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Incidence of post transplant diabetes mellitus in Erbil Teaching Hospital

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Abstract

Background and objective: The onset of post-transplant diabetes mellitus has been linked to higher rates of cardiovascular disease and infection. The aim of this study was to evaluate the incidence of post renal transplant diabetes. More specifically, they study tried to find out the demography of patients with post transplant diabetes mellitus, their anthropometric measures, the incidence rate in different periods and among different demographic variables.

Methods: Seventy patients transplanted in different centers in Iraq were enrolled in the study. The patients were followed up for more than one year during their visits and or admission to the Dialysis Unit in Erbil Teaching Hospital during the period between 1/12/2006 and 1/4/2008. The statistical package for the social sciences (version 14) was used for data entry and analysis.

Results: Fifty four patients were male and 16 patients were female. Their ages ranged between 14 and 65 years with a mean of 36 years. Thirty one percent of them developed post transplant diabetes mellitus; 14% developed post transplant diabetes mellitus at early while 17% developed post transplant diabetes mellitus at late period. A significant association was found between increased age and triglyceride and post transplant diabetes mellitus.

Conclusion: Post transplant diabetes mellitus is an important complication that the transplant physicians should screen for in every transplanted patient. Increasing age and serum triglyceride levels may be regarded as predictors for the development of post transplant diabetes mellitus.

Keywords: Incidence; Post transplant diabetes mellitus; Hypertension; Erbil; Iraq.

Introduction

With improvements in patient and graft survival after transplantation in the last decade, increasing attention has been placed on non-immunologic outcomes that contribute to patient morbidity and mortality.[1-2] The onset of post-transplant diabetes mellitus (PTDM) has been linked to higher rates of cardiovascular disease and infection, and it is a major cause of morbidity and mortality.[1] Risk factors for PTDM in kidney transplant recipients are similar to those in the non-transplant population[2]. The consequences of diabetes are also the same, such as increased risk of cardiovascular disease, infection, nephropathy, neuropathy, and retinopathy.[1-3] International consensus guidelines regarding the definition of new-onset diabetes mellitus (DM) after transplantation used standard World Health Organization (WHO) and American Diabetic Association (ADA) criteria for diagnosis of DM as well as impaired glucose tolerance.[1-2] Importantly, the use of glycated hemoglobin (HbA1c) is not recommended before three months post-transplant, as the test may not be valid until new hemoglobin has been synthesized and glycated for the appropriate period in the diabetogenic

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post-transplant setting.[2] Because of varied definitions, the incidence of PTDM is difficult to determine. It has also changed over the past decades with changes in definition, immunosuppression regimens, and patient demographics. The incidence of PTDM was systematically reviewed by many studies,[1,4-7] 12 months cumulative incidence estimation of PTDM were reported to be within the range of 2-53%. In 1979, rates as high as 46% were reported; this rate was attributed in part to the use of high doses of steroids, occurring as long as 20 months post-transplant.[4] Subsequent estimates are that the development of DM occurs among approximately 9%, 16%, and 24% at 3, 12, and 36 months post-renal transplantation, respectively.[5-7] Many of the same risk factors that predispose non-transplant patients to DM have been identified as risk factors for its development after transplantation. In addition, unique factors, such as immunosuppression, HLA mismatch, donor gender, and the underlying renal disease, may also enhance the risk of PTDM.[8] The factors including increased age,[4-5,9] obesity,[9-12] race and ethnicity,[5-6,13-16] family history,[16] HLA matching and donor characteristics,[1,5] infection such as Hepatitis C Virus (HCV)[5,17-20] and Cytomegalovirus, [21-22] type of underlying renal disease [23-24] and medications such as glucocorticoids,[25-28] Calcineurin inhibitors,[3,5,7,18,14,29-33] Sirolimus[34-35] and immunosuppressive combination regimens such as combination of tacrolimus and azathioprine.[32,36] The risk of PTDM in Iraq is unknown. Studying PTDM, their associated risk factors and choices of immunosuppressive therapy will help the physician to have a better understanding of the incidence of PTDM and manage their associated risk factors as well as paying careful attention to the choice of the immunosuppressive regime to decrease the risks of PTDM. The objectives of this study were to find out the demography of patients with PTDM, their anthropometric measures, the incidence rate of PTDM in different periods and among different demographic variables.

Methods

Design, setting and time of the study:
This is longitudinal analytic study included following 82 patients with kidney transplantation in different centers in Iraq. The patients were followed up for more than one year during their visits and or admission to the Dialysis unit in Erbil Teaching Hospital during the period between December 1st, 2006 and April 1st, 2008.

