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New onset diabetes post renal transplantation

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1.1.1 DEFINITION

The term diabetes mellitus describes several disorders of abnormal carbohydrate metabolism that are characterized by hyperglycemia. It is associated with relative or absolute impairment in insulin secretion along with varying degrees of peripheral resistance to the action of insulin[1].

DIAGNOSIS

The diagnosis of diabetes is presently based on the diagnostic criteria revised in 2003 by the American Diabetes Association (ADA)[2] (Table 1). The International Diabetes Federation 2006 Conference held in Cape Town, South Africa, has made no further revision of the criteria[3] .

Table 1.

Diagnostic Thresholds for Diabetes and Lesser Degrees of Impaired Glucose Regulation

Category	Fasting Plasma Glucose	2-Hour Plasma Glucose
Normal	<100 mg/dL (<5.6 mmol/L)	<140 mg/dL (< 7.8 mmol/lL)
IFG	100-125 mg/dL (5.6-6.9 mmol/L)	-
IGT	-	140-199 mg/dL (7.8-11.0 mmol/L)
Diabetes*	≥126 mg/dL (≥7.0 mmol/L)	≥200 mg/dL (≥11.1 mmol/L)

Reproduced from: Kim SH, Chunawala L, Linde R, Reaven CM. Comparison of the 1997 and 2003 American Diabetes Association classification of impaired fasting glucose. J Am Coll Cardiol 2006;48:293

1.1.2 CLASSIFICATION

1. **Type 1 Diabetes Mellitus (β-cell destruction, usually leading to absolute Insulin deficiency)**
    - Immune-mediated
    - Idiopathic
2. **Type 2 Diabetes Mellitus (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)**
3. **Other specific types :**

    A. Genetic defects of beta cell function

    MODY (Maturity-onset diabetes of the young)

    B. Genetic defects in insulin action (rare)

    C. Diseases of the exocrine pancreas

    - Pancreatitis
    - Trauma or pancreatectomy
    - Neoplasia
    - Cystic fibrosis
    - Haemochromatosis
    - Toxins
    - Drugs

D. Endocrinopathies

- Acromegaly
- Cushing's Disease or syndrome
- Phaeochromocytoma
- Hyperthyroidism

E. Drug or chemical induced

- Thiazides
- Glucocorticoids
- Thyroid hormone
- β-agonists
- Calcineurin inhibitors

F. Infections

- Congenital rubella
- CMV

4. GESTATIONAL DIABETES

1.1.3 COMPLICATIONS

The complications of diabetes can be categorized as follows:

Table 2.

Acute	**Chronic**
Diabetic ketoacidosis (DKA)	Macrovascular: Cardiovascular eg. myocardial infarction Cerebrovascular eg. Stroke Peripheral vascular disease
Hyperosmolar non-ketotic coma	Microvascular: Nephropathy Neuropathy Retinopathy

Patients could also be affected by the treatment of the diabetes, viz. hypoglycemia which is life-threatening if not corrected expeditiously.

The cause of diabetic complications is not precisely known and may be multifactorial.

POPULAR THEORIES:

The formation of glucotoxins:

(a) POLYOL PATHWAY

- process where glucose is reduced to sorbitol by the enzyme aldolase reductase.
- Sorbitol appears to be a tissue toxin and mostly responsible for the microvascular complications.

(b) GLYCATION OF PROTEINS

Terminology: GLYCATION – nonenzymatic addition of hexoses to proteins

GLYCOSYLATION – enzymatic addition of hexoses to proteins

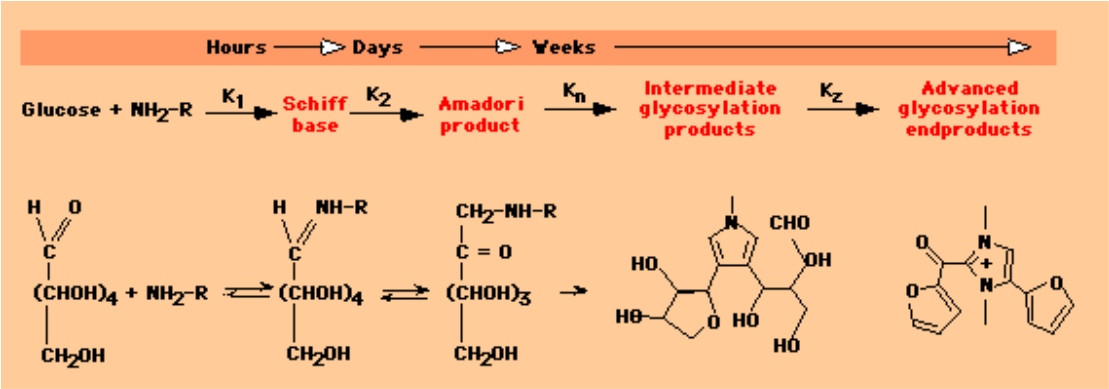
Glycation: The effect of glycation on protein predisposes to altered or disturbed function, eg. albumin, haemoglobin, lens protein, fibrin, collagen and lipoproteins. Glycated low density lipoprotein (LDL) is not recognized by the normal LDL receptor, and its plasma half life is increased. Glycated collagen is less soluble and more resistant to degradation by collagenase than native collagen and this may result in basement membrane thickening or the waxy skin syndrome (pseudoscleroderma).

