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Evaluating the incidence, risk factors and glycaemic control of new-onset diabetes mellitus in kidney transplant recipients: a single centre study

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ABSTRACT

This study aimed to evaluate the incidence and risk factors for development of post-kidney transplant diabetes mellitus (PTDM) and its glycaemic control in a single centre. Adult kidney transplant recipients (n = 164) under follow-up at Penang Hospital, Malaysia since transplantation (mean follow-up time: 11.04±6.26 years) were retrospectively reviewed. Data were retrieved from year 1984 to 2010. PTDM was defined according to the American Diabetes Association Guideline. Clinical covariates of PTDM were determined by using binary logistic regression analysis. Thirty six patients (22.0%) developed PTDM with a cumulative incidence of 5.5%, 6.7%, 12.2% and 17.7% respectively at 1, 3, 5 and 10 years post-transplantation. Multivariate analysis showed that the number of concurrent diseases in the patients (OR = 2.26, p = 0.007) and fasting blood sugar (FBS) level at 6 months post-transplant (OR = 4.10, p = 0.001) were independent predictors of PTDM. The mean FBS level at the time of diagnosis for PTDM was 11.21±5.57 mmol/L. Treatments with anti-diabetic drug(s) were given and the FBS levels were under controlled (mean value of 6.50±1.14 mmol/L) at six months after the PTDM diagnosis. Close monitoring of blood sugar level particularly early after kidney transplantation is necessary for the detection of PTDM.

INTRODUCTION

Over the past three decades, kidney transplantation has become the treatment of choice for many end-stage kidney failure patients, due to improved short- and long-term survival benefits over dialysis treatment (Kälble *et al*., 2009). The establishment of transplantation has been made possible by the introduction of immunosuppressant therapy (NICE, 2004). However, evidence demonstrates that post-transplant diabetes mellitus (PTDM) is an increasingly common complication of kidney transplantation (Cosio *et al*., 2001). PTDM increases the risk of graft-related complications such as graft rejection, reduced graft function, graft loss and infection (Miles *et al*., 1998; Roth *et al*.,1989) and reduces the survival of transplant recipients (Jindal and Hjelmesaeth, 2000; Kasiske *et al*., 2003). It is also a major determinant of the increased cardiovascular morbidity and mortality seen in transplant recipients (Kasiske *et al*., 1996). The incidence of PTDM in the first year after transplantation found to be varied from 2 to 50% (Montori *et al*., 2002). The time to onset of new onset diabetes appears to be at greatest risk during the first 6 months post transplantation, although the number of patients developing the condition continues to increase with time thereafter. For those who develop diabetes after transplantation, the management should follow the American Diabetic Association (ADA) guidelines for the treatment of patients with type 2 diabetes (ADA, 2003; Benhamou and Penfornis, 2002). Intensive blood glucose control in these patients confers significant benefits in terms of preventing complications (DCCT Research Group, 1993; UKPDS Group, 1998). Previous reports have identified the importance of ethnicity, with a greater risk of developing PTDM in African Americans and Hispanics than in white recipients (Benhamou and Penfornis, 2002; Miles *et al*., 1998; Vesco *et al*., 1996).

