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The Diabetes Mellitus Incidence in Recipients of Renal Allograft in Al-Nassiyria City

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Abstract

BACKGROUND: Immunosuppressive drugs is the main cause of Post-transplant diabetes mellitus, which consider as one of the highly commonest transplant complications.

Aim: To assess the Post-transplant diabetes mellitus incidence and determine the other factors which may play a role in this complication development.

Method: 105 non-DM study population included in this study transplanted renal allograft, since 1999. Post-transplant diabetes mellitus was identified by the requirement of the hypoglycemic drug which started after transplantation by a range of more than one month. All patients after transplantation received prednisone and cyclosporine and no one received tacrolimus.

Results: At 1st, 3rd, 5th, and 10th years follow up after transplantation, five, eight, eleven and lastly nineteen percent developing Post-transplant diabetes mellitus., the correlated variables was determined as independent variables for the rapid increment in the Post-transplant diabetes mellitus numbers, which, higher BMI- before transplant, age of recipient the younger than 45 years significantly differ from older age with $P < 0.0001$

Conclusions: Post-transplant diabetes mellitus risk continuously increases with post-transplant time. Transplanted patients show increment in Post-transplant diabetes mellitus incidence whose recipients characteristics changes is the full explanation of this matter. The assumption of a cause of this increment is due to the introduction of better absorbed CsA formulations, which resulted in higher diabetogenic drug cumulative exposure in addition to other factors.

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Introduction :

Post renal transplantation immunologic events control improved impressively in the previous two decades (1). Consequently, the acute rejection episodes number as an early post-transplant sequel had been dramatically declined also graft-survival, chiefly throughout post-transplant- first year, which has substantially improved [1,2] It is obviously noticed due to the role of employing immunosuppressive protocols in large portion, this improvement result as a consequence of the usage this protocol recently. (2).

Post-transplant immunologic phenomena control improvement had been accompanied by graft survival improvements in a significant way (3). Renal transplantation success still has a major threat , which is the high mortality as a continuous complication. [4,5] Cardiovascular cause of mortality the excess burden in transplant recipients mortality [6] seeking and correcting of cardiovascular risk associated variables is censoriously important. Several risk cardiovascular factors have been identified in previous studies in patients with renal disease at end-stage and also in transplanted patients[7,8] However, the mortality rate is much higher among patients carrying both cardiovascular disease and renal disease and exposed to transplant than those who were free from cardiovascular diseases, even though when they had similar profile and workup before [9]. These results suggest that other risk factors of cardiovascular need to be considered in patients with kidney disease. One of those factors is likely to be insulin resistance that occurs commonly in patients receiving immunosuppressive medications and is related to increased risk of cardiovascular[10,11]. However, important information is lacking about this serious complication of transplantation. (12) we try to evaluate the PTDM development in recipients of renal transplant , who treated in one institute with protocols of immunosuppressive drug that used uniformly. In a precise way, we assessed the DM development timing post renal transplantation, the effect of various variables on this timing, and if the introduction of this new immune-suppressive drug has a role in the overall PTDM incidence and its presentation pattern .

The last point is a significant thoughtfulness for the reason that in adding to corticosteroids, newly immunosuppressive drugs, which have obviously contributed meaningfully to improvements in transplantation, are diabetogenic. It is our hopefulness that a best criteria of PTDM, first on clinical practices, will enable its earlier detection and management also aid e future trials designation which avert the progress of this disturbing transplantation complication.

Patients and Methods:

This study includes a follow up analytical study of 105 patients

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transplanted from August of 1999 to February of 2012. All those population received kidney from living donors. These data were collected in the post renal transplant unit in Al Hussein teaching Hospital in Al-Nassiyria city.

Inclusion criteria: No one of our studied population had a positive history of Dm, or was on oral hypoglycemic medication before renal transplant and also none was on the hypoglycemic drug at the first month post transplant, to avoid selection bias

The PTDM diagnosis was made on the diagnostic criteria of DM, by FBS, RBS at least 2 reading with scientific approach or when the mandatory need to starting hypoglycemic drug whether oral hypoglycemic medication and/or insulin.

Ethical consideration: verbal consent was taken from all participants.

Statistical analysis: by using excel sheet, SPSS version 14, to determine the frequency, percentages, means ± SD., Student t test for the comparison of the means and for the not normally distributed the nonparametric test had been used. Correlation regression analysis also done.