Inclusion criteria:
All patients with kidney transplant were recorded in this study.

Exclusion criteria:
Twelve patients were excluded in the study because they had DM. The remaining seventy patients were enrolled in the study.

Laboratory examinations:
A complete history and physical examination and previous blood tests with new blood tests were performed and reported. Oral glucose tolerance tests were not performed to our patients. Fasting and random blood sugars were reviewed, and new blood sugar tests were performed.[1] The results of the HLA matching were questioned for every patient and reported. For related donors, the HLA matching and the degree of compatibility were reported as haplotype matching. For unrelated donors, only white cell cross match was done.

Diagnostic criteria:
Post transplant diabetes mellitus (PTDM) was diagnosed according to the WHO and ADA criteria for the diagnosis of DM,[5] such as symptoms of diabetes plus casual PG concentration ≥200 mg/dl (11.1mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss, or FPG ≥126 mg/dl (7mmol/l). Fasting is defined as no caloric intake for at least 8 hours, or 2 hours PG ≥200 mg/dl (11.1mmol/l) during an oral glucose tolerance testing using a glucose load

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containing an equivalent of 75 g anhydrous glucose dissolved in water. Normal fasting plasma glucose (FPG) 110<mg/dl (6.1mmol/l). Impaired fasting glucose (IFG) ≥ 110 mg/dl (6.1mmol/l) and 126 <mg/dl (7 mmol/l). Normal glucose tolerance: 2-hour PG 140 <mg/dl) 7.8 mmol/l). Impaired glucose tolerance: 2-hour PG ≥ 140 mg/dl (7.8 mmol/l) and 200 <mg/dl (11.1 mmol/l). The body mass index (BMI) was calculated for our patients from the equation below:
BMI = weight (kg)/height (m^2).
Hypertension, defined as systolic blood pressure more or equals 140 mm/Hg and or diastolic blood pressure more or equals 90 mm/Hg, or patient's blood pressure controlled with antihypertensive medication.[37] All patients included in this study received steroid in the form of prednisolone tablets (5-10 mg) daily after transplant, only five patients of them received steroid also before transplant between 1-3 years (patients their renal failure due to nephrotic syndrome). All patients received compensation of chemotherapy drugs, 49 patients (70%) on Cyclosporine plus Mycophenolate Mofetil (Cyclo/MMF), while 21 patients (30%) on cyclosporine plus Azathioprine (Cyclo/AZA), no patients found to be on Tacrolimus in this study.

Ethical consideration:

The research protocol was reviewed and approved by Ethical Committee of the center of Iraqi Board of Medical Specialization in Medicine. The anonymity of the participants was preserved.

Data entry and data Analysis:

The statistical package for the social sciences (version 14) was used for data analysis. Differences between means of continuous variables were measured using t-test. A *P* value ≤0.05 was considered statistically significant.

Results

Socio-demographic characters of the total sample:

Seventy patients were enrolled in this study. Most frequent age group was 30-39 years old, 54 patients were males (77.1%) and 16 patients were females (22.9%), 18 patients found to be smoker (25.7%), 52 patients (74.3%) received kidney from unrelated donor while 18 patients (25.7%) received kidney from related donor (Table 1).

Table 1: Socio-demographic characteristics (N=82).

Variables		No.	Percentage
Age group	<20	1	1.43
	20-29	19	27.14
	30-39	25	35.71
	40-49	15	21.43
	≥50	10	14.29
Gender	Female	16	22.90
	Male	54	77.10
Family History of DM	Positive	15	21
	Negative	55	79
Smoker	Yes	18	25.7
	No	52	74.3
Donor Relationship	Unrelated	52	74.30
	Mother	4	5.70
	Brother	5	7.10
	Sister	4	5.70
	Son	2	2.90
	Uncle	1	1.40
	Uncle Son*	2	2.90

*Uncle Son: Cousin.

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Patients' height in centimeter (cm) ranged from 100 to 190 with a mean of 166.02 cm. Their weight in kilograms (Kg) ranged from 35 to 97 with a mean of 68 Kg. Their BMI ranged from 19.67 to 42 with a mean of 24.7. The duration of transplant ranged from 4 months to 23 years (Table 2). Forty eight patients (68.8%) did not develop DM after transplant, while 22 patients (31.4%) developed PTDM after transplant of which 10 patients (14%) developed PTDM within three months of transplant (early period) and 12 patients (17%) develop PTDM after three months after transplant (late period) (Table 3). Regarding treatment of PTDM, patients developed transient PTDM didn't need long term treatment while patients developed late period PTDM needed long term treatment; 8 patients of them were treated with insulin, 2 of them were treated with glimepiride, and 2 of them treated with gliclazide.