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The differing incidence of new-onset diabetes after transplantation in patients of different ethnicity may reflect differential pharmacokinetics and diabetogenic effects of immunosuppressive agents (Soule *et al*., 2005). For instance, African Americans require 37% higher doses of tacrolimus to achieve comparable blood concentrations compared with whites. Hence, African Americans may expose to a higher diabetogenic effects of Tacrolimus (ADA, 2003; Kasiske *et al*., 1996). Other risk factors for developing PTDM were older age (Boudreaux *et al*., 1987), family history (Hjelmesaeth *et al*., 1997), hepatitis C infection (Kasiske *et al*., 2003), increasing HLA mismatches (Kasiske *et al*., 2003), obesity (BMI $\geq$ 30kg/m^2) (Boudreaux *et al*., 1987; Cosio *et al*., 2001; Jawad and Rizvi, 2000), donor source (Boudreaux *et al*., 1987; Sumrani *et al*., 1991), acute rejection (Al-Uzri A *et al*., 2001; Cosio *et al*., 2001; Hjelmesaeth *et al*., 1997; Rao *et al*., 1992; Roth *et al*., 1989; Sumrani *et al*., 1991; von Kiparski A *et al*., 1990), the type of immunosuppressive agents used to prevent and treat rejection (Cosio *et al*., 2001; Hjelmesaeth *et al*., 1997; Rao *et al*., 1992; Roth *et al*., 1989; Sumrani *et al*., 1991; Vesco *et al*., 1996; Yoshimura *et al*., 1988) and the dose of corticosteroids (Hjelmesaeth *et al*., 1997; Jawad and Rizvi, 2000; Kasiske *et al*., 2003; Pirsch *et al*., 1997).

Currently, there is limited documentation on PTDM risk in the Asian population, particularly among the multiple ethnic groups of Malay, Chinese and Indian in country like Malaysia. This study was therefore aimed to evaluate the incidence and risk factors that pre-dispose kidney transplant patients to the development of PTDM according to the Asian population. This identification will provide an insight into how risk profiling and management of kidney transplant recipients could be improved to avoid or delay the development of diabetes mellitus after transplantation. This study also sought to assess the glycaemic control of PTDM patients in a single centre including the prescribed drug regimens.

METHODS

This was a retrospective single centre study based at the Haemodialysis Unit, Penang Hospital, Malaysia. The study population was all kidney transplant patients aged over 18 years old who were under follow up at Penang Hospital since their transplantation. Patients' data were retrieved from 30th April 1984 to 30th June 2010. Patients with graft failure or death within 1 year post-transplant, multi-organ transplant recipients, patients who had a diagnosis of diabetes mellitus prior to transplant (either as native kidney disease or co-morbidity) and those with incomplete medical records were excluded. Data were collected from patients' medical record at Hemodialysis Unit. This study has granted ethics approval from Research and Ethics Committee of Ministry of Health Malaysia.

For each studied subject, the following clinical characteristics were considered possible risk factors for development of PTDM: age at transplant, gender, race, weight and serum creatinine, dialysis prior to transplant, type of donor (living/ cadaveric), Hepatitis C antibody (HCV) status at time of transplant, acute rejection post-transplant, dialysis dependent first week post-transplant, trough levels of calcineurin inhibitors (cyclosporine and tacrolimus), number of concurrent diseases and presence or absence of hypertension. As information on family history of diabetes, numbers of human leukocyte antigen mismatches and hematuria or proteinuria post-transplant were not systematically documented in the patient medical records, these variables were not considered in the study. Besides, the date of diagnosis of PTDM, anti-diabetic drugs that prescribed, levels of fasting blood glucose (FBS) since time of transplant were also assessed. However, the random blood sugar and glycated haemoglobin (HbA1c) level were not assessed as these tests were not routinely performed among the patients.

Definition of PTDM

PTDM was defined as a random (any time of day without regard to time since last meal) plasma glucose concentration $\geq$ 200 mg/dL (11.1 mmol/L) or a fasting (no caloric intake for 8 hours) plasma glucose $\geq$ 126 mg/dL (7.0 mmol/L), confirmed upon repeat testing on a different day, as recommended by the American Diabetes Association (ADA). (ADA, 2003).

Target for control of PTDM

Currently, there is no specific mention on the target for control of PTDM. The natural progression of diabetes post kidney transplantation resembles that of Type 2 diabetes because of the insidious onset and patients may be asymptomatic for years before the symptoms become clinically evident (Kasiske *et al*., 2003). Hence, glycemic recommendations for adults with Type 2 diabetes mellitus (according to the ADA) will be used as the target for control of PTDM (ADA, 2003). These target of control include HbA1C < 7.0%, fasting plasma glucose 70–130 mg/dl (3.9–7.2 mmol/L) and random blood glucose < 180 mg/dl (< 10.0 mmol/L).

