Diabetes mellitus is now being recognised as a pandemic. The global projections for affected persons by 2030 are now nearing 370 million. This is important because the associated complications of diabetes can be dire. They may be acute and life-threatening (diabetic ketoacidosis) or chronic. Chronic hyperglycaemia results in the macrovascular and microvascular complications associated with the disease.

Life expectancy of diabetics is dramatically reduced compared with non-diabetics, largely as a consequence of the increased prevalence of ischaemic heart disease and cerebrovascular events in this population. Diabetes is an independent risk factor for both cardiovascular disease and mortality from coronary heart disease. Diabetes is also the leading cause of end-stage renal disease worldwide. These consequences affect patient quality of life and also significantly impact on health care costs. Diabetes-related expenditure for 2002 related to direct costs of drug acquisitions in the USA was estimated to be $132 billion and for 2007 is thought to have exceeded $174 billion, with indirect costs (loss of productivity, premature mortality, disability) amounting to $40 billion.
New-onset diabetes after renal transplantation

There are no specific criteria for the diagnosis of new-onset diabetes mellitus after renal transplantation (NODM), so the diagnosis is based on the World Health Organization (WHO) and American Diabetes Association (ADA) criteria for the diagnosis of diabetes in the general population. The natural progression of NODM resembles that of type 2 diabetes (T2DM) because of the insidious onset, and patients may be asymptomatic for years before the symptoms become clinically evident. This asymptomatic period is detrimental because it increases the duration of exposure to the adverse effects of hyperglycaemia before treatment is initiated. Unlike T2DM, however, NODM can be reversible, but these individuals are at increased risk for the subsequent development of full-blown diabetes mellitus later on in life (Table I).

Standard immunosuppressive therapy to prevent allograft rejection includes calcineurin inhibitors and corticosteroids, both of which are diabetogenic. The diabetogenicity of the different agents varies considerably and the choice of immunosuppressive therapy can greatly influence the risk of the patient developing diabetes (Table II). Patients who receive tacrolimus have been reported to be about 5 times more likely to develop NODM than those who receive cyclosporin (CyA). Kamar et al. reported prevalences of NODM of 10.2% v. 3.8% (tacrolimus v. CyA), and Cho et al. found a prevalence of 57.1% with tacrolimus at 6 months after transplantation. A South African review of 17 patients receiving tacrolimus found that 47% became diabetic. A recent study showed that greater preservation of allograft function was achieved with tacrolimus, but at the expense of an increased risk of NODM.

The risk of NODM appears to be greatest during the first 6 months after transplantation, although the number of patients developing the condition continues to increase thereafter. The prevalence of NODM is significant, as shown by Montori et al., with a range of 1.8 - 21.7%.

NODM has serious consequences because of the association with reduced graft function and patient survival and an increased risk of graft loss. The association between NODM and graft failure has been explained in some studies by the higher risk of infections and death in these patients. Diabetes is also a major determinant of the increased cardiovascular (CVS) morbidity and mortality seen in transplant patients. The relative risk for the development of ischaemic heart disease more than 1 year after transplantation was 2.78 for males and a staggering 5.4 for females who developed NODM.

### Table I. Risk factors for development of NODM after renal transplantation

| Modifiable                                               | Non-modifiable                                      |
|---------------------------------------------------------|----------------------------------------------------|
| Obesity: BMI >25 kg/m²                                   | Age – older age at transplantation                  |
| Immunosuppressive agents (tacrolimus v. cyclosporin)    | Ethnicity and genetic predisposition, e.g.          |
| glucocorticoid use                                      | African-American, Hispanic and Native American      |
| Physical inactivity and weight gain                     | Family history of diabetes mellitus                 |
| Pre-transplant impaired fasting glucose                 | Hepatitis C virus infection                          |

BMI = body mass index.

