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Original article

Viral infections and Body Mass Index (BMI) as Major Risk factors for Post Transplantation Diabetes Mellitus - A Retrospective Study in Punjab, Pakistan

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Abstract: Background Recent therapeutic advancements have paved the path for complex restorative procedure like kidney or liver transplantation, but the increasing incidence of post transplantation diabetes mellitus (PTDM) in graft patients has become a major challenge**. Objective**: We aim to study the risk factors associated with the development of PTDM in our context. **Methods**: Data of 648 post transplant patient registered at the Punjab Human Organ Transplant Authority (PHOTA) was analyzed for the prevalence of PTDM. The data was taken after proper consent from the patients and their records available in the institute (pre-transplant data) and their current clinical reports (post-transplant data). **Results**: The prevalence of PTDM was higher (40.2%) in elder individuals (above age 51) with family history of diabetes (42.9%), and non- related organ donor (29.9%) as compared to a close relative (26%). The incidence of PTDM in liver transplant patients was higher (32.9%).The prevalence of PTDM in obese individuals was 28.4% with a post-transplant HbA1c value of more than 6.5%; the incidence of patients with high HbA1c value increased from 5.2% to 18.2% (post-transplant patients with > 6.5% HbA1c value). A strong association of HCV infection with PTDM was established 19.7% versus 17, 9% with an increased value of HbA1c (> 6.5%).Reported cases of PTDM in CMV positive group were noted however, no statistical significant correlation was established between them. **Conclusion**: High BMI and HCV infection are considered as risk factors for PTDM and these conditions should be addressed prior to transplant surgery to minimize the morbidity and mortality related to PTDM.

Keywords: Post-Transplant diabetes mellitus, PTDM, new onset diabetes mellitus, NODAT, kidney, liver

1. Introduction

Post-transplant diabetes mellitus (PTDM), also known as new onset diabetes mellitus (NODAT) is a common but severe complication in solid organ transplantation (SOT) patients (Cehic et al., 2018; Jenssen and Hartmann, 2019). PTDM has become a major cause of high mortality, and morbidity and have a high prevalence rate, worldwide. The reported incidence of PTDM after any solid organ transplantation ranges from 2% to 53% (Pham et al., 2011, Aravinthan et al., 2019). According to studies the incidence of PTDM range from 2.5% to 25% in liver transplant recipients, 4% to 25% in kidney transplant recipients, 4% to 40% in heart transplant recipients, and 30% to 35% in lung transplant recipients (Pham et al., 2016; Lieber et al., 2019; Herzer et al., 2020). PTDM is linked with increased incidence of other health issues in transplant patients including, cardiovascular disorders and various kinds of infection (Siraj et al., 2010; Ahmed et al., 2020).

Even though the pathophysiology of PTDM is not fully understood, the primary determinants include the malfunction of pancreatic β-cell, development of insulin resistance, and impaired insulin secretion (associated with the use of mammalian target of rapamycin complex 1 inhibitors and calcineurin inhibitors), and HCV (hepatitis C) infection that can cause insulin resistance and postoperative weight gain, are all believed to play a role (Prokai et al., 2012, Shivaswamy et al., 2016; Rodriguez-Rodriguez et al., 2019).

Certain risk factors have been identified as to play a crucial role in the trigger and clinical pathogenesis of PTDM. For instance, studies have shown that the use of immune suppressants and corticosteroids are important determinants of PTDM in transplant patients (Wauters et al., 2012; Chevallier et al., 2021). That is why it is critical to comprehend the significance of immunosup-

pressive drugs and glucocorticoids (such as calcineurin, ciclosporin, tacrolimus, betamethasone etc.) in the development of PTDM.