Glycosylation : Glycated proteins also form cross-linked proteins termed Advanced Glycation End products (AGEs) through a series of biochemical reactions which are poorly understood (Fig 1.)

Receptors for AGE are present on macrophages and endothelial cells. Binding of AGE to its receptors may induce the synthesis or release of cytokines, vascular adhesion molecules, endothelin-1 and tissue factors.

As a result of the inflammatory component, glycation and AGE seem to predispose to more macrovascular complications, however, both sorbitol and AGE pathways contribute to both micro- and macrovascular complications.

Figure 1.



Formation of advanced glycosylation end products Schematic representation of the formation of advanced glycosylation end products in the presence of persistent hyperglycemia. (Adapted from Bucala, R, Vlassara, H, Cerami, A, Drug Development Research 1994; 32:77.)

Perhaps as important as the effect of glucotoxins, hyperglycemia has also been shown to alter cellular signaling pathways such as protein kinase C (PKC), MAP kinases and PI3K/AKt cascades, which can cause vascular cell dysfunction, apoptosis and specific pathologies in a variety of vascular and cardiovascular tissues. The significance of these cascades in the pathogenesis of diabetic complications has led to the development of a new therapeutic agent PKC &#946 isoform inhibitor (Ruboxistaurin). This agent has yielded positive results to prevent visual acuity loss in diabetic patients with macular oedema, in clinical trials. There has also been some benefit when used for patients with diabetic peripheral neuropathy. This supports the theory that hyperglycemia- induced changes in cell signaling is an important cause of diabetic complications[4].

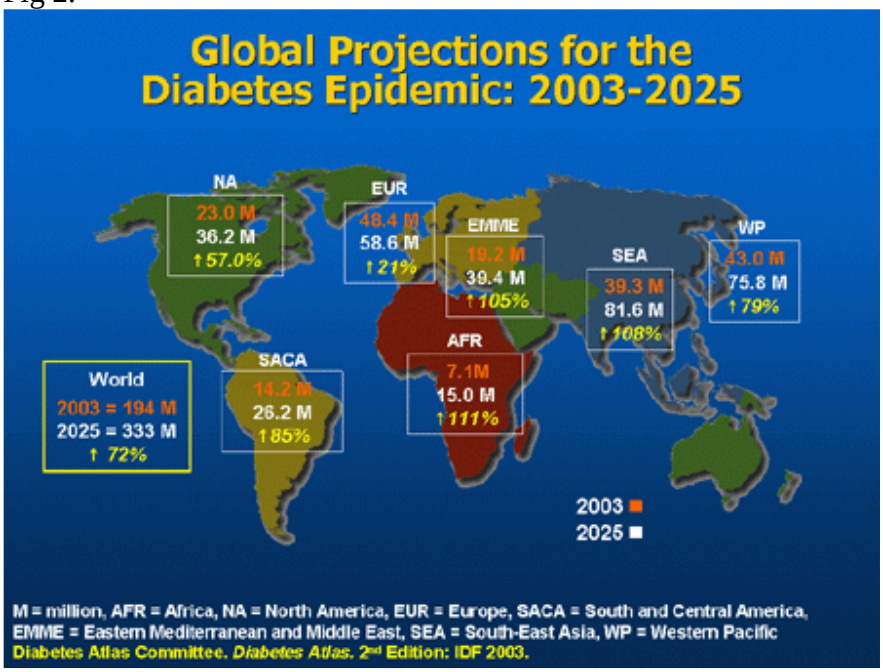
1.1.4 GLOBAL PREVALENCE AND COST

GLOBAL PREVALENCE:

Diabetes is now being recognized as a pandemic[6]. This global problem was emphasized at the International Diabetes Federation conference in Cape Town, South Africa (IDF 2006), and again at the European Association for the Study of Diabetes Conference in Amsterdam (EASD 2007).

In 2004, an estimated 194 million people worldwide[5] were affected with diabetes (Fig 2) and that figure is expected to rise to 370 million by 2030[6]. Facts from the IDF 2006[7] reveal that an estimated 246 million people are already affected across the world; a figure that is expected to reach 380 million within the next 20 years.

Fig 2.



Of concern is that 7 million more people are afflicted with diabetes every year. The highest number of people affected are from developing countries, where the double edged sword of economic progress has brought with it 'lifestyle diseases' such as obesity – previously a disease of the affluent.

There seems to be an increased prevalence of diabetes in certain population groups: eg. American data shows higher diabetes prevalence in the African-American, Native Americans and Hispanic sub-groups. South African ethnic variation in the prevalence of diabetes is presented in Table 3. below:

Table 3. Prevalence of type 2 diabetes in different South African population groups[8-14]

Population	Region (number of participants)	Prevalence %	Age range (yrs)
African	Cape Town urban (729)	8.0	30+
African	QwaQwa rural (853) Manguang urban (758)	4.8 6.0	25+
African	Durban urban (479)	5.3	15+
Mixed	Cape Town urban (200)	28.7	65+
Mixed	Cape Town peri-urban (974)	10.8	15-86
European	Cape Town peri-urban (396)	3.0	15-69
Indian	Durban urban (2479)	13.0	15+

There is a higher prevalence of type 2 diabetes among the South African Mixed (coloured) , Indian and Urban Black population compared with their rural and White counterparts.