Table 2: Anthropometric and transplant duration variables (N=82).

Variables	N	Minimum	Maximum	Mean	Std Deviation
Height	70	100	190	166.02	13.26
Weight	70	35	97	68.03	11.55
BMI	70	19.67	42	24.72	3.70
Transplant duration	70	4	276	32.21	44.15

Table 3: Incidence of patients with PTDM with drugs received (N=82).

PTDM and drugs used		Frequency	%
PTDM	None	48	68.6
	Early	10	14.3
	Late	12	17.1
	Total	70	100
	Insulin	8	66
Drugs used in late PTDM	Glimepiride	2	17
	Gliclazide	2	17

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Hypertension was found in 25 patients (35.7%) before transplant while 14 patients (20%) developed hypertension after transplant. The cause of renal failure was idiopathic in 63 patients (90%), nephritic syndrome in five patients (7.2%), Alport disease in one patient (1.4%) and adult polycystic kidney disease in one patient (1.4%) (Table 4). All patients enrolled in this study received steroid in the form of prednisolone tablets (5-10 mg) daily after transplant. Only five patients received steroid also before transplant between 1-3 years (patients their renal failure due to nephrotic syndrome). All patients received compensation of chemotherapy drugs, 49 patients (70%) on Cyclosporine plus MycophenolateMofetil (Cyclo/MMF), while 21 patients (30%) on cyclosporine plus Azathioprine (Cyclo/AZA), no patients found to be on Tacrolimus in this study. Regarding virology of the patients, 64 patients (91.4%) were tested negative, three patients (4.3%) were tested HBsAg positive, two patients (2.9%) were tested anti HCV Antibody positive, and one patient (1.4%) was HBsAg positive and anti HCV antibody positive.

Table 4: Frequency of some diseases, virology & drugs used for immunosuppression (N=82).

Variables		Frequency	Percentage
Hypertension	None	31	44.3
	Before transplant	25	35.7
	After transplant	14	20
Renal failure causes	Unknown	63	91
	Nephrotic syndrome	5	7
	Polycystic kidney disease	1	1
	Alport disease	1	1
Drugs used for immunosuppression	Cyclo/MMF	57	70
	Cyclo/AZA	25	30
Virology	Negative	64	92
	HBV	3	4
	HCV	2	3
	HBV+HCV	1	1

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Regarding the difference of mean±SD of PTDM by demographic, anthropometric measurements and blood lipid tests, it was found that age, triglyceride level higher than 161 mg/dl and random blood sugar showed statistically significant differences between positive and negative cases of DM (P value <0.05), Table 5. No significant difference of mean±SD of variables such as gender of transplanted patients, family history, donor relation to transplanted patients, hypertension before or after transplant, virology of the transplanted patients, smoking, cause of renal failure before transplant and drugs used for immunosuppression.

Table 5: Association of PTDM with anthropometric measurements & blood lipid tests (N=82).

DM							
Variables	**Negative**			**Positive**			***P* value**
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	
Age	48	34.125	9.4703	22	41	13.7495	0.018
Height	48	165.396	15.2814	22	167.409	7.2352	0.457
Weight	48	67.0958	12.2869	22	70.0909	9.7341	0.277
BMI	48	24.6206	4.1201	22	24.955	2.6402	0.684
Transplant duration	48	25.7708	31.091	22	46.2727	62.7787	0.158
FBS	48	100.542	20.5074	22	109.091	31.6708	0.255
RBS	48	134.917	36.0973	22	177.318	53.9712	<0.001
Total cholesterol	48	191.229	35.639	22	193.318	23.5117	0.772
Serum TG	48	144.896	31.4989	22	161.818	37.6243	0.045
LDL	48	137.292	17.1029	22	143.182	14.2716	0.139
HDL	48	28.8333	1.9497	22	28.8182	1.3323	0.97

