrepancy in different study samples, durations of the studies, and the tests employed.

The results of the present study revealed that there was a slightly significant difference between the two groups regarding their WBC count (P<0.05), which gave way to this conclusion that PTDM incidence cannot be well predicted through WBC. According to research, WBC has been reported as an effective factor in prediction of graft survival following orthotopic liver transplantation.

According to the results of the present study, RBS (or random glucose) is an effective factor in the development of PTDM. This finding is in agreement with reports of the American Diabetes Association (ADA) and the World Health Organization (WHO) that referred to a random glucose level of 200 mg/dL (11.1 mmol/L) as one of the predictive factors for PTDM.

Patients with renal disease have frequently been reported to have dyslipidemia. A large number of patients with renal disease have been reported to undergo atherogenic changes in the composition and level of lipoproteins, which are referred to as risk factors for cardiovascular diseases (CVD) in the general population. Given the patient population and the time point of examining the serum lipids following transplantation, a range of 16%-72% has been reported for dyslipidemia prevalence in patients with renal transplantation.

Although there is no clear understanding of the pathogenesis of lipid pattern changes in patients with renal transplant, it seems to be multifactorial. Among these, immunosuppressive therapy and concomitant steroid are probably the most significant. The present study investigated the lipid profiles of patients with renal transplantation in order to specify the nature of lipid abnormalities and also performed a critical analysis on the collected data to interpret their utility for therapeutic interventions.

Depending on the time the post-transplantation serum lipid levels were obtained, 16%-78% of recipients might develop post-transplant hyperlipidemia. Most patients (82%) develop hypercholesterolemia within 6 months following transplantation, while the highest incidence rate of hypertriglyceridemia has been reported to be 12 months after transplantation.

There is a poor understanding of the hyperlipidemia pathogenesis in renal transplant recipients; however, it seems to be multifactorial. Age, gender, body weight, renal dysfunction, pre-transplant lipid level, concomitant use of diuretics or beta blockers, proteinuria, steroid use, diabetes mellitus, and cyclosporine use have been pinpointed as factors associated with post-transplant hyperlipidemia. However, it is not clear how these factors contribute to the incidence of hyperlipidemia after transplantation.

It has been reported that early after transplantation, there is a relationship between hyperlipidemia and immunosuppressive therapy; however, persistent hyperlipidemia in the late post-transplantation period can be caused by factors other than immunosuppressive therapy. Post-transplantation morbidity and mortality among long-term renal transplant survivors have been attributed to CVD. Patients who develop CAD after renal transplantation have been reported to be older males, have diabetes with higher cholesterol levels, smoke more, and experience more episodes of acute renal allograft rejection, and thus have received a greater cumulative dose of steroids. According to several clinical studies, there is a correlation between chronic allograft rejection and hyperlipidemia. The most consistent predictor of chronic allograft failure has been reported to be increased serum TG levels. However, this relationship between hyperlipidemia and chronic allograft failure can be caused by reasons other than the cause of renal allograft failure. Hyperlipidemia should be assessed immediately after transplantation and followed by the measurement of serum lipid concentrations as soon as indicated or once a year. Certain therapeutic implications can be concluded from the inverse correlation between duration of transplant and lipid abnormalities. For example, the lipid profile varies during the first 8-12 months following transplantation. Therefore, it should not be considered as therapy basis. Hyperlipidemia treatment decision needs to be according to the lipid levels and the existence of positive risk factors for CAD such as age >55 years in females, age >45 years in males, current cigarette
smoking, family history of premature CAD, HDL-C <35 mg/dL, diabetes mellitus, and blood pressure >140/90 mm Hg in spite of antihypertensive therapy.

In patients with renal transplantation, hyperkalemia is often observed in association with renal tubular acidosis. It can also be seen without the presence of any of the factors mentioned above. The translocation of potassium and glucose from the extracellular to the intracellular compartment can be reduced by insulinojenia or insulin resistance. It can also lead to hyperglycemia and hyperkalemia in the post-transplant setting, particularly in insulin-dependent diabetic patients. The time course of hyperkalemia following renal transplantation has been described in a small number of studies. In a study conducted on type-1 diabetic patients in 1996, on average, renal transplantation patients developed hyperkalemia up to day 100 after the transplantation, and only 2 patients developed hyperkalemia 8 months following transplantation. Hyperkalemia has been reported to be more frequent in patients on tacrolimus compared to those on cyclosporine.

6. Conclusion
The results of the current study revealed that hypertension, pre-transplantation diabetes, BUNn, family history of diabetes, RBS, and serum creatinine level can influence and predict the development of PTDM. Moreover, mortality among transplant patients can be due to graft survival failure; therefore, its early diagnosis and prevention are recommended. Although the administration of immunosuppressive drugs (CsA) has been reported to increase graft survival chances among transplant recipients, administering drug in wrong doses can lead to an increase in incidence of PTDM. According to the results of the current study, CsA administration should begin from 10 mg/kg/d in the first week and decrease to 8-9 mg/kg/d during weeks 2-5 after transplantation.

Limitations of the present study
As a limitation of the present study, intragroup analysis was not conducted in the case group so as to achieve a deeper understanding of PTDM causes. The short duration of the experiment was another limitation of the study. More prolonged studies are recommended, in which groups of PTDM patients with individual and biological differences should be compared.

Authors’ Contributions
Both authors contributed equally to this study.

Conflict of Interest Disclosures
The authors declare that they have no conflicts of interest.

Ethical Approval
The necessary ethical approval was obtained from the Ethics Committee of the College of Nursing, Hawler Medical University. Moreover, the required permission was obtained from the President of Zheen International Hospital in Erbil, the Kurdistan Region of Iraq. In addition, a thorough explanation of the method and objectives of the study was provided to the subjects, and they were ensured that their information would be kept confidential and that they could withdraw from the study whenever they wished. Finally, the subjects signed an informed consent form.

Research Highlights

What Is Already Known?
Renal transplantation failure is associated with the consumption of immunosuppressive drugs such as cyclosporine. Consumption will lead to post-transplant diabetes mellitus particularly during the early months following transplantation which can cause death.

What This Study Adds?
The incorrect administration of immunosuppressive drugs, including CsA, can lead to an increase in the development of post-transplant diabetes mellitus among patients with CKD who have undergone renal replacement therapy. PTDM development can be reduced by applying a dosage of 10 mg/kg/d during the first week and 8-9 mg/kg/d during weeks 2-5 following transplantation.

References


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