FINANCIAL BURDEN OF DIABETES:

The life expectancy of diabetics is dramatically reduced compared with non-diabetics, largely as a consequence of the increased prevalence of myocardial infarction and strokes in this population. Diabetes is an independent risk factor for both cardiovascular disease and mortality from coronary heart disease[15-17]. Diabetes is also the leading cause of end-stage renal disease worldwide[17].

These complications impact on the patient's quality of life and also have a significant impact on healthcare costs. Direct costs of drug acquisitions in the USA for 2002 were estimated to be $132 billion, and indirect costs (loss of productivity, premature mortality disability) amounted to $40 billion[18].

The annual direct healthcare costs of diabetes worldwide, in the 20-79 years age group, are estimated to be approximately 153 billion international dollars and may be as much as as 286 billion.

The projected figures for 2025 puts the total healthcare costs for diabetes worldwide at between 213 billion and 396 billion international dollars. This would mean that the proportion of the world's healthcare budget being spent, in 2025, on diabetes care, will be between 7% and 13%, with higher prevalence countries spending up to 40% of their budget[19]. So, the economic impact of diabetes is quite substantial and significant.

1.2 NEW ONSET DIABETES POST RENAL TRANSPLANTATION

1.2.1 Definition and Diagnosis

The diagnosis of new onset diabetes post renal transplantation is based on the World Health Organisation (WHO) and the American Diabetes Association (ADA) criteria for the diagnosis of diabetes mellitus in the general population, as there are no specific criteria for the diagnosis in this specialized group of patients.

1.2.2 Epidemiology

The natural progression of diabetes post renal 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[19,20]. This asymptomatic period is detrimental as it increases the duration of exposure to the adverse effects of hyperglycemia before treatment is initiated[21]. Unlike Type 2 diabetes, however, diabetes post renal transplantation can be reversible, but these individuals are at higher risk for the subsequent development of full blown diabetes mellitus later on in life (Table 4).

Table 4: Risk Factors for development of new-onset diabetes post-transplant[34]

Modifiable	**Non-Modifiable**
Obesity : BMI > 25 kg/m^2	Age – older age at transplantation
Immunosuppressive agents (Tacrolimus vs Cyclosporine)	Ethnic denomination and genetic predisposition eg. African-American, Hispanic and Native American
	Family history of diabetes
Pre-transplant impaired fasting glucose	Hepatitis C virus infection

1.2.3 IMMUNOSUPPRESSIVE AGENTS:

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 5. 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.
Cyclosporine	Leads to reduced β-cell volume which causes decreased insulin synthesis and secretion
Tacrolimus	Causes morphological damage to β-cells, impairing insulin synthesis and secretion in animal studies, and causing insulin resistance and hyperinsulinemia in clinical studies.

There also seems to be a higher predilection for the development of post-transplant diabetes (PTDM) based on Tacrolimus versus Cyclosporine (CyA) use – up to five times higher with Tacrolimus use[18,22]. (Refer *Appendix B*). Kamar[22] reported an incidence of 10.2% for patients on Tacrolimus versus 3.8% for those on CyA and Cho et al[23] found an incidence of 57.1% with Tacrolimus at 6 months post-transplantation. A South African review of the diabetogenic effect of Tacrolimus in South African patients undergoing

kidney transplantation[24] found that eight out of the 17 patients on Tacrolimus developed diabetes (47%) .Of those, 6 were Black patients (75%), but this did not reach statistical significance.

The agents that seem to be neutral are Azathioprine (Imuran), Sirolimus (Rapamune) and Mycophenolate Mofetil (MMF/Cellcept)[25,26]. Sirolimus may, however, lead to hyperlipidemia. Egidi and Gaber [27] described their single-centre experience of converting patients from calcineurin inhibitor regimens to sirolimus and MMF because of chronic nephrotoxicity or PTDM. This was in response to the high incidence of PTDM in the African –American group. In order to better understand the factors related to the development of PTDM, pre- and post-transplant C-peptide levels were collected. Differences were found in the pattern of C-peptide and glucose tolerance among patients who developed PTDM : a group consisting of mainly young African-American patients, developed an early insulin-dependent PTDM with complete disappearance of the C-peptide levels despite them being normal pre-transplant. These individuals enjoyed the greatest benefit from conversion from a CyA regimen to a sirolimus-based one with regression of diabetes in 60% .

1.2.4 Time to onset

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. Sharma et al[21], in his study of 1023 kidney transplant patients reported that 60% of cases of new onset diabetes were recorded in

the first 3 months post transplantation; 20% between 3 and 12 months, and the remaining 20% after the first year. Koselj et al[28], reported in their study, that 70% of patients with new onset diabetes after kidney transplantation were diagnosed within 6 months with a mean time to onset of 5.6 months post renal transplantation.

1.2.5 INCIDENCE AND PREVALENCE:

The incidence and prevalence of new onset diabetes (in most cases defined only by the patient's requirement for insulin) post transplantation, has been shown to increase progressively, with the condition being diagnosed in some patients up to 1 year after transplantation[29]. Montori et al[30] systematically reviewed the range of 12-month cumulative incidence of new onset diabetes after transplantation reported in 19 studies (which involved 3611 patients with no history of diabetes) and found it to be 1.8 – 21.7%.