Statistical analysis

The collected data were entered into SPSS® version 18.0 for analysis. Results were expressed as mean ± standard deviation (SD) or as a percentage. Mean values in the PTDM and no PTDM group were compared using Students *t*-test (or by Mann-Whitney U test if the data were not normally distributed). Categorical variables were compared using chi-square test. Subsequently, clinical variables of interest were included in binary logistic regression analysis to compute adjusted odds ratios, 95% confidence intervals (CI) and p values. All the variables were further entered into a multivariate analysis. Statistical significance was determined by a p value of less than 0.05.

RESULTS

Demographic &Transplant Characteristics

One hundred eighty-two patients received kidney transplant without another graft were under follow up at Penang Hospital since their transplantation. Eighteen of them were

excluded due to the following reasons: diabetes mellitus prior to transplant (n = 11), follow-up in another centre (n = 2) or with missing information (n = 5).The analysis was then performed in 164 patients.

A summary of demographic profiles and relevant transplant characteristics is presented in Table 1. Majority of patients consist of male (61.6%) and Chinese individuals (81.1%). About 80% of the patients were aged below 45 years old at transplantation. The year of post-transplantation in the studied patients were ranged from 0.43 (156 days) to 28.2 years with a mean of 11.04±6.26 years. There were small number of patients presented with acute rejection after transplantation (14.6%) and 6.7% of them had delayed graft function as defined by the requirement for hemodialysis in the first week post-transplant. About 96% of the patients had hypertension and majority of them (97%) had at least one concurrent disease at the last follow-up. The mean number of concurrent diseases was 2.21±1.02. The common concurrent diseases among the patients were hypertension (78.5%), hyperlipidemia (56.0%), hyperuricemia (11.5%), ischemic heart disease (5.5%), gastritis (4.5%), bronchial asthma (4.0%), pulmonary tuberculosis (3.5%), anaemia (3.0%), hepatitis B (3.0%) and hepatitis C (2.5%).

Table. 1: Patient and transplant characteristics.

Characteristics	N	%
Age at transplant		
< 45 years	129	78.7
> 45 years	35	21.3
Gender		
Male	101	61.6
Female	63	38.4
Ethic group		
Chinese	133	81.1
Malay	17	10.4
Indian	14	8.5
Donor type		
Cadaveric	81	49.4
Living	83	50.6
Pre-transplant dialysis		
Yes	156	95.1
No	8	4.9
HCV status		
Positive	10	6.1
Negative	154	93.9
Acute rejection post-transplant		
Yes	24	14.6
No	140	85.4
Dialysis dependent 1st week post-transplant		
Yes	11	6.7
No	153	93.3
Hypertension*		
Yes	158	96.3
No	6	3.7
Number of concurrent diseases		
No concurrent disease	5	3.0
1 disease	31	18.9
2 diseases	73	44.5
3 diseases	39	23.8
4 diseases	13	7.9
5 diseases	2	1.2
6 diseases	1	0.6

*Hypertension defined as any treatment for high blood pressure and/or a systolic value > 140 mmHg or diastolic value > 90 mmHg within 2 years post-transplant.

Incidence and Characteristics of PTDM

PTDM was diagnosed in 36 (22.0%) of 164 patients after kidney transplantation (Table 2). The mean age at transplant for the PTDM group was significantly higher than those without PTDM. Besides, patients who developed PTDM had significantly higher FBS at 6 months post-transplant and number of concurrent diseases as compared to those without PTDM.