### Table II. Mechanisms of immunosuppressive diabetogenicity

| Immunosuppressive | Mechanism                                                                                   |
|-------------------|---------------------------------------------------------------------------------------------|
| Corticosteroids   | Effects are related to dose and duration of treatment. Leads to the development of insulin resistance which is shown as an increase in glucose production by the liver and a decrease in glucose uptake by peripheral tissues, i.e. muscle and fat. There is also decreased pancreatic response to oral glucose. |
| Cyclosporin       | Leads to reduced beta-cell volume, which causes decreased insulin synthesis and secretion. |
| Tacrolimus        | Causes morphological damage to beta cells, impairing insulin synthesis and secretion in animal studies, and causing insulin resistance and hyperinsulinaemia in clinical studies. |
increase in CVS mortality remains higher than that in the general population, even after stratifying for age, gender and race. In addition, recent analysis has revealed that costs in patients who develop NODM are $12 000 - 13 000 higher than in transplant patients without diabetes by the end of the first year after the transplant. These costs rise to $19 000 - 22 000 by the end of the second year.

While the prevalence of post-transplant NODM has been reported for the African-American, Hispanic and white populations of the USA, and for some European as well as Asian communities, the prevalence in our various racial groups in South Africa is not known. This study was therefore conducted to provide a South African perspective and to review a single-centre experience at Johannesburg Hospital.

**Methods**

A retrospective analysis of patient files from the transplant period 1 July 1994 - 30 June 2004 was conducted. Data collected were age, race, gender, weight, date of transplant, type of transplant (cadaver/living donor), date of onset of diabetes, plasma glucose, HbA1c, cholesterol, immunosuppressive regimens, cumulative dose of corticosteroids used, cytomegalovirus (CMV) infection, graft rejection and loss, cardiovascular morbidity and overall mortality.

Diabetes was defined according to ADA and WHO criteria: fasting glucose ≥ 7.0 mmol/l or random glucose ≥ 11.1 mmol/l. Patients known to be diabetic before transplantation were excluded from the study.

**Statistical analyses**

Qualitative variables were compared using Fisher’s exact test and quantitative variables using the Wilcoxon rank test. Cox regression was employed to determine the association between diabetes and immunosuppressive regimens, adjusted for covariates. The Kaplan-Meier method was used to display time to onset of NODM, as well as the association between diabetes and race, and also displayed ‘survival time’ to onset of NODM, as well as the association between diabetes and race.

**Results**

Three hundred and ninety-eight renal transplant patient files were reviewed. Of the recipients 138 were white, 193 black, 32 coloured (mixed race) and 25 Indian; 10 were of unknown ethnicity. Of the patients 62 became diabetic (15.6%). This corresponds to an incidence rate of 3/1 000 per month. Of the patients who became diabetic, 60.7% (31/62) were male and 41.0% (25/61) were female, as opposed to a distribution of 63.3% (212/335) males (63.3%) and 36.7% (123/335) females among those who did not (p=0.526).

The mean time to onset of diabetes was 22 months (range 1 week - 100 months). The highest incidence of diabetes occurred in the first 6 months after transplantation (43/62, 69.4%) (Table III).

The mean age of the patients who did not develop diabetes was 36.36 years and that for the diabetic patients was 44.54 years (p<0.0001).

Of the white patients 9.4% (13/138) developed NODM, of the black patients 20.2% (39/193) (p=0.100), of the coloured patients 12.5% (4/32), and of the Indian patients 12.0% (3/25). The time of conversion to diabetes for the respective groups is shown in Fig. 1. The lack of statistical significance in the development of new-onset diabetes after transplantation between the various races is probably due to an underpowered study and subsequent type 2 statistical error.

The interaction between race, diabetes and weight is shown in Fig. 2. The mean weight of the non-diabetic patients was 62.8 kg and that of the diabetic patients 69.4 kg (p=0.0066). For an increase in weight of 5 kg the relative risk (RR) was 1.2 (95% confidence interval (CI) 1.05 - 1.39). For a weight increase of 10 kg the RR was 1.45 (95% CI 1.11 - 1.92).