The type of immunosuppressive regimen used, was found to explain 74% of the variability in incidence, with high dose steroids being associated with the highest incidence. Woodward et al[31] analyzed data from the United States Renal Data System (USRDS) and showed that 13.2% of peritoneal dialysis patients and 14.9% of haemodialysis patients experienced new onset diabetes during the first year post transplantation. In a second study by Kasiske et al[32], the cumulative incidence of new onset diabetes after kidney transplantation among 11 659 patients was found to be 9.1%, 16%, and 24%, at 3, 6, and 36 months, respectively. A further study of 503 kidney transplant patients reported a 16% incidence of new onset diabetes after transplantation[33].

1.2.6 COMPLICATIONS

Studies indicate that the development of diabetes after transplantation has serious consequences because of the association with reduced graft function and patient survival and increased risk of graft loss[19,35-37]. The development of PTDM was shown to be associated with a significant decrease in graft survival at 3 and 4 years, compared with recipients without diabetes (71% vs. 86% and 54% vs. 82%, respectively; p = <0.05)[38]. A recent analysis of Medicare beneficiaries on the USRDS database has also revealed that the development of PTDM was associated with a 63% increased risk of graft failure and a 46% increase in the risk of death-censored graft failure (p= <0.0001 vs no diabetes for both comparisons)[32].

The relative risk of graft loss 12 years post-transplantation was found to be 3.72 times greater in the group with diabetes post-transplantation than in the non-diabetic group[34].

The association between new onset diabetes after kidney transplantation and graft failure has been explained in some studies by the higher risk for death in these patients.

However, other studies have reported that the association between the condition and graft failure remains even when the data are censored for death[32]. Other explanations for the effects of PTDM on graft survival include:

a) Diabetes-related nephropathy[20]

b) Presence of poorly controlled Hypertension[41]

c) Use of lower dosages of immunosuppressive regimens[34]

Kasiske et al[32] also postulated that the association between PTDM and reduced graft survival may, in some instances, be due to early acute rejection and subsequent use of higher doses of immunosuppression.

The increased mortality associated with PTDM is likely to be related to the increased risk of infections and other complications that can arise following the development of the condition. This theory is supported by the findings of 3 studies:

1. Sumrani et al[42], showed that infections were a major complication and that 54% of patients experienced infectious complications compared with 17% in the control group.
2. Miles et al[34], found that the frequency of sepsis as a cause of death was greater in kidney transplant recipients with diabetes compared with patients without diabetes.
3. Johny et al[43], in his study of 631 kidney transplant recipients reported a higher incidence of infection-related deaths in patients with diabetes compared to those without the condition.

Diabetes is also the major determinant of the increased cardiovascular morbidity and mortality seen in transplant patients[18,39,40]. The relative risk for the development of ischemic heart disease more than one year post transplantation was 2.78 for males, and a staggering 5.4 for females (Refer *Appendix C*). The disparate risk of cardiovascular morbidity and mortality that female diabetic post transplant patients have when compared with their male counterparts is quite sobering[18] and the exact mechanism for the increased risk is not fully understood, but is thought to be related to the effect of female sex

hormones on thrombosis and inflammation. Furthermore, the increase in cardiovascular disease mortality observed among kidney transplant recipients remains higher than the general population, even after stratifying for age, gender and race[44].

1.2.7 COST

In addition , recent analysis has revealed that the costs of developing post transplant diabetes are $12,000-$13,000 higher compared those without diabetes by the end of the first year following transplantation.These costs rise to $19,000-$22,000 by the end of the second year[18,32].

1.2.8 RATIONALE FOR THE STUDY

While the incidence of post-transplant diabetes has been reported for the African-American, Hispanic, and White population of the United States of America, and for some European as well as Asian communities, the prevalence of PTDM 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 the Johannesburg Hospital.

2. THE STUDY

2.1 STUDY DESIGN

2.1.1 AIMS

To determine

- the incidence of diabetes in patients post renal transplantation
- the association of diabetes with particular immunosuppressive regimens and ethnicity
- outcomes in terms of morbidity and mortality associated with diabetes post transplant i.e. infections, cardiovascular disease, graft function and survival, and overall patient survival

2.1.2 METHODS

A retrospective analyses of patient files from the transplant period 01/07/1994 to 30/06/2004 was conducted.

Data collected : Age

Race

Gender

Weight

Date of transplant

Type of transplant (cadaver/ living donor)

Date of onset of diabetes

Random plasma glucose

Fasting plasma glucose

$HbAI_C$

Lipid profile

Immunosuppressive regimens

Cumulative dose of corticosteroids used

High dose corticosteroids for acute rejection

CMV infection

Graft rejection

Graft loss

Cardiovascular mortality

Overall mortality

Diabetes was defined according to American Diabetes Association (ADA) and World Health Organization (WHO) criteria: Fasting glucose ≥ 7.0mmol/l (126mg/dl) or random glucose ≥ 11.1mmol/l .

Cardiovascular mortality was defined by fatal arrhythmia or ischemia (unstable angina or myocardial infarction)

Patients known to be diabetic prior to transplantation were excluded from the study.