After transplantation, all PTDM patients were prescribed with prednisolone. One-third of them were started on tacrolimus while 66.7% were given cyclosporine as immunosuppressive treatment. Two patients were switched from cyclosporine to tacrolimus prior to PTDM development. Once PTDM was developed, one patient was switched from tacrolimus to cyclosporine but this did not result in resolution of PTDM. None of the PTDM cases involved discontinuation of calcineurin inhibitor. The time of diagnosis of PTDM were ranged from 0.16 years (59 days) to 15.8 years with a mean of 5.4±4.6 years after transplantation (Figure 1). The cumulative incidences of PTDM after 1, 3, 5 and 10 years post-transplant were 5.5%, 6.7%, 12.2% and 17.7%, respectively. Overall cumulative incidence of PTDM was 22.0% after 15.8 years. Development of PTDM showed fastest growth within first year post-transplant.

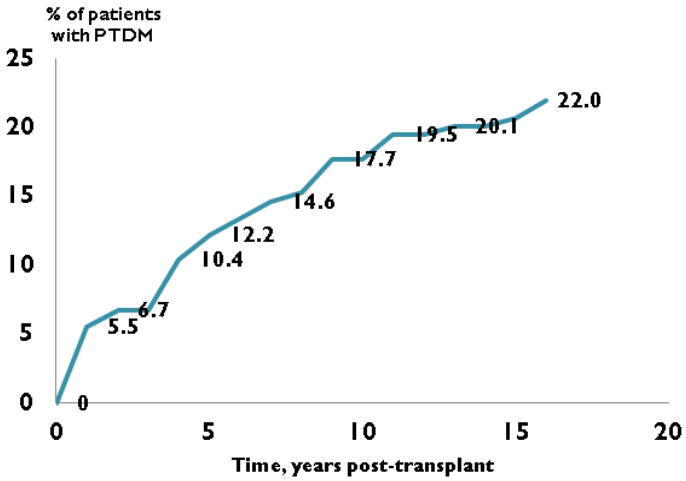

Fig. 1: Cumulative Incidence of PTDM over Time, Years Post-transplant.

Clinical Variables associated with PTDM

Overall, the mean body weight of patients with PTDM at any time point following transplantation was significantly higher than patients without PTDM (Table 3). However, there was no difference found between the two groups on the serum creatinine levels at any time point post-transplantation. Comparisons of calcineurin inhibitor (cyclosporine and tacrolimus) trough levels between these two groups of patients found similar trend with no significant differences throughout the study period.

The results of univariate and multivariate analysis are displayed in Table 4. The occurrences of one or more concurrent diseases and the patients' FBS at 6 months post-transplantation were independently associated with the onset of PTDM based on the multivariate analysis results.

Table. 2: Characteristics of the patients with PTDM and without PTDM.

Demographic data	PTDM, n (%)	No PTDM, n (%)	p value
Number of patients	36 (22.0%)	128 (78.0%)	
Mean age at transplant	41.5±11.1	34.0±9.8	< 0.001†
FBS 6 months post-transplant, mmol/L	5.97±1.70	4.89±0.54	0.001†
Mean no. of concurrent disease	2.53±1.082	2.12±0.985	0.032†
Gender			
Male	26 (72.2%)	75 (58.6%)	0.137‡
Female	10 (27.8%)	53 (41.4%)	
Ethic group			
Chinese	28 (77.8%)	105 (82.0%)	0.097‡
Malay	2 (5.6%)	15 (11.7%)	
Indian	6 (16.6%)	8 (6.3%)	
Donor type			
Cadaveric	20 (55.6%)	61 (47.7%)	0.402‡
Living	16 (44.4%)	67 (52.3%)	
Pre-transplant dialysis			
Yes	34 (94.4%)	122 (95.3%)	0.831‡
No	2 (5.6%)	6 (4.7%)	
HCV status			
Positive	1 (2.8%)	9 (7.0%)	0.346‡
Negative	35 (97.2%)	119 (93.0%)	
Acute rejection post-transplant			
Yes	5 (13.9%)	19 (14.8%)	0.886‡
No	31 (86.1%)	109 (85.2%)	
Dialysis dependent 1st week post-transplant			
Yes	5 (13.9%)	6 (4.7%)	0.051‡
No	31 (86.1%)	122 (95.3%)	
Hypertension*			
Yes	35 (97.2%)	123 (96.1%)	0.750‡
No	1 (2.8%)	5 (3.9%)	
Prednisolone treatment			
Yes	36 (100%)	126 (98.4%)	0.450‡
No	0 (0%)	2 (1.6%)	
Cyclosporin treatment			
Yes	24 (66.7%)	97 (75.8%)	0.272‡
No	12 (33.3%)	31 (24.2%)	
Tacrolimus treatment			
Yes	12 (33.3%)	29 (22.7%)	0.191‡
No	24 (66.7%)	99 (77.3%)	