The mean total cholesterol (treatment naïve) for non-diabetics was 5.54 mmol/l and that for the diabetic patients 5.92 mmol/l (p=0.06).

Overall patient survival (calculated in months from date of transplantation to death or the end of the study period) was 79.3% in the non-diabetic group compared with 73.7% in the diabetic group (hazard ratio (HR) 1.45, p=0.237) (Fig. 3).

The association between the immunosuppressive regimen used and the development of NODM is set out in Table IV.

The mean cumulative doses of steroids that the patients were exposed to was 3 781 mg in the diabetic group (calculated from the time of transplant to the onset of diabetes) and 8 552 mg in the non-diabetic group (calculated from the time of transplant to the end of the study).

Complications associated with diabetes are set out in Table V. While the diabetic patients were hospitalised more frequently than the non-diabetic patients (51/62, 82.6% v. 91/333, 27.33%, respectively), this did not reach statistical significance (p=0.113).

The risk of diabetes according to type of transplant received is set out in Table VI. Of the 62 diabetic patients, 5 (8.1%) (p=0.994) had received more than one transplant, while for the non-diabetic group the
Infection with CMV occurred in 17/62 (27.4%) diabetic patients (p=0.004, crude odds ratio (OR) 2.5, crude OR adjusted for weight 5.7) and in 43/331 (13.0%) non-diabetic patients. Data for hepatitis C infection are not available.

The association between pre-existing renal disease and diabetes in 56 cases in which the former was documented was as follows: hypertension 32/56 (57.1%) (p=0.007), glomerulonephritis 5/56 (8.9%), adult polycystic kidney disease 4/56 (7.1%), unknown 14/56 (25.0%), and pre-eclampsia 1/56 (1.8%).

**Discussion**

The prevalence of NODM at our institution was significant at 15.6%. Montori et al., Woodward et al. and Kasiske et al. all reported similar incidences. The mean time to onset of diabetes was also very much in keeping with the literature, with 69% of our patients having developed diabetes by 6 months after transplantation.

Our study did not show that black patients were at significantly greater risk of developing diabetes than the other ethnic groups, which is not in concordance with data showing that African-American patients are more affected. This may imply genetic predisposition in these individuals. Another factor that supports this theory is the fact that there was not much difference in mean weight between the diabetic and non-diabetic black patients. The other ethnic groups gained an average of between 5 and 10 kg of weight before they became diabetic (Fig. 2). This shows a significant difference (p=0.0056) in the effect of weight gain on diabetes onset between the ethnic groups, as well as an interesting similarity, the white and coloured groups being almost identical. For a weight gain of 5 kg the relative risk of becoming diabetic was 20%, and for a 10 kg weight gain the relative risk rose to 46%. There was a significant interaction between CMV infection, weight and diabetes onset, with the crude OR being 2.5 for CMV and diabetes and the OR when adjusted for weight double that at 5.7. Indeed, the literature strongly suggests that active CMV infection may increase the risk of developing NODM by affecting beta-cell mass, insulin secretion or both.

The age at onset of diabetes was also significant, as shown by the finding that the mean age of the diabetic patients was almost a decade more than that of the non-diabetic patients (44.5 v. 36.4, p≤0.0001). The variation with regard to gender was not significant. A recent study indicated that women are more likely to develop NODM even after adjustment for age, but our study population was not large enough to discriminate between the sexes.