2.1.3 STATISTICAL ANALYSES

Qualitative variables were compared using the Fisher's Exact test, and the Wilcoxon test was used for quantitative variables. 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 new onset diabetes, as well as the association between diabetes and race, and also displayed "survival time" or overall mortality

2.2 RESULTS

Three hundred and ninety eight renal transplant patient files were reviewed. There were 138 White recipients, 193 Black, 32 Coloured (mixed race), 25 Indian and 10 recipients of unknown ethnicity. The number of patients who became diabetic in the study period was 62/398 (15.58%). This corresponds to an incidence rate of 3 per 1000 patients per month. There were 36/61 (59.01%) male and 25/61 (40.9%) female patients who became diabetic compared with 212/335 (63.28%) and 123/335 (36.72%) respectively, of those who were not diabetic, p = 0.526.

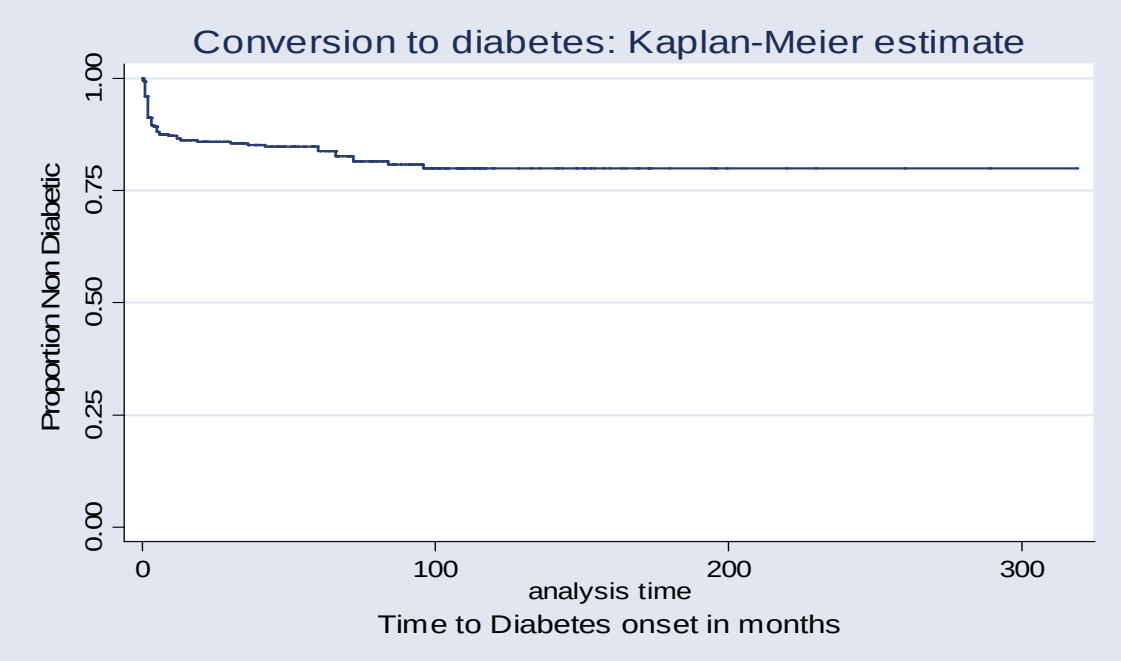
The mean time to onset of diabetes was 22 months (range 1 week to 100 months). The highest incidence of diabetes occurred in the first six months post transplant (43/62 or 69% of patients) – Table 6, Fig 3.

Table 6. Time to onset of diabetes

Duration (months) Post-transplant	**Number of patients who became diabetic**
1	12
2	18
3	6
6	7
12	3
> 12	16

The mean age of the non-diabetic patients was 36.36 years and 44.54 years for the diabetic patients, p = < 0.0001.

Fig 3.



The ethnic variation in incidence of PTDM (Fig 4) was as follows:

White patients : 13/138 or 9.42%

Black patients : 39/193 or 20.21% , p = 0.100

Coloured (mixed race)patients : 4/32 or 12.5%

Indian patients: 3/25 or 12%

The interaction between race, diabetes and weight is shown in Fig 5.

Fig 4.

