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Post-transplant Diabetes Mellitus (PTDM), a Retrospective Review Studying the Effect of Early Steroid Withdrawal in Libyan Recipients

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Abstract

Post-transplant diabetes mellitus (PTDM) is the most, and, frequent complication observed following solid organ transplantation. PTDM or the Kidney transplant recipients develop are also at increased risk of cardiovascular events and other adverse outcomes including infection, reduced patient survival, graft rejection, and accelerated graft loss compared with non-diabetics.

In general new onset of diabetes mellitus after transplantation has been reported to occur in 4% to 25% of renal transplant recipients, 2.5% to 25% of liver transplant recipients, and approximately 2% to 53% of all people. 230 renal transplant recipients with functioning grafts were used in this study. This study took about 5 years in order to screen the incidences of PTDM and other risk factors.

The aim is to study the incidence of new-onset of diabetes mellitus in kidney transplant recipients and correlate it with protocol of withdrawing steroids after one month after transplantation.

The results confirm the importance of corticosteroids in the development of post transplantation new onset of diabetes mellitus in Libyan population. The data indicates that Libyan male patients are more vulnerable to PTDM than Libyan female patients.

Keywords: PTDM, transplant recipients; diabetes mellitus; corticosteroids; corticosteroids receptor immunosuppressive.

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المستخلص

تعد الاصابة بداء السكرى بعد عمليات زراعة الكلى من أكثر المضاعفات الملاحظة بعد زراعة الاعضاء كما أنها تضاعف من عوامل الاختطار لأمراض القلب والاوعية الدموية وغيرها من المضاعفات كالالتهابات والموت المبكر ورفض العضو المزروع وتسارع فشل العضو المزروع مقارنة بالمرضى غير المصابين بداء السكرى . وبصفة عامة سجلت الاصابة بداء السكرى بعد زراعة الكلى نسبة تتراوح بين 4% –25% ، وبين 2.5%–25% عند مرضى زراعة الكبد. تم في هذه الدراسة ادماج 230 حالة من مرضى زارعي الكلى الذين تؤدى كلاهم وظيفتها بصورة جيدة واخدت هذه الدراسة مدة 5 سنوات لاكتشاف حدوث حالات الاصابة بداء السكرى بعد عمليات زراعة الكلى وعوامل الاختطار معها. الهدف من هذه الدراسة هو معرفة نسية الاصابة بداء السكرى للمرضى الذين زرعت لهم كلى وعلاقتها بإيقاف علاج عقار الكورتيزون بعد شهر من الزراعة . أثبتت النتائج اهمية عقار الكورتيزون في الاصابة بداء السكرى بعد زراعة الكلى للمرضى الليبيين و أشارت الى ان الاصابة بهذا المرض أكثر حدوثا عند الرجال من النساء.

Introduction

Corticostteroids are a class of steroids that are produced in the adrenal cortex of humans. They are involved in a wide range of physiological processes including immune response, stress response and regulation of inflammation, carbohydrate metabolism, protein catabolism, behavior and blood electrolyte levels (Nussey et al., 2001; Blackburn et al., 2002).

Corticosteroids are form an essential compound of most immunosuppressor regions. They are nowadays used in renal transplantation because of their efficacy in reducing acute rejection and improving graft survival. Steroids, however, are associated with numerous mid effects that lead to increased patients morbidities mortalities (Veenstra et al., 1999).

High incidences of PTDM are associated with the type of initial maintenance immunosuppression, race, ethnicity, obesity and hepatitis C infection. It is a strong independent predictor of graft failure and mortality. Efforts should be made to minimize the risk of its important implication (Kasiske et al., 2003; Cole et al., 2008).

Efforts to reduce PTDM, while maintaining low rates of AR, will have the potential of improving long-term outcomes. Therefore, the new studies have shown that early steroid withdrawal have limited impact on PTDM, but it is associated with a higher incidence of AR (Vincent et al., 2008; Woodle et al., 2008). It is known that PTDM is associated with steroids as well as calcineurin inhibitors, especially tacrolimus (Chadban et al. ,2008).

The number of acute rejection episodes in early post-transplant has declined dramatically and graft survival, particularly during the first year post-transplant, has improved substantially (Schweitzer et al.,1991). It is clear that in large part, these improvements are consequences of the use of better immunosuppressive protocols and employing newer, more potent immunosuppressive drugs. High patient mortality, however, continues to be the major threat to the success of renal transplantation (Vanrenterghem et al., 2005). Because the excess of mortality in transplant recipients is largely due to cardio vascular causes (Benfield et al., 2010), searching for variables associated with increased cardiovascular risk and correcting those variables are critically important. Previous studies have identified several cardiovascular risk factors in patients with end-stage renal disease and in transplant patients (Hocker et al., 2010; Pelletier et al., 2006). However, it has also been pointed out that the cardiovascular mortality of patients with kidney disease is much higher than that of patients without kidney problems who have a similar risk profile (Sola et al., 2002). The latter results suggest that other cardiovascular risk factors need to be considered in patients with kidney disease. One of those factors is likely to be insulin resistance that commonly occurs in patients receiving immunosuppressive medications and is clearly associated with increased cardiovascular risk (Gregoor et al., 2002; Boletis et al., 2001; Ahsan et al., 1999). A plasma or serum glucose level lower than 140mg/dL is normal and requires no follow-up. If the glucose level is 140mg/dl or higher after a three hour OGTT(Oral Glucose Tolerance Test) is performed, it is considered normal blood glucose level reading and without fasting first, a reading of under 200 mg/dl is considered normal. A level of over 200 mg/dl, especially with symptoms of frequent urination, excessive thirst, etc. will indicate a strong possibility of diabetes.