Moreover, the understanding the drug–drug interactions in these patients, as they are treated with various other drugs in addition to immunosuppressive treatments, is also important to control the risk of PTDM (Lucena et al; 2020). Other risk factors for PTDM include unhealthy lifestyle, obesity, source of donor (deceased or living), inflammation and viral infections (e.g., hepatitis C virus and cytomegalovirus, CMV) have been reported. Studies show that solid organ transplant recipients with specific terminal-organ diagnosis such as, end stage liver disease due to hepatitis C infection, end-stage kidney disease due to polycystic kidney disease, have been reported to be at increased risk for PTDM compared with those without such diagnosis (Jenssen & Hartmann, 2019; Ambarsari, 2020).

The pathophysiology studies of PTDM and Type 2 Diabetes Miletus (T2DM) shows that the two have different triggers and clinical course. These findings are also significant for the proper and effective diagnosis and treatment of PTDM. In 2003, the first International Consensus Guidelines for new-onset diabetes after transplantation (NODAT) were published (Davidson et al., 2003) and the American Diabetes Association and World Health Organization (WHO) recommend the use of HbA1c (HbA1c >6.5%) for the diagnosis of diabetes after the transplant patient have been discharged and are off their immune suppressants and at least a year has passed. Other diagnostics criteria include random glucose >200 mg/dL (11.1 mmol/L) with symptoms and two-hour glucose after a 75-g OGTT of >200 mg/dL (11.1 mmol/L) (Pham et al., 2016).

The present study aims to collect and analyze the prevalence of PTDM in kidney and liver-transplant patients and determine the association of various risk factors, including pre-transplant diabetes, body mass index (BMI), viral infections (HCV, CMV) and demographic characteristics, that may play a vital role in morbidity and pathogenesis of PTDM in the cohort samples.

2. Materials and Methods

2.1. Study Design

This study was conducted in Punjab Human Transplant authority (PHOTA) from 5 June 2020 till 25 August 2020 included all those patients who were registered in PHOTA and had undergone solid organ transplantation (liver and renal transplantation). There are 34 hospitals both private and public in Punjab which was registered for transplantation procedures. The pre-transplant data was taken from the records available in the institute.

The survey was conducted by well trained and experienced research coordinators/interviewer. IRB approval for the research was taken from Services institute of medical Sciences no: IRB 2020/678/SIMS. Proper permission was taken from DG PHOTA to conduct the study and use the data for publication and research use only. Patient privacy was taken into account and no patient names were used only allotted ID numbers were used to maintain record. A MOU was officially signed between PHOTA and Services Institute of Medical Sciences for a period of one year. The selected patients were contacted telephonically and questioned after formal informed consent. The data was entered on preformed Performa which was in turn entered on SPSS for analysis. The patients were advised to get either their HbA1c or random blood sugar checked by lab and send the reports. Information regarding other blood tests including HCV, CMV status was taken from the record. History pertaining to their family history of diabetes was taken verbally on telephone. Data pertaining to BMI of the patient was available from the records. However family history related to diabetes was enquired telephonically and added to the records. The operational definitions of the variables are defined below.

PTDM: Detection and persistence of hyperglycemia with or without symptoms in post-transplant patient.

HbA1C test is used to diagnose PTDM. An HbA1C level of more and equal to 6.5% was the cutoff for diagnosis of diabetes.

CMV infection is detected using CMV PCR test, (qualitative)

2.2. Study Population

Cross sectional design with survey method was adopted and convenient sampling was done. Out of 1799 registered cases, 754 post–transplant patients were approached only due to time constraints. Out of them, 80 patients were found to be expired while 26 were on waiting list for transplant, so these respondents were excluded from the data collection. So, data detail of 648 patients (who were alive) was taken, making response rate of 86% approximately.

2.3. Inclusion criteria

All those patients aged 11 years and above registered with PHOTA for solid organ transplantation were included. Liver and kidney transplant patients were recruited.

2.4. Aim/Objective

To study the association between CMV infection and hepatitis C infection as risk factor for development of post-transplant diabetes

3. Results

3.1. Demographic Parameters Analysis

The demographic data or the baseline characteristics of the study population were collected and analyzed for the prevalence of PTDM (Table 1). The following parameters were individually evaluated and their association with PTDM was determined.