*****Hypertension defined as any treatment for high blood pressure and/or a systolic value > 140 mmHg or diastolic value > 90 mmHg within 2 years post-transplant. †Mann-Whitney U Test ‡Chi-square Test

Table. 3: Clinical variables of the patients at different periods of post-transplantation.

	Mean ±SD		p value
	PTDM (n = 36)	**No PTDM** (n = 128)	
Body weight (kg)			
At transplant	58.84±9.58	53.28±11.63	0.009*****
6 months	63.42±9.10	56.21±11.67	0.001*****
1 year	66.20±9.84	57.69±12.57	< 0.001*****
2 years	68.27±10.35	59.54±13.40	0.001*****
5 years	75.52±12.35	62.01±14.00	< 0.001*****
10 years	75.52±11.18	63.19±12.13	0.001*****
15 years	75.00±13.95	64.65±12.25	0.030*****
Serum Creatinine (µmol/L)			
At transplant	182.93±157.76	163.80±115.31	0.467†
3 months	129.87±40.39	122.15±25.98	0.195†
6 months	127.66±36.19	124.19±29.37	0.572†
1 year	128.62±39.91	125.74±34.13	0.676†
2 years	128.51±49.79	119.98±27.64	0.196†
5 years	119.07±25.17	122.94±36.03	0.583†
10 years	115.60±15.31	131.13±38.65	0.132†
15 years	120.00±10.42	133.68±37.89	0.292†
Cyclosporin trough level (mmol/L)			
3 months	270.15±64.10 (n = 16)	328.76±144.82 9 (n = 61)	0.120†
6 months	204.57±60.15 (n = 16)	231.78±82.42 (n = 70)	0.217†
1 year	184.74±54.49 (n = 16)	182.97±55.22 (n = 66)	0.909†
2 years	171.85±47.11 (n = 15)	168.89±63.91 (n = 61)	0.867†
5 years	156.76±66.59 (n = 11)	141.45±52.80 (n = 53)	0.406†
10 years	176.05±82.66 (n = 3)	144.12±75.05 (n = 27)	0.493†
15 years	117.58±36.11 (n = 6)	138.85±59.56 (n = 21)	0.417†

Tacrolimus trough level (mmol/L)			
3 months	10.5±1.7 (n = 9)	8.7±3.4 (n = 26)	0.134†
6 months	8.5±2.2 (n = 10)	7.81.6 (n = 28)	0.341†
1 year	6.9±2.5 (n = 12)	6.8±1.8 (n = 22)	0.882†
2 years	5.4±1.3 (n = 10)	6.1±2.0 (n = 14)	0.304†
5 years	5.3±1.3 (n = 7)	6.1±1.8 (n = 7)	0.319†

*****Student t-test
†Mann-Whitney U test

Table. 4: Predictors of PTDM defined by univariate analysis & multivariate analysis.