The demography patients are shown in Table 1

Table 1. Characteristics of the Patient Population

Patient Characteristic	Value
Age in years	42.2±19
Gender (Males)	64%
Weight at Time of Transplant by Kg	69.4±18

In most patients, of triple therapy with prednisone, azathioprine or mycophenolate mofetil(cellcept), maintenance immunosuppression consisted and cyclosporine (CsA). We exclude those patients which already on tacrolimus due to higher incidence of diabetes among them(4). This note had been reported and studied more.

Results:

PTDM incidence: figure one displaying the PTDM cumulative incidence with post-transplant time., the percentage of cases of PTDM increased linearly with time post-transplant. The cumulative percentage of PTDM at 1^{st} , 3^{rd} , 5^{th} , 10^{th} , was 7.1%, 10.4%, 13.2%, and 20.5%, respectively.

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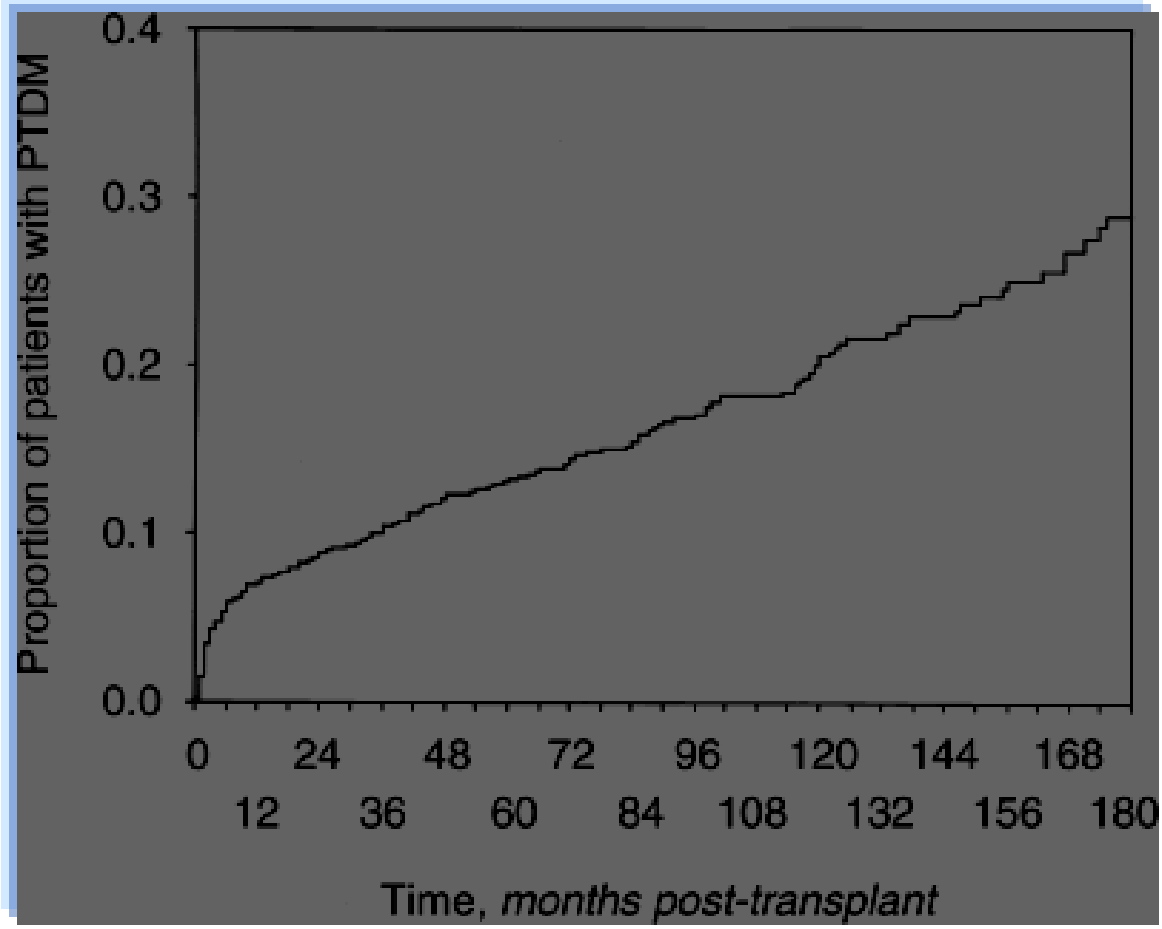

Figure one: PTDM incidence with post-transplant time (Kaplan–Meier plots)

Figure two show PTDM patients proportion, where they divided into 2 age group (≥45years age and < 45 years old age) at the transplantation time. Where PTDM risk significantly higher in older recipients both during the six months and beyond post-transplant. The rate of increase in PTDM cases after the first six months was significantly faster in older than in younger individuals. According to figure 2, the age related to PTDM among recipients is statistically independent of all other variables tested.