Material and Methods

Blood samples (5ml) of 230 renal transplant recipients with functioning grafts, were collected over period of five years in Kidney Transplant Center in Tripoli, Libya.

The following tests were performed; urine examination for glucose, fasting glucose (FBG), Oral Glucose Tolerance Test (OGTT) and glucosalated heamoglobin A one C (HbA1C). Assay was done at least weekly for four weeks and every three months for one year.

Study Population

Adult recipients (≥18 years of age) of a first deceased or living kidney donor only transplant were considered eligible for the study. Only non-diabetic patients

were eligible; all patients were required to have a normal 2-hour 75-g OGTT (<7.8 mmol/l) performed within 1 month of the date of transplantation. Patients with an OGTT of 7.8 to 11.0 mmol/l were classified as having impaired glucose tolerance and were included in the study, while patients with an OGTT >11.0 mmol/l were excluded. In addition, patients were excluded if they had pre-transplant Panel Reactive Antibody >20%, or if they received a zero A, B or DR mismatched kidney. Patients were also excluded if they were unable to provide informed consent or were hepatitis C antibody positive.

Diagnosis of Diabetes and Glucose Intolerance

1- Diabetes symptoms with randomized plasma blood glucose ≥200 mg/dL (11.1 mmol/L) or fasting plasma glucose (FPG) (at least 8 hours fast) ≥126 mg/dL (7.0 mmol/L).
2. Fasting intolerance FPG ≥110 mg/dl (6.1 mmol/l) and < 126 mg/dl (7.0 mmol/l).
3. Oral test for glucose intolerance (glucose load at 75g of glucose dissolved in water) 2-hour plasma glucose ≥140 mg/dL (7.8 mmol/L) and < 200 mg/dL (11.1 mmol/L).

Results

The results of 230 renal transplant recipients with functioning grafts, performed between 2004 to 2009, were screened for the incidences of PTDM and other risk factors, including gender, age, tissue typing type of immunosuppression treatment, presence of hepatitis and Clinical impact of PTDM (Figure 1).

This first study on Libyan population shows that the males patients are more affected with Post Transplantation DM than females (Figure 2) especially the age group between 46-55 age old men, the Libyan women patients are more affected than women with new onset diabetes mellitus after treated with steroid hormone (Corticosteroids) and Figure 2 show that the risk factor of onset diabetes mellitus after post transplantation is very few in Libyan women with group age 26-35.

PTDM adversely affects long-term allograft survival. In one study, for example, graft survival at 12 years was 48 and 70 percent in those with and without PTDM, respectively.

The incidences of PTDM after 1, 3, and 5 years post transplantation in these patients were < 4%. Taking into account the risk factors with regard to gender or presence of hepatitis, B and/or C, 252 post kidney transplantation patients were checked for diabetes by measuring their fasting plasma glucose.

Accordingly, 8 patients (3.2%) were found to have diabetes millets (plasma glucose >126 mg%) and 14 patients (5.5%) having impaired fasting plasma glucose(> 110 mg% and<126mg%)

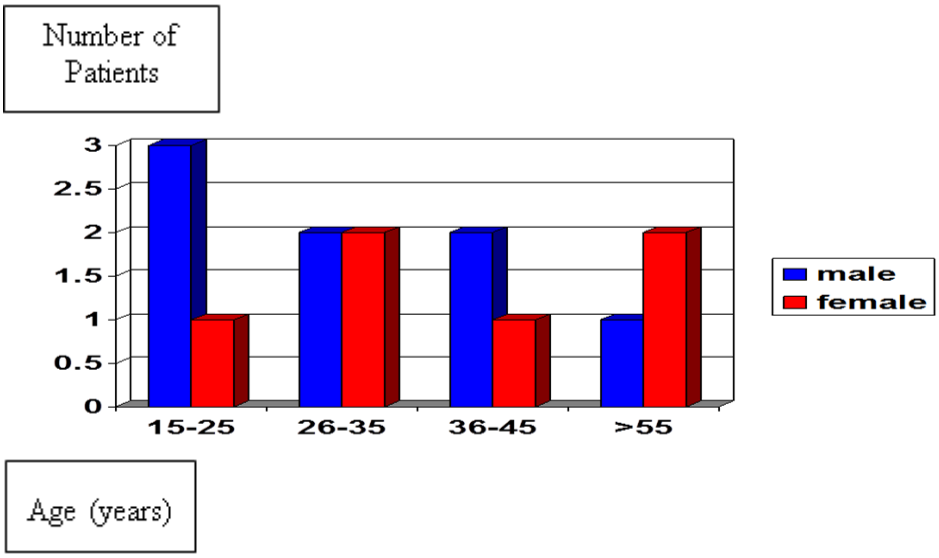

Figure 1. Risk factors for post-transplant diabetes development (Patients with impaired fasting glycaemia).