Variable	Odds Ratio	95% CI	p value
Univariate analysis results			
Age at transplant	1.07	1.03-1.11	< 0.001
Gender			
Female	0.54	0.24-1.22	0.141
Male	reference		
Race			
Chinese	0.36	0.11-1.11	0.075
Malay	0.18	0.029-1.09	0.062
Indian	reference		
Dialysis dependent 1st week post-transplant			
No	0.31	0.087-1.07	0.063
Yes	reference		
Tacrolimus treatment			
No	0.59	0.26-1.31	0.194
Yes	reference		
No. of concurrent diseases	1.48	1.03-2.13	0.036
FBS 6 months post-transplant	3.64	1.80-7.36	< 0.001
Weight(kg) at transplant	1.04	1.01-1.08	0.011
Multivariate analysis results*			
No. of concurrent diseases	2.26	1.25-4.09	0.007
FBS 6 months post-transplant	4.10	1.78-9.45	0.001

*****Only variables with p value < 0.05 were showed in the table

Drug Management of PTDM

Among the patients who developed PTDM, 61.1% (n = 22) required either single or multiple oral agents for treatment and 16.7% (n = 6) required insulin therapy. Meanwhile, 13.9% (n = 5) of the patients were on combination therapy of oral agents and insulin. PTDM resolved in 8.3% (n = 3) of the cases, as defined as discontinuation of oral agents or insulin therapy. Types of anti-diabetic agents that prescribed to PTDM patients are shown in Table 5.

Table. 5: Types of anti-diabetic agents prescribed to PTDM patients at last follow-up.

Type of anti-diabetic agent	n	%
Biguanide		
Metformin	21	42.0
Sulphonylurea		
Gliclazide	14	28.0
Glibenclamide	1	2.0
Dipeptidyl peptidase-4 Inhibitor		
Sitagliptin	1	2.0
Alpha-glucosidase Inhibitor		
Acarbose	1	2.0
Insulin		
Humulin R	1	2.0
Humulin 30/70	10	20.0
Humulin N	1	2.0

Blood Sugar Monitoring

The average value for FBS at the time of diagnosis for patients with PTDM was 11.21±5.57 mmol/L. For recipients without PTDM, their FBS levels were well controlled since transplantation, with fluctuations at mean of 4.95±0.76 mmol/L. For patient with PTDM, the FBS were under controlled at six months after the PTDM diagnosis with the mean value of 6.50±1.14 mmol/L. The average value of FBS at 1, 3, 5 and 10 years post-transplant were 6.78±1.83 mmol/L, 6.15±1.17 mmol/L, 6.36±2.12 mmol/L and 7.10±0.92 mmol/L respectively.

DISCUSSION

In this study, PTDM was found in 22.0% of kidney transplant recipients and the 1, 3 and 5 years cumulative incidence were 5.5%, 6.7% and 12.2% respectively. Recent studies using similar criteria for diagnosing PTDM as per ADA guidelines showed a higher 1 year cumulative incidence of PTDM which ranged from 7.0% to 19.0% (Chien *et al*., 2008; Gourishankar *et al*., 2004; Kiberd *et al*., 2006; Roland *et al*., 2008). Indeed, a similar research conducted at Singapore also revealed higher cumulative incidence of PTDM than the present study, which was 15.8%, 22.8% and 24.5% at 1, 3, and 5 years following transplantation (Bee *et al*., 2011). Nevertheless, both studies showed similar trend whereby the development of PTDM demonstrated fastest growth within the first year post-transplantation.

The average time (mean 5.4±4.6 years) to PTDM diagnosis in this study was longer as compared to findings from other countries (Koselj *et al*., 2002; Sharma *et al*., 2003). A single center study conducted in Slovenia revealed that the diagnosis of

PTDM was established at a mean of 5.6 months post-transplantation (mean follow-up after transplantation was 8.6 years) (Koselj *et al*., 2002). Another single center study from India which involved a mean observation period of 3.7 years post-transplant found that the mean time of presentation to PTDM was 7.56 months (Sharma *et al*., 2003). The longer observation period (mean 11.04 years) in the present study may explain the dissimilar of the PTDM onset time with the above mentioned studies. Besides, this study showed that PTDM can develop at any time, even after 10 years following transplantation. Indeed, studies which examining PTDM rates over longer periods revealed that the risk for development of PTDM increases continuously with time from transplantation (Cosio *et al*., 2001; Driscoll, 2007).