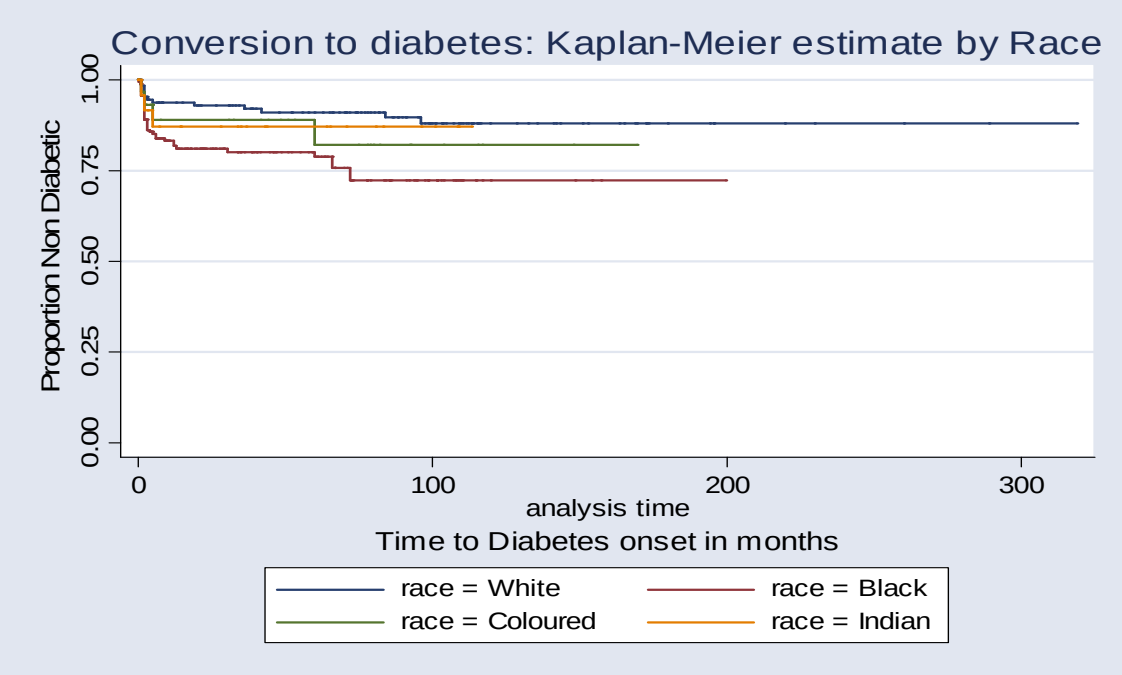
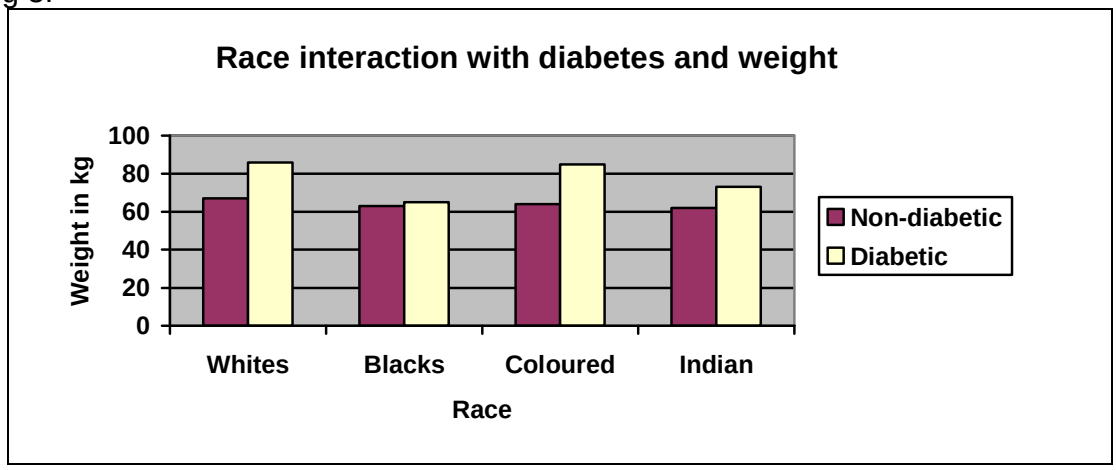


Fig 5.

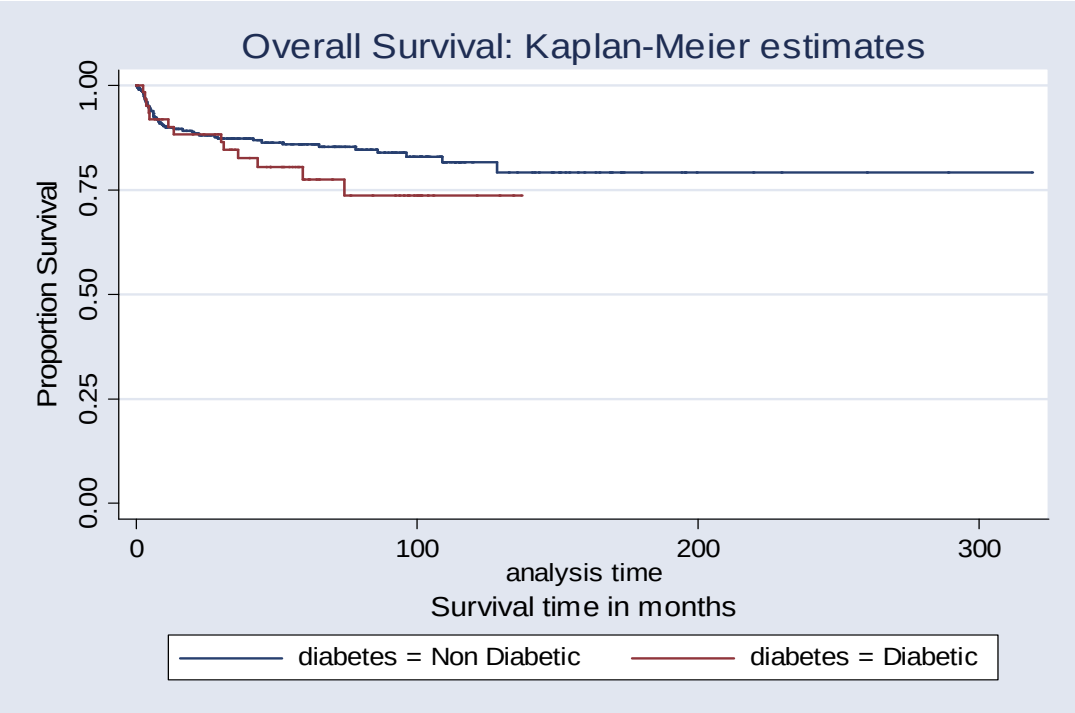


The mean weight of the non-diabetic patients was 62.83kg and the diabetic patients had a mean weight of 69.4kg, p = 0.0056. For an increase of weight of 5kg, the RR = 1.2 (95% CI 1.05 – 1.39). For a weight gain of 10kg, the RR = 1.45 (95% CI 1.11 – 1.92).