3.2. Sex and Age

Both male and female patients were included in the study, however, the number of males patients (85%) who received organ transplant was higher as compared to the females (15%). The data for the occurrence of PTDM among the two groups showed that the incidence of PTDM was almost the same in both genders, with 24.6% of males and 25% of females were found to develop PTDM. The age-related incidence shows that the participants in the age group 51 and above were at the highest risk of developing PTDM (40.2%). However, the lowest morbidity rate was seen is participants who were aged between 31-40 years old (19.5%).

3.3. Organ Transplant and Donor Source

The patient data was analyzed separately for the type of organ transplant. i.e. kidney or liver and the source of organ, i.e., blood relative or distant relative. The results for organ-specific risk for the incidence of PTDM showed it was higher in patients with liver transplant (32.9%) as compared to 23.7% incidence rate in kidney transplant patients. The data for organ-source showed that the incidence was higher (29.6%) when the organ belonged to a distant relative as compared to 26% when organ was from close relatives.

3.4. Family history of Diabetes

Patient data was analyzed for the having a family history of diabetes and was studies as a risk factor for the development of PTDM. The results showed that 42.9% of the patients who had family history of diabetes showed an increased HbA1c value, i.e., greater than 6.5%. While in individuals without any family history of diabetes, only 16.2% developed PTDM (Table 2).

3.5. Body Mass Index

The pre-transplant BMI data of patients was analyzed as a risk factor of PTDM. The post-transplant HbA1c values in the patients showed that the body mass index values were directly proportional to the incidence of PTDM. It was found that 19 (28.4%) of the patients belonging to the obese group (BMI of 27 and above) were found to have HbA1c value of more than 6.5%. The incidence of PTDM, in relation to HbA1c values showed that 16.5% of individuals with normal BMI (18.5-22.9) had crossed the normal and moderate threshold of serum HbA1c value (Figure 1).

Table 1: The demographic data of solid organ transplant patients and frequency of PTDM

Characteristics	Frequency	Percentage (%)	PTDM (Yes %)
Gender			
Male	548	84.6	24.6%
Female	100	15.4	25%
Age			
11-20 years	56	8.6	25%
21-30 years	175	27.0	21.1%
31-40 years	190	29.3	19.5%
41-50 years	145	22.4	26.9%
51 and above	82	12.7	40.2%
Height			
150 - 159 cm / 4.11"-5.25"	72	11.1	23.6%
160 - 169 cm/ 5.29"-5.65"	274	42.3	23.4%
170 - 179 cm/ 5.69"-5.10"	296	45.7	26.4%
180 and above/ 5.11"- above	6	.9	16.7%
Weight			
Less than 50 kg	24	3.7	25%
50-59 kg	145	22.4	24.1%

60-69 kg	377	58.2	22%
70-79 kg	54	8.3	27.8%
80-89 kg	22	3.4	31.8%
90-99 kg	20	3.1	55%
100 and above kg	6	.9	50%
Organs			
Liver	73	11.3	32.9%
Kidney	575	88.7	23.7%
Donor Relation			
Blood Relation	594	91.7	24.2%
Distant Relation	54	8.3	29.6%
Diagnosis Category			
End-Stage Renal Disease (ESRD)	570	88.0	23.7%
Chronic Liver Disease (CLD)	66	10.2	31.8%
Others	12	1.9	33.3%