Early detection and appropriate treatment of transplant recipients who developed PTDM can eliminate the long term consequences of the condition (Davidson and Wilkinson, 2004). Early detection could be done by identifying the potential risk factors for PTDM. Multivariate analysis in this study found that occurrence of concurrent diseases was an independent predictor of PTDM. To the best of our knowledge, there is no study which identifies the association between PTDM and number of concurrent diseases. However, there is evidence which suggested that patients with components of the metabolic syndrome (hypertriglyceridemia, hypertension, and hyperuricemia) may have a higher tendency of developing PTDM (Davidson and Wilkinson, 2004). FBS level at first 6 months post-transplant was another independent predictor of PTDM observed in this study. Further, recipients who developed PTDM found to have significant higher FBS level at first 6 months post-transplant than those without PTDM. These findings are consistent with other studies that reported the predictive value of plasma glucose levels in the early period of post-transplant for PTDM (Cosio *et al*., 2005; Joss *et al*., 2007). Cosio *et al*. analysed a database of 490 adult kidney transplant recipients from America and showed that development of hyperglycaemia during the first week post-transplant was statistically the strongest predictor of PTDM at one year (Cosio *et al*., 2005). Joss *et al*. found that random blood glucose level at day 7 after transplantation independently predicted development of PTDM (Joss *et al*., 2007). Hence, frequent blood glucose monitoring particularly during the early period of post-transplant is crucial for the detection of PTDM.

Ageing has consistently been shown to be a risk factor for PTDM, especially in patients over the age of 40 (Boudreaux *et al*., 1987; Sumrani *et al*., 1991). This is perhaps not surprising considering the influence of age on the incidence of diabetes mellitus in the general population (Fletcher *et al*., 2002). Although the mean age at transplant was significantly higher in patients with PTDM compared with those without PTDM in the present study, the multivariate analysis was unable to detect any significant relationship between age and development of PTDM. The relative small sample size may explain this non-significant finding. Besides, gender found to has no significant effect on the risk of diabetes after transplantation. This is in agreement with a study done by Baum *et al*., which reported that gender did not statistically affect the development of PTDM (Baum *et al*., 2002).

Conflicting evidence exists regarding the association of body weight with PTDM. Weight has been shown to be associated with the development of diabetes after transplantation in most studies (Cosio *et al*., 2002; Kasiske *et al*., 1996; Roth *et al*., 1989; Sumrani *et al*., 1991). Conversely, some studies found a weak association between the PTDM with either body weight or body mass index (BMI) (Hathaway *et al*., 1994; Soule *et al*., 2005). Indeed, according to the International Consensus Guidelines on PTDM (Davidson *et al*., 2004), intra-abdominal fat or waist-to-hip ratio may be the more important indices for PTDM than body weight or BMI. In this study, the mean body weight of patients that developed PTDM was significantly higher than the non-PTDM group. Nevertheless, weight did not showed to be a predictor of PTDM based on the multivariate analysis. The association of BMI with PTDM was not able to be evaluated in the present study as the height of each patient was not documented in the medical record. Besides, data on intra-abdominal fat and waist-to-hip ratio were also not available in the patient record.

Research findings from Western countries have revealed the role of ethnicity in the development of PTDM (Benhamou *et al*., 2002; Miles *et al*., 1998; Vesco *et al*., 1996). The present study showed contradict result where there was no significant different in the incidence of PTDM among the 3 studied ethnic groups. There was also no association between ethnic background and PTDM development. However, the small sample size of Malay and Indian patients as compared to the Chinese in the studied population is one of the limitations of this study.