Discussion and Conclusion

Early corticosteroids withdrawal play a role in reducing the development of post transplantation new onset diabetes mellitus in Libyan population. It is clear, however, that the field is at an exciting stage. The next few years should provide a big step forward in our understanding of how these important anti-inflammatory molecules exert their effects, with concomitant advances in the clinical treatment of inflammatory disease.

In the present study, we evaluated the incidence of PTDM in a Libyan group of renal allograft recipients with transplants in a single institution (Libyan National Organ Transplantation Program), and treated with uniform corticosteroids immunosuppressive protocols. The incidences of PTDM reported here is similar to that incidences reported in other studies. However, there is a significant variability in the reported incidences of PTDM, most likely because of at least three reasons. First, the criteria used to diagnose PTDM are quite variable among studies. Second, variability in the immunosuppressive protocols used in different transplant centers will have an impact in the incidence of PTDM. For example,

the incidence of PTDM is significantly higher in transplant recipients treated with tacrolimus than in those treated with Corticosteroids (Shiraswamy et al., 2016; Wallia et al., 2016).

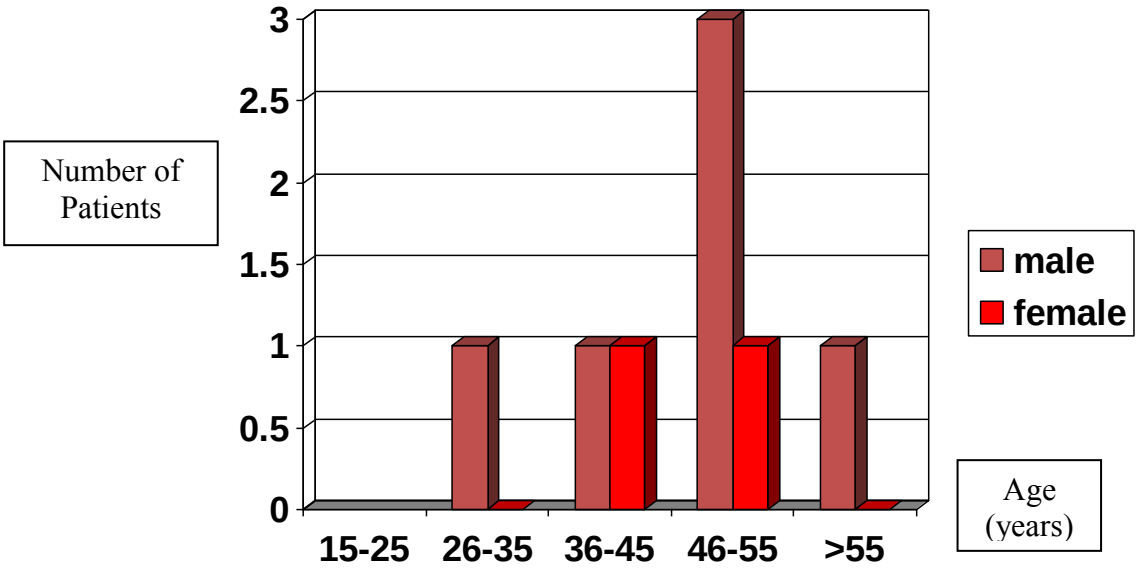

Figure 2. Patients with Post Transplantation DM transplant recipients older than 45 years of age were 2.2 times more likely to develop PTDM than those younger than 45 at the time of transplantation (P< 0.0001).

The development of post-transplant diabetes mellitus PTDM is associated with a high risk of complications, such as infections and cardiovascular disease. Identifying patients at high risk of developing PTDM by close monitoring of glucose level and prompt therapy of hyperglycemia are warranted. One of these modifiable risk factors is Corticosteroid therapy. Comparing our study with others surely showed that early corticosteroids withdrawal has a role in reducing the development of post transplantation new onset diabetes mellitus (Penformis and Kury-Paulin, 2006).

It was suggested in the literature that African and Hispanics are at increased risk for developing PTDM compared to whites. Thus, the risk of developing PTDM as defined by the 2003 International Guidelines was double in Africans compared to whites. Eighteen similar data from the USRDS demonstrated that PTDM was more common among African Americans (RR=1.68, P< 0.0001) and Hispanics (RR=1.35, P< 0.0001) compared with Caucasians.

This study shows that the most important modifiable risk factors of development post-transplant diabetes mellitus PTDM is corticosteroid therapy. We show here that early corticosteroids withdrawal has a crucial role in reducing the development of post transplantation new onset diabetes mellitus and that the Libyan women interact more positively with corticosteroids than Libyan men in avoiding development post-transplant diabetes mellitus PTDM.

Authors' Contributions

The corresponding author Dr. Abdulhafid Shebani certifies that all co-authors have approved and agreed to the contents of manuscript and that the submitted work has not been considered for publication or published previously.

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