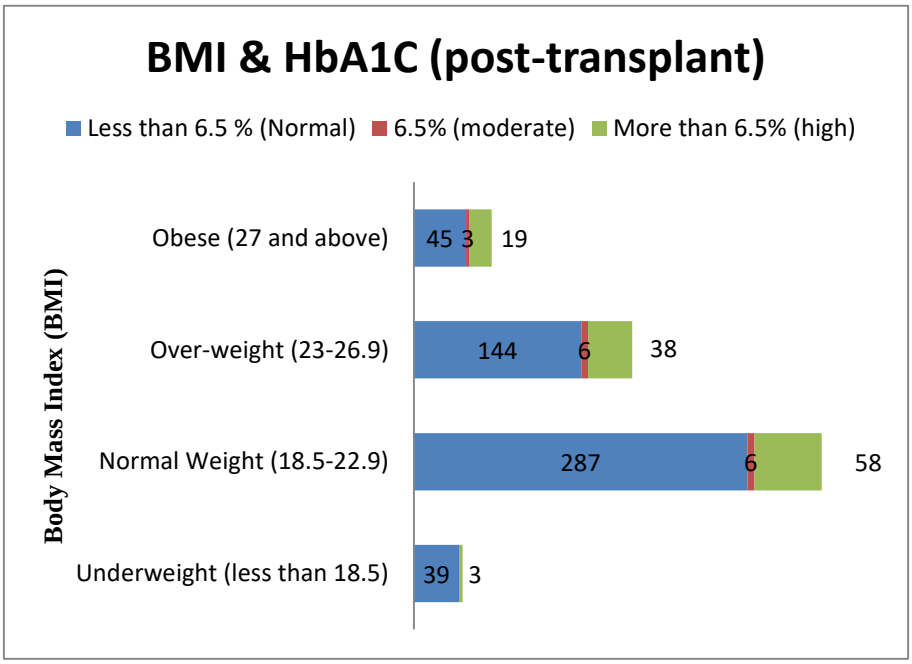

Figure 1: The relationship between BMI and post-transplant values of HbA1c in patients

3.6. Pre & Post Transplant HbA1c values of the patients

The patient's data was analyzed for their pre- and post-transplant HbA1c values. The results showed that the pre-transplant values of HbA1c were normal (< 6.5%) in 94.3% of the patients and only 5.2% had high values (> 6.5%). The post-transplant HbA1c analysis showed that 79.5% of patients had normal values and 18.2% had high HbA1c values. So, the incidence of patients with high HbA1c value increased from 5.2% to 18.2% in post-transplant patients (Figure 2).

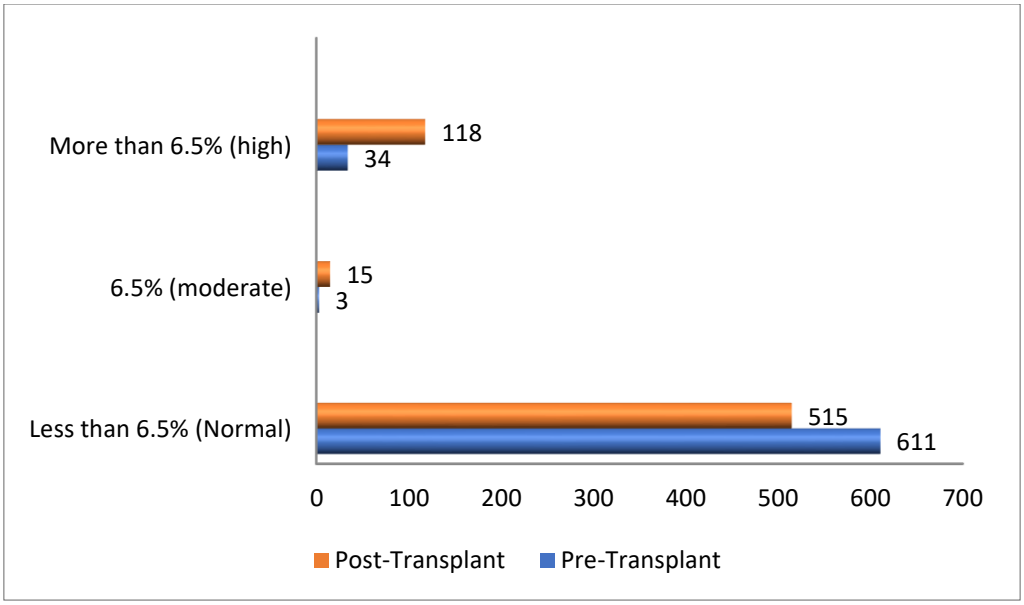

Figure 2: The comparison of pre-transplant and post-transplant HbA1c values of the patients