Of the patients who were on a tacrolimus-based regimen 20.3% became diabetic, i.e. 1 out of every 5 patients. While this did not reach statistical significance when compared with CyA, it is
still consistent with the findings of institutions worldwide.\textsuperscript{11,13,15,20} Of the patients on CyA 14.4\% became diabetic. There appeared to be a large number of patients on mycophenolate mofetil (MMF) who became diabetic, but when adjusted for concurrent use with the calcineurin inhibitors 64.7\% were also on tacrolimus and 35.3\% on CyA. Of the patients who took thiazide diuretics 17.2\% became diabetic, and of those, 71.4\% were also on CyA and 19\% on tacrolimus. The patients who developed diabetes appear to have been exposed to lower cumulative doses of corticosteroids (mean 3 781 mg) than the non-diabetic group (8 552 mg); however, it would have been a more pertinent comparison had the duration of exposure been looked at concurrently. A recent French study\textsuperscript{8} did just that and found that the cumulative doses of corticosteroid were similar between the groups and were not statistically significant. The diabetogenicity of corticosteroid therapy is well known,\textsuperscript{24,28-30} but not borne out in this study and other recent studies.\textsuperscript{8,27}

While the mean total cholesterol (treatment naïve) was higher in the diabetic group than in the non-diabetic patients, in keeping with findings by Kyu Yeon Hur et al.,\textsuperscript{27} this did not reach statistical significance, probably owing to small numbers.

With regard to complications, diabetic patients had significantly more infections, 96.8\% versus 76.0\% in non-diabetics \((p <0.0001)\), and were also more frequently hospitalised (82.3\% v. 72.7\% of non-diabetics). Cardiovascular morbidity and mortality

\begin{table}[h]
\centering
\caption{The association between immunosuppressive regimen used and diabetes}
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Agent} & \textbf{Diabetic patients (No., \%)} & \textbf{Used in combination with CyA (No., \%)} & \textbf{Used in combination with tacrolimus (No., \%)} \\
\hline
CyA & 51/353, 14.4 & & \\
Tacrolimus & 16/79, 20.3 \textsuperscript{(p=0.228)} & & \\
Rapamune (sirolimus/rapa) & 5/44, 11.4 & & \\
Mycophenolate mofetil (MMF) & 17/142, 12.0 & 6/17, 35.3 & 64.7, 11/17 \\
Thiazide diuretics & 21/122, 17.2 & 15/21, 71.4 & 4/21, 19.0 \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Complications associated with diabetes}
\begin{tabular}{|l|c|c|}
\hline
\textbf{Complication} & \textbf{Diabetic patients (No., \%)} & \textbf{Non-diabetic patients (No., \%)} \\
\hline
Infections & 60/62, 96.8 \textsuperscript{(p<0.0001)} & 254/334, 76.0 \\
Cardiovascular morbidity and mortality & 7/62, 11.3 \textsuperscript{(p= 0.824)} & 35/333, 10.5 \\
Graft rejection & 12/60, 21.7 \textsuperscript{(p = 0.145)} & 102/329, 31.0 \\
Graft loss & 4/62, 6.5 \textsuperscript{(p=0.078)} & 49/332, 14.8 \\
Proteinuria & 39/59, 66.1 \textsuperscript{(p=0.006)} & 151/329, 46.5 \\
Serum creatinine (mean) (µmol/l) & 220.7 \textsuperscript{(p=0.730)} & 263.21 \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Type of transplant received and risk of diabetes}
\begin{tabular}{|l|c|c|}
\hline
\textbf{Type of transplant} & \textbf{Diabetic (No., \%)} & \textbf{Non-diabetic (No., \%)} \\
\hline
Cadaver & 55/62, 88.7 \textsuperscript{(p=0.060)} & 252/336, 75.0 \\
Related living donor & 6/62, 9.7 & 75/336, 22.3 \\
Non-related living donor & 1/62, 1.6 & 9/336, 2.7 \\
\hline
\end{tabular}
\end{table}
The incidence of NODM is as significant in the South African setting as it is worldwide. The first 6 months after transplantation pose the greatest risk for the development of diabetes, although the number of patients developing the condition continues to increase thereafter. The course of NODM resembles that of T2DM but differs in that it may be reversible. South African black patients are most at risk, as are their African-American counterparts. An older age group and weight gain also portends a greater risk for the development of diabetes, as does active CMV infection.