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Discussion

In this study, the incidence of DM in the first three months post transplantation was (14%); interestingly, no one of those patients developed permanent DM that required treatment. High dose steroids (IV or oral) used for induction or for treating acute rejection episodes and high doses of cyclosporine initially used for induction, both might contribute to the hyperglycemia initially observed in those patients.[4-7,9] Many studies associated the use of high dose of immunosuppression with early hyperglycemia and was not mentioned as a risk factor for developing permanent DM later.[1,4-7] In this study, the exact dose of steroid used initially was not reported, and the rejection episodes were not entailed. This group of PTDM was treated transiently for few days with subcutaneous insulin, and no one of those patients needed long term therapy. No association between steroid use and DM in this study was observed. In the current study, increased age was statistically associated with the development of PTDM (*P* <0.018), permanent DM requiring treatment was found in (17%). Although other studies have reported higher incidence than the current study such as a study conducted in 2004[38] reported the incidence of hyperglycemia in the first month post transplantation to be (38.7%) and after that up to 6 months to be (22.6%) but the number of patients in such study was small and the follow up period was short. There are other studies recorded similar low incidences as our study. Kasiske et al. in 2003 reviewed the incidence and risk factor for developing PTDM in 11659 patients; they found that the incidence of PTDM was (19%) and increasing age and hepatitis C virus was associated with the development of PTDM.[5] Roth et al. in 1989 reported an incidence of (18.6%) of PTDM in 908 patients followed up for ten years. Increased age greater than forty years associated with higher incidence of PTDM. High BMI was also significant risk factor.[39] In the current study, high serum triglyceride level was significantly associated with the development of PTDM. The mean triglyceride level of more than 161 mg/dl in our study was associated with the development of PTDM. Cosio et al. in 2002 included 1811 patients transplanted in a single institution between 1983 and 1998 also found hypertriglyceride of more than 200 mg/dl was particularly pronounced in PTDM and elevated triglyceride levels correlated with the development of PTDM independent of other risk factors. Increasing BMI and African American was also associated with increase the risk of development of PTDM.[10] Vesco et al. in 1996 reviewed the incidence and risk factors of PTDM in 1325 patients and found that a high BMI and increasing age is also associated with the development of PTDM. Triglyceride level more than 200 mg/dl was associated with the development of PTDM.[40] Although many studies proved an association between high BMI and the development of PTDM,[1,4-7] in our study there was no difference in the mean BMI in diabetics and nondiabetics and when compared with other studies. The mean BMI was higher than that reported among our patients. This difference is probably related to the nutritional status of the patients and adequacy of dialysis before transplantation. Generally speaking, the adequacy of dialysis in our country is suboptimal, and malnutrition with weight loss is a usual feature of our patients. Small sample size may also have affected the results. Family history was positive in 27% of patients with PTDM versus 18% nondiabetics, but it does not reach statistically significant association. In many studies, the association of hepatitis C virus infection with PTDM was reported. A meta-analysis in 2005 of ten studies including 2,502 patients found that anti-HCV positive patients were nearly four times more likely to have PTDM compared with uninfected individuals.[21] In addition, at least one group has shown decreased incidence of new-onset diabetes with the

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treatment of hepatitis C infection before transplantation.[41] In our study, there was no statistically significant association between hepatitis C virus infection and PTDM. This might be attributed to the small number of patients infected with hepatitis C virus in this study, in addition in our country, we almost exclude patients infected with hepatitis C virus from the waiting list for the transplant. Polycystic kidney disease may confer an increased risk of PTDM, although this has not been consistently observed.[24-25,42] In our study, there was only one patient with polycystic kidney disease transplanted and he developed PTDM. Pulsed high-dose therapy for acute rejection also appears to be a particularly strong risk factor for PTDM.[40] The use of pulse steroid therapy of our patients was not recorded and all of them were on the same dose of steroid therapy (10 mg/day). There was no attempt to stop steroid or to lower the dose to calculate the difference. A review of 11,659 USRDS patients reported that initiation with tacrolimus as maintenance therapy was associated with a 1.53 relative risk of PTDM over that observed with non-tacrolimus containing regimens.[5] Another study found that the incidence of PTDM by two years after transplantation was increased approximately 70% in renal transplant patients on tacrolimus versus cyclosporine-based regimens.[7] In our study, cyclosporine use was not associated with the development of PTDM; all patients were receiving the drug without level monitoring. No patient in our study received tacrolimus. Mycophenolatemofetil (MMF) was used in 70%, Azathioprine was used in 30% of the patients included in this study, and there was no statistically significant association with the development of PTDM. Azathioprine, mycophenolatemofetil (MMF) do not have independent diabetogenic effects.[5] The use of azathioprine and MMF in our study was actually associated with a decreased risk of PTDM (16% and 22%, respectively). This benefit may be due to the ability to permit the use of lower doses of corticosteroids, although this is unproven.

Conclusion

The incidence of PTDM is high compared to other studies. Post transplant DM is an important complication that the transplant physicians should screen for in every transplanted patient. Increasing age and serum triglyceride levels may be regarded as predictors for the development of PTDM. The choice and the doses of immunosuppressive therapy is another modifiable risk factor for PTDM, and careful attention should be giving to the choice of immunosuppressive

Conflicts of interest

The authors report no conflicts of interest.

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