3.7. Family History of Diabetes, Viral Infections and Prevalence of PTDM

The patient data was analyzed for the presence of family history of diabetes and viral infections including hepatitis-C virus (HCV) and cytomegalovirus (CMV). The results for individual virus are given below:

Table 2: Relationship between Family History of Diabetes, Hepatitis-C & CMV-Infection with HbA1c (post-transplantation)

		Family History of Diabetes		Hepatitis-C		CMV-Infection	
		Yes	**No**	**Positive**	**Negative**	**Positive**	**Negative**
HbA1c (Post-Transplant)	**Less than 6.5% (Normal)**	27 (55.1%)	488 (81.5%)	92 (78.6%)	423 (79.9%)	318 (79.1%)	197 (80.1%)
	6.5% (Moderate)	1 (2.0%)	14 (2.3%)	2 (1.7%)	13 (2.4%)	11 (2.7%)	4 (1.6%)
	More than 6.5% (High)	21 (42.9%)	97 (16.2%)	23 (19.7%)	95 (17.9%)	73 (18.2%)	45 (18.3%)

The data analysis of family history of diabetes and PTDM shows that 55.1% patients with history of diabetes and 81.5% patients with no family history of diabetes had their HbA1c vales in normal range (<6.5%) after receiving the transplantation. While on the other hand, 42.9% patients with family history of diabetes and 16.2% with no family history of diabetes had increased values of HbA1c (>6.5%) after transplantation. However, patient with no family history of diabetes had high level of HbA1c then others.

The data analysis of prevalence of HCV and incidence of PTDM in patients showed that 78.6% who were positive for HCV and 79.7% HCV negative patients had their HbA1c values in the normal range (< 6.5%) after receiving the organ transplant. 19.7% of HCV positive patients were found to have increased value of HbA1c (> 6.5%) after undergoing a kidney or liver transplantation surgery. The incidence of PTDM (HbA1c more than 6.5%) in HCV negative patient was found to be 17.9% (Table 2).

However, the data analysis of prevalence of CMV and incidence of PTDM in transplant patients showed that 79.1 % who were positive for CMV infection and 80.1 % CMV negative patients had their HbA1c in the normal range (< 6.5%) after receiving the organ transplant. Further, the data

showed that 18.2 % of transplant patients who were found to be positive for CMV had increased HbA1c (> 6.5%) values after more than a year of transplantation surgery. Based on the HbA1c values, the incidence of PTDM in CMV negative patient was found to be 18.3% (Table 2).

4. Discussion

The present study analyzes the patient data of 648 transplant patients for the prevalence of post transplantation diabetes miletus (PTDM) after one year of the surgical procedure. The age-related demographic data suggests that age has a directly proportional relationship with the risk of developing PTDM. 40.2 % of the elderly individuals that belonged to the age group of above 51 developed PTDM as compared to only 20% young transplant patients. Similar findings have been reported by Malik et al. who found that old age was an independent-baseline PTDM risk factor and older recipient had a higher chance (P<0.001) of developing diabetes after organ transplant (Malik et al., 2021).