The immunosuppressive regimen used plays a large role in putting patients at risk for diabetes: we now know that even at our institute, the use of tacrolimus was associated with a higher risk of diabetes than CyA. Corticosteroid therapy did not appear to impact much on the onset of diabetes. The use of diuretics in combination with calcineurin inhibitors increases the risk of development of diabetes after transplantation.

Development of diabetes was also associated with cadaveric grafts and was more likely if the patient had been hypertensive prior to transplantation. There were more hospitalisations among diabetic patients, probably because of the significantly greater number of infections in this group compared with the non-diabetics. Diabetic patients were more proteinuric, but this did not translate to reduced graft function as the mean serum creatinine level was actually lower in the diabetic group. Diabetes was not associated with increased graft loss or rejection.

The numbers of diabetic patients with cardiovascular morbidity and mortality were not adequate to reach statistical significance, but among those who did succumb, high cholesterol levels may have been contributory. Diabetic patients died sooner than non-diabetic patients, and diabetes conferred an increased HR for death.

Study limitations

As this was a retrospective study from patient records, the data retrieved were not always complete, e.g. we could not measure body mass index (BMI). We did not look at the association of diabetes with hepatitis C infection, which is well described. β-blocker use or the full lipid profile (only total cholesterol was assessed). The cumulative dose of corticosteroid was not calculated according to duration, which makes comparison between groups difficult.

Recommendations

Patients need to be risk-stratified before transplantation according to family history of diabetes, BMI, measurement of waist circumference, the presence of pre-diabetes (impaired fasting glucose or impaired glucose tolerance), age and ethnicity. The immunosuppressive regimen should then be tailored to the individual. Patients need to be rigorously monitored for diabetes, especially in the first 6 months after the transplant. If a patient becomes diabetic while on tacrolimus, sirolimus may be substituted.

Patient management once diabetes has developed after a transplant has not been studied; however, the guidelines do not differ from management of such a patient in the general population. For a detailed discussion we recommend the articles by Davidson et al.9 and Wilkinson et al.32

A prospective study to address the study shortfalls is recommended, to provide a more detailed evaluation of the condition.

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SA’s favourite rusk can now be enjoyed by diabetics too

From humble beginnings in 1939 in Molteno in the Eastern Cape, Ouma Rusk has been firmly entrenched in the South African way of life. Time and again Ouma has proved to be the perfect anytime, anywhere treat, and it’s the snack that accompanies us everywhere: to work, school, on road trips, camping, even overseas on holiday. Ouma Rusk truly are proudly South African, and as our most iconic food export, are highly sought after among ex-pats around the world.

But until recently, diabetics were precluded from enjoying this much enjoyed and beloved treat. Which is why, in keeping with healthier eating trends worldwide and a growing awareness of lower GI ratings, Ouma recently introduced Nutri Rusk to the range.

A completely new recipe allows diabetics to enjoy Nutri Rusk as an intermediate treat, subject to their doctors’ or dieticians’ approval. For added peace of mind, Nutri Rusk carries the much-respected GI Foundation of South Africa accreditation. Ingredient listings and nutritional information below will assist you in advising your patients. Nutri Rusk are available in 500g and 1kg boxes and convenient single wrapped servings.

Nutrient | Per 100g | Per 30g serving
--- | --- | ---
Protein | 9.7g | 2g
Total Fat | 9g | 2.7g
Of which: | | |
Polysaturates | 1.9g | 0.6g
Monounsaturates | 3.7g | 1.1g
Saturates | 3.4g | 1.0g
Cholesterol | Not detected | |
Fibre | 1.5g | |
Carbohydrate | 66.7g | 20.0g
Sodium | 411mg | 123mg
Energy | 1565kJ | 470kJ

**Ingredient List**
Wheat Flour, sugar, raisins, digestive bran, vegetable shortening, raising agent (E450, E500, E170), peanuts, coconut, oats, buttermilk powder, flavour (honey), vitamin premix.

**Nutritional Information**
A single rusk serving = about 30g

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