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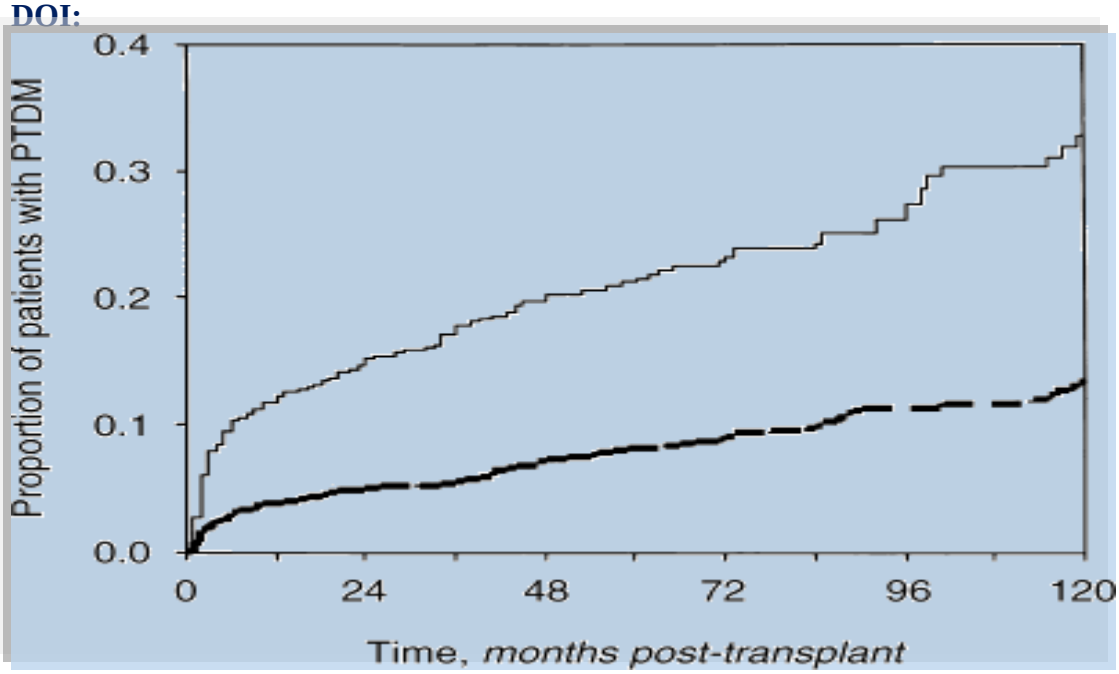

Figure two: Incidence of PTDM with time post-transplant in recipients (Kaplan–Meier plots)

heavy dashed line-< 45 years , thin solid line- older than 45.

Table two : exhibitions the univariate and multivariate Cox regression analysis and showed the correlated variables significantly with the development of PTDM. Statistically, the strongest correlation was that between the age of the patient at the time of transplantation and PTDM. Thus, recipients older than 45 years old were 2.9 times more likely to become diabetic post-transplant than younger recipients

Table 2. Correlated Variables with the PTDM development.

Variable	Univariate analysis	Multivariate	P value
Age	2.9	2.2	0.001
Gender	0.7		>0.05
Weight	1.5	1.4	0.001

The data represent the results of univariate and multivariate Cox analysis.
[a] relative risk (RR) calculated by Cox regression
[b] R.R for patients who were < or> 45 years old
[c] R.R according to weight by kg: <60, 60–70, 70–80, and> 80