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

The overall patient survival (calculated in months from date of transplantation to death or end of study period) was 79.3% in the non-diabetic group compared with 73.7% in the diabetic group, HR = 1.45, p = 0.237, Fig 6.

Fig 6.



The association between the immunosuppressive regimen used and the development of PTDM is shown in Table 7.

Table 7. The association between immunosuppressive regimen used and diabetes

Agent	**Diabetic Patients (%)**	**% Used in combination with CyA**	**% Used in combination with FK**
Cyclosporine (CyA)	14.44 (51/353)		
Tacrolimus (FK)	20.25 (16/79) , p = 0.228		
Rapamune (Sirolimus/Rapa)	11.36 (5/44)		
Mycophenolate Mofetil (MMF)	11.97 (17/142)	35.29 (6/17)	64.71 (11/17)
Thiazide Diuretics	17.21 (21/122)	71.43 15/21)	19.05 (4/21)

The cumulative dose of steroids that the patients were exposed to was 3781mg in the diabetic group (calculated from the time of transplant to onset of diabetes). In the non-diabetic group the mean cumulative dose of corticosteroids was 8552mg (calculated from the time of transplant to end of study). Forty-two out of sixty-two (67.74%) of patients who developed PTDM also at some point in their therapy, were given intravenous corticosteroid pulses (p=0.351), compared with 206/335 (61.49%) of the non-diabetic group.

Table 8. ASSOCIATION OF DIABETES WITH COMPLICATIONS

Complication	Diabetic Patients	Non-diabetic patients
Infections	60/62 96.77%; p= <0.0001	254/334 76.04%
Cardiovascular mortality	7/62 11.29% p= 0.824	35/333 10.51%
Graft rejection	13/60 21.67% p= 0.145	102/329 31%
Graft loss	4/62 6.45% p= 0.078	49/332 14.76%
Proteinuria	39/59 66.1% p= 0.006	151/325 46.46%
Serum creatinine(mean) in µmol/l	220.66 p= 0.730	263.21

While diabetic patients were also more frequently hospitalized : 51/62 , 82.26% versus the non-diabetic patients (91/333, 72.67%), this did not reach statistical significance (p=0.113).

Table 9. The type of transplant received and risk of diabetes

Type of transplant	Diabetic	Non-diabetic
Cadaver (CD)	55/62 88.71% P = 0.060	252/307 75%
Related living donor (RLD)	6/62 9.68%	75/336 22.32
Non-related living donor (NRLD)	1/62 1.61%	9/336 2.68%

Five of the 62 diabetic patients, 8.06% (p = 0.994) were transplanted more than once, compared with the non-diabetic group, 91.96% of whom were recipients of first grafts.

Infection with CMV (Cytomegalovirus) occurred in 17/62 (28.33%) diabetic patients, P = 0.004, Crude OR = 2.5, Crude OR adjusted for weight = 5.7. With regard to HIV infection, 1/62 (1.61%) of patients also became diabetic.

Data for Hepatitis C infection is not available.

Association between pre-existing renal disease and diabetes is shown in Table 10:
Table 10

Pre-existing renal disease	Diabetic	Non-Diabetic
Hypertension	32/56 (57.14%) P=0.007	71/309 (22.97%)
Glomerulonephritis	5/56 (8.92%)	46/309 (14.89%)
Adult Polycystic Kidney Disease	4/56 (7.14%)	10/309 (3.2%)
Unknown	14/56 (25%)	114/309 (36.89%)
Pre-eclampsia	1/56 (1.78%)	2/309 (0.65%)

3. **DISCUSSION**

The incidence of new onset diabetes at our institution was significant at 15.58%. Montori[30] , Woodward et al[31] and Kasiske et al[32] all reported similar incidences.

The mean time to onset of diabetes was also very much in keeping with the literature: 69% at 6 months post transplantation (Sharma et al[21], and Koselj et al[28]).

Even though there were more Black patients who developed diabetes when compared with the other ethnic groups, this did not achieve statistical significance, probably related to the small numbers in our study, which is not in concordance with data[49] showing that African American patients are more affected. This may allude to genetic predisposition in these individuals. Another factor that supports this theory is the fact that the mean weight for Black patients was not much different between the diabetic group versus the non-diabetic group. The other ethnic groups gained between 5-10kg of weight before they became diabetic (Fig.5). This shows a significant difference in weight and diabetes onset between the ethnic groups, as well as a significant interaction between races, with the White and Coloured groups being almost identical. For a weight gain of 5kg, the relative risk of becoming diabetic was 20%, and for a 10kg weight gain , the relative risk rose to 46%. There was a significant interaction between CMV infection, weight and diabetes onset, with the Crude OR = 2.5 for CMV and diabetes, but the OR when adjusted for weight was double that at 5.7. Indeed, the literature[48,50,51] strongly suggests that active CMV infection may increase the risk of developing PTDM by affecting β-cell mass, insulin secretion or both.