The risk of PTDM also varies with the type of organ being transplanted. The present data suggests that the incidence of PTDM was higher in individuals who received kidney transplant (32.9%) as compared to the liver transplant patients (23.7%) who underwent the surgery in the same time frame. Similar findings have been previous reported that indicate that around 19%-35% of liver transplant patients develop diabetes after some years of therapeutic surgery (Lv et al., 2015; Hartog et al., 2015). Various factors come into play with the pathophysiology of PTDM and liver transplant. According to Aravinthan and colleagues (2019) about quarter of non-diabetic patients who received liver transplant developed PTDM after a year of surgery. The organ-source was also analyzed as potential risk factor for PTDM. The results suggested that individuals who received a transplant from blood relatives had a lower rate of PTDM (24.2%) as compared to individuals in which the organ-source was distant relatives (29.6%). These findings can be understood by the fact that blood relatives have lower chances of HLA-mismatch as compared to individuals who are distantly related. According to van der Burgh et al. an increased HLA-mismatch is a risk factor for PTDM (van der Burgh et al., 2020).

Moderate to high HbA1c levels are indicative of pre-diabetic and diabetic conditions, respectively (Li, et al., 2018). Similarly, PTDM and HbA1c levels have been found to be directly associated and individuals with high HbA1c pre-transplant and post-transplant levels have high risk of developing PTDM (Ahmed et al., 2020). In the present study, the patient's data was analyzed for their pre- and post-transplant HbA1c values. The incidence of patients with high HbA1c value increased from 5.2% to 18.2% in post-transplant patients (Figure 2).

Various researches consider increased body mass index (BMI) or obesity as a risk factor for diabetes miletus. And recent studies also show that individuals with increased BMI or are obese and receive an organ transplant are at high risk of developing PTDM in future. Present study also shows that there was an increased incidence of PTDM in individuals who have a high BMI (BMI of 27 kg/m2 and above). The post-transplant HbA1c values in the patients showed that the body mass index values were directly proportional to the incidence of PTDM. It was found that 19 (28.4%) of the patients belonging to the obese group were found to have HbA1c value of more than 6.5% (Figure 1). These findings are in consistence with the findings of Chowdry and colleagues who have reported obesity as a main risk factor for PTDM.

Similarly, various researches supports the notion that individual with high Body Mass Index (> 25 kg/m2) or increased circumference of the waist, are at an increased risk of type-2 diabetes as well as PTDM. They suggest that obesity can predate the transplant, but weight gain after transplant can significantly contribute to the risk of developing PTDM (Shivaswamy et al., 2016; Malik et al., 2021). The pathophysiology of PTDM and its link with obesity have been widely studies. According to Stinkens and co-researchers (2015) in obese individuals the presence of increased fat mass occurs due to dysfunction of adipose tissue. This abnormality causes altered lipid storage capacity and inflammation, which leads to the development of insulin resistance and reduced glucose metabolism by stimulating an excess storage of fat in the pancreas.

The link between presence of viral infections, including HCV and CMV in transplant patients and incidence of PTDM was also analyzed in post-transplant patients. Data suggests that 19.7% of HCV positive patients were found to have increased value of HbA1c (> 6.5%) after undergoing a kidney or liver transplantation surgery (Table 3). These findings can be understood by the idea that the Hepatitis C infection has been shown to be associated with insulin resistance (Desbois & Cacoub, 2017). Similarly, Roccaro and colleagues (2018) have reported that treatment of HCV using antiviral therapy in liver transplant recipients led to a decrease in incidence of PTDM.

5. Conclusions

The high prevalence of PTDM in liver and kidney transplant patients indicates that certain factors, both manageable and non-manageable, play an important role in the pathophysiology of the disease. The present study suggests that increased BMI and HCV infection are high risk factors for

developing PTDM. Both of these factors are considered manageable as with taking appropriate measures, obesity and HCV can be managed that would decrease the incidence of PTDM and related morbidities in transplant patients.

Supplementary Materials: None.

Author Contributions: Hafeeza Naz: data collection, project administration, draft preparation; Amena Moazzam Baig: Conception, methodology, writing, supervision, administration and draft preparation; Zulekha Mehmood: data collection, analysis, draft preparation; Javeria Mushtaq: data collection and draft preparation; Murtaza Haider; draft preparation and data collection.

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Data Availability Statement: None

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