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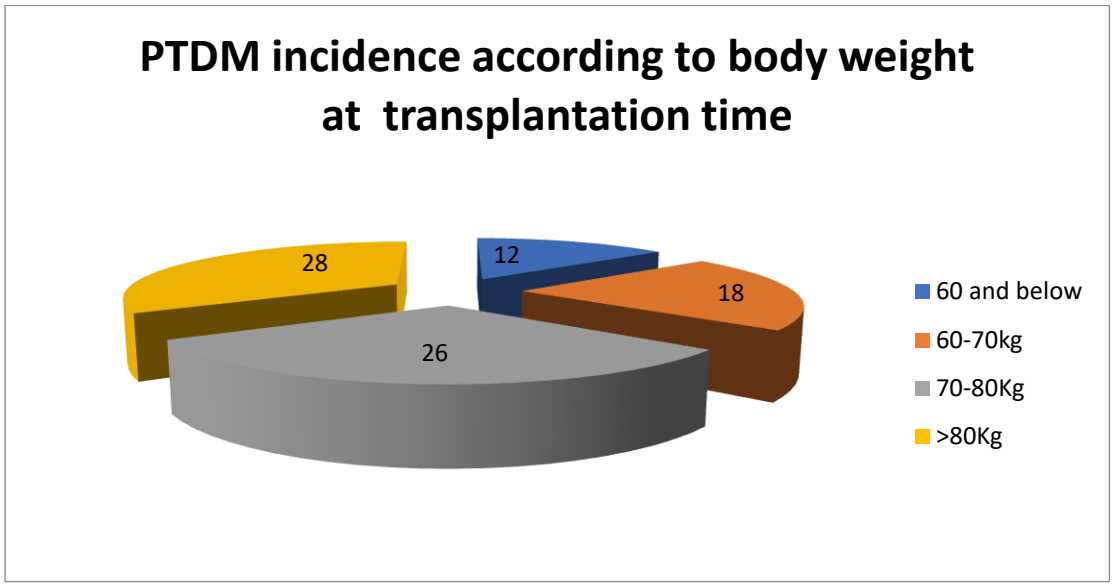

Figure three: Males **show** significantly higher PTDM incidence than in females (15.2% vs. 10.4%, where P = 0.002). However, A multivariate analysis proved that gender not an independent diabetes risk factor as shown in Table 2.

DISCUSSION

PTDM incidence among recipients of renal allograft, who underwent transplantation in the same institution has been assessed within the current study, also they underwent the uniform protocols of CsA-based immunosuppressive. The PTDM incidence reported in this study was comparable to many other studies. However, there was a considerable inconsistency in the reported PTDM incidence, which might be mainly due to at least three explanations. 1stly , the diagnostic criteria of PTDM are fairly variable among studies [(12)]. Secondly , discrepancy in protocols of immune-suppressive treatment usage in different centers of transplant which in turn had an impact on PTDM incidence, for e.g. , PTDM incidence significantly lower among those who treated with corticosteroid than those who treated with tacrolimus among transplant recipients [(13)]. As a final point, the reported PTDM incidence differ according to the patient follow-up length, as shown in the current study here, the proportion of PTDM develop patients rises continuously post-transplantation with increasing of follow-up time. This point explained by 2 distinct periods of development of PTDM. 1st one : a period of high risk, involves the post transplant -first year. 2nd one : includes the rest of the post-transplant time when there is a constant increment in PTDM patients number. In the current study , PTDM diagnosed as the hypoglycemic medications need.

We exhibited here that PTDM risk factor is the weight. However other studies showed that for similar body weights patients, the PTDM risk still higher in African Americans[(14,15,16)]. It

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should be highlighted that in recipients of renal transplant, the PTDM risk increases continuously for every bodyweight increment above 60 kg, obviously under what may be well thought-out to be an overweight range in most patients[15]. One of the commonest problems in post transplant recipient is weight gain. However, in this study, we did not find a significant correlation between weight gain in post-transplant especially during the first year and PTDM but rather between pretransplant weight and PTDM.

Recipient age is the variable that was found to be the strongest predictor for PTDM , in all races , genders, and weight in allograft renal transplanted patients [15] where these finding (PTDM is higher in older recipients) has 2 different components. 1stly, equated with younger recipients, patients older than 45 years have a noticeable rise in the occurrence of PTDM throughout the first year(twelve months) post-transplant when the corticosteroids highest doses had been received. 2nd , after 1st (12)months post-transplant, the rate of rise in the PTDM cases number is faster in older than in younger patients. It appears rational to hypothesize that PTDM may encompass at least 2 sub-populations of entities. The chief point, including diabetes, develop patients at an early time of post-transplant, mainly symbolizes patients who had insulin resistance preceding the transplant which was worsen by steroids of high doses , demanding the start of hypoglycemic treatment. The additional points : group of patients who develop PTDM before 1st (12) months post-transplant. and may characterize resently attained diabetic individuals, either with insulin resistance hyperinsulinemia and or with hypoinsulinemia : exhibitions the univariate and multivariate Cox regression analysis and shows the correlate variables significantly with the development of PTDM. Statistically, the strongest correlation found was between the age of the patient at the time of transplantation and PTDM. Thus, recipients older than 45 years old were 2.9 times more likely to become diabetic post-transplant than younger recipients12).