Several studies showed that transplantation with a cadaveric kidney, as compared with a living donor kidney, were associated with increased development of diabetes after transplantation (Boudreaux *et al*., 1987; Kasiske *et al*., 2003; Sumrani *et al*., 1991). Whereas in this study, the donor type of transplanted kidney was not associated with PTDM. A clear biologic explanation for the increased risk conveyed by cadaveric donor transplant for developing PTDM is still unknown. Nevertheless, based on the findings from previous studies, it is reasonable to assume that individuals without a potential living donor should be identified as higher risk for developing PTDM during the transplant work-up process and should be educated and cautiously monitored and managed (Boudreaux *et al*., 1987; Kasiske *et al*., 2003; Sumrani *et al*., 1991).

Hepatitis C infection was previously found to be a significant co-morbidity in kidney transplant recipients, occurring in 10% to 40% of patients. It is associated with an increased risk of both graft failure and mortality (Bloom *et al*., 2002). Additionally, a strong association has been demonstrated between HCV status and the development of PTDM, particularly in patients receiving tacrolimus-based immunosuppressant therapy (Bloom *et al*., 2002). However, this association was not seen in the present study. This may due to the relatively small number of patients that had hepatitis C infection in this study.

The occurrence of one or more acute rejection episodes were independently predictive of PTDM development based on a previous research (Marin *et al*., 2005). This is likely due to the exposure of short term high dose steroid during acute rejection episodes that subsequently precipitates hyperglycaemia. Few studies have shown an association between pulse steroid therapy and the onset of PTDM (Vesco *et al*., 1996; von Kiparski A *et al*., 1990). Furthermore, the diabetogenic effects of corticosteroids are known to be dose-related (Hjelmesaeth *et al*., 1997). However, the present study failed to detect any association between occurrence of acute rejection and the development of PTDM since only very small number of the patients had rejection after transplant.

Several studies have revealed a strong link between the types of immunosuppression regimens with the development of PTDM. For instance, tacrolimus was reported to be up to five times more diabetogenic than cyclosporine (Kasiske *et al*., 2003; Knoll and Bell, 1999; Koselj M *et al*., 2002; Vincenti *et al*., 2002). In this study, no significant different were observed between PTDM and non-PTDM group with regards to the type of immunosuppressive agents used. Additionally, there was no association between trough levels of cyclosporine or tacrolimus at any time point following transplant and development of PTDM. These findings were comparable to a study conducted by Gourishankar *et al*. which found no association between therapy of calcineurin inhibitors and development of diabetes after transplant. Gourishankar et al. comment that trough monitoring may not be the ideal surrogate marker of calcineurin inhibitor exposure as compared to abbreviated area under the curve (AUC) or peak monitoring (Gourishankar *et al*., 2004). As both the AUC and peak monitoring were not performed in the studied centre, the impact of these monitoring parameters could not be evaluated.

To date, there is limited data on the glycaemic control of PTDM. A slightly higher percentage of patients (10.5%) was reported to have PTDM resolved in Gourishankar *et al*. study (Gourishankar *et al*., 2004) as compared to 8.3% in the present study. This study also revealed that glycaemic control of PTDM was well after six months post diagnosis by using drug therapy.

Strengths and limitations

The present study significantly found that the number of concurrent diseases is a risk factor for PTDM which has not been reported previously. However, this was a retrospective study that might have sampling bias and errors which depend on completeness and the quality of existing records. This study confines to a single center and involved a relatively small sample size. Patient sample was not homogenous in terms of ethnicity as majority of them were Chinese. Hence, it may not generally represent other ethnic groups in Malaysia.

CONCLUSION

Two clinical variables were found to be independently associated with the onset of PTDM, which were occurrence of one or more concurrent diseases and the patient FBS at 6 months post-transplant. Practitioners should always be emphasized on this condition and aggressive monitoring of blood glucose early after transplantation is necessary.

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CONFLICTS OF INTEREST

All the authors have no conflict of interest in connection with this paper.

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