It has been mentioned that introduction of newer preparations of CsA in mid-1995 has resulted in higher exposure to this drug that is diabetogenic most likely due to direct inhibition of insulin synthesis and/or secretion mediated by a direct toxic effect on insulin producing cells of the pancreas[12, 15]. Of interest, the increase in PTDM has occurred despite the fact that the cumulative doses of corticosteroids have been reduced. Since 1995, other changes in immunosuppressive protocols were introduced in our program and in most transplant programs, including the substitution of Imuran for Cellcept and, since mid-1998, the use of anti-IL-2R antibodies. However, there is no evidence that these drugs are diabetogenic[12].

Improvements in graft survival over the last two decades[3] have made it

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increasingly clear that patient death is a frequent cause of renal transplantation failure(4,5)–. Because most of the excess mortality of renal allograft recipients is due to cardiovascular causes[6], it is particularly worrisome to note that the incidence of PTDM is increasing in this population of patients. PTDM increases patient morbidity and likely mortality following transplantation In addition, the increase in PTDM may also indicate that there has been an increase in the number of patients with insulin resistance, another worrisome event since this metabolic anomaly is also associated with increased cardiovascular risk[16]. The results of these studies will help in identifying patients at high risk for PTDM, thus encouraging close monitoring of glucose levels and prompt therapy of hyperglycemia.

Conclusions: PTDM risk continuously increases with post-transplant time. Recently transplanted patients show increase in PTDM incidence, which, recipients characteristics changes is the full explanation of this matter. The assumption of cause of this increment is due to introducing of better absorbed CsA formulations, which resulting in higher diabeto-genic drug cumulative exposure in addition to other factors

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نسبة الإصابة بداء السكري لدى متلقي الطعم الخيفي الكلوي بمدينة الناصرية

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النبذة المختصرة:

الخلفية: العقاقير المثبطة للمناعة هي السبب الرئيسي لمرض السكري بعد الزرع ، والذي يعتبر أحد أكثر مضاعفات الزرع شيوعًا.

الهدف: تقييم حدوث PTDM وأيضًا تحديد العوامل الأخرى التي قد تلعب دورًا في تطور هذا التعقيد.

الطريقة: 105 مجموعة من الأشخاص الذين شملتهم الدراسة من غير سكر المشمولين في هذه الدراسة زرعوا طعم خيفي كلوي ، منذ عام 1999. تم تحديد PTDM من خلال متطلبات الأدوية الخافضة لسكر الدم ، والتي بدأت بعد الزرع حسب النطاق لأكثر من شهر واحد ، حيث جميع المرضى. بعد الزرع ، تلقوا بريدنيزون وسيكلوسبورين ، لا أحد يتلقى عقار تاكروليموس.

النتائج: في السنوات الأولى والثالثة والخامسة والعاشرة - المتابعة بعد الزرع ، خمسة وثمانية وأحد عشر وأخيرًا تسعة عشر بالمائة من تطوير PTDM. ، تم تحديد المتغيرات المرتبطة كمتغيرات مستقلة للزيادة السريعة في أرقام PTDM ، والتي ، ارتفاع مؤشر كتلة الجسم - قبل الزرع ، يختلف عمر المتلقي الأصغر من 45 عامًا بشكل كبير عن كبار السن مع P 0.0001>

الاستنتاجات: يزداد خطر PTDM باستمرار مع وقت ما بعد الزرع. يظهر المرضى الذين تم زرعهم مؤخرًا زيادة في حدوث PTDM ، والتي تتغير خصائص المستلمين هو التفسير الكامل لهذه المسألة. يرجع افتراض سبب هذه الزيادة إلى إدخال تركيبات CsA التي تمتص بشكل أفضل ، مما يؤدي إلى زيادة التعرض التراكمي لعقار السكري الجيني بالإضافة إلى عوامل أخرى.