The age at onset of diabetes was also significant as shown by the finding that the mean age for diabetic patients was almost a decade more than the non-diabetic patients (44.5 vs 36.4). The variation with regard to gender was not significant, however a recent study[45] indicated that women were more likely to develop PTDM even after adjustment for age, but the study population was not large enough to discriminate between the sexes.

Of the patients who were on a Tacrolimus (FK)-based regimen, 20.25% became diabetic i.e one out of every 5 patients treated with FK. While this did not reach statistical significance when compared with CyA, it is still consistent with the findings of institutions worldwide[18,30,32,36]. 14.44% of the patients on CyA became diabetic. There appeared to be a large number of patients on MMF who became diabetic but when adjusted for concurrent use with the calcineurin inhibitors: 64.71% were also on FK, and 35.29% on CyA. 17% of the patients who took thiazide diuretics became diabetic, and of those, 71.43% were also on CyA, and the remaining 19% were on FK.

It seems that diabetic patients were exposed to lower cumulative doses of corticosteroids (3781mg) compared with 8552mg in the non-diabetic group; however, it would have been a more significant comparison had the duration of exposure been looked at concurrently. A recent French study[22] did just that and found that the cumulative doses of corticosteroid were similar between the groups and was not statistically significant. The diabetogenicity of corticosteroid therapy is well known[41,46-48], but not borne out in this study and some more recent studies[22,45].

The mean total cholesterol (treatment naïve) was significantly higher in the diabetic group versus the non-diabetic patients. This is in keeping with findings by Kyu Yeon

Hur et al[45].

With regard to complications, diabetic patients had significantly more infections, 96.77% p = < 0.0001. Diabetic patients were also more frequently hospitalized : 82.26% vs 72.67% of the non-diabetics. Cardiovascular morbidity and mortality statistics, while appearing greater in the diabetic group, did not achieve statistical significance probably owing to small numbers. Proteinuria was significant in the diabetic group 66.1%, p = 0.006, whereas graft rejection and graft loss were not, when compared to the non-diabetic group.

The difference in overall patient survival between the study groups did not achieve statistical significance, however diabetes did confer a hazard ratio of 1.45 which means that once the patient becomes diabetic, there is a 45% increase in risk of death at any given point in the disease. While the survival rates approximated the non-diabetic group, the diabetic patients did die sooner (Fig 6).

Fifty-five of the 62 patients who became diabetic, received cadaveric grafts, p = 0.06. Sumrani[42] and Davidson[18] reported similar findings. The reason may be that the immunosuppressive regimen used in these patients had to be intensified to prevent graft rejection.

The only pre-existing renal condition to have a significant association with the onset of Diabetes, was hypertension at 57%, p = 0.007. Two recent studies supports this finding[22,23]. While there is no clear pathogenetic link between hypertension and diabetes, these patients could be predisposed because of concurrent metabolic syndrome, or

as a result of certain medications eg. thiazide diuretics and β-blockers that were used post-transplant for blood pressure control. Epidemiologically, we know that β-blockers might predispose to diabetes, but a recent study[23] did not find a significant association.

4. CONCLUSION

The incidence of new onset diabetes post-transplantation is as significant in the South African setting as it is worldwide. The first six months after transplantation poses the greatest risk for the development of diabetes, and the risk increases with time post-transplantation. PTDM has a course that resembles Type 2 diabetes 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 gained also portends a greater risk for the development of diabetes, as does active cytomegalovirus infection (CMV).

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 significant percentage of patients who became diabetic, compared with Cyclosporine. Corticosteroid therapy did not appear to impact much on the onset of diabetes and the use of diuretics in combination with calcineurin inhibitors poses a greater risk for the development of diabetes post-transplant.

The onset of diabetes was associated with the receipt of cadaveric grafts and was also more likely if the patient had been hypertensive prior to transplantation.

There were more hospitalizations among the diabetic patients, probably related to 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 was actually lower in the diabetic group. There was no association with increased graft loss or rejection.

The numbers of diabetic patients with cardiovascular morbidity and mortality were not adequate to reach statistical significance , but for those who did succumb, the higher cholesterol levels may have been contributory. Diabetic patients died sooner than the non-diabetic patients and diabetes conferred a worrying hazard ratio for death among these patients.

5. **RECOMMENDATIONS**

There exists very little doubt that the onset of diabetes post transplantation is a sinister, but fortunately preventable and in some cases, reversible condition.

Patients need to be risk stratified prior to transplantation according to: family history of diabetes, body mass index (BMI), the presence of pre-diabetes (impaired fasting glucose or impaired glucose tolerance), age and ethnicity. The immunosuppressive regimen then needs to be tailored to the individual. Patients need to be rigorously monitored for diabetes especially for the first six months post transplant. If a patient becomes diabetic while on tacrolimus, sirolimus may be substituted.

The management of a post transplant patient who has become diabetic has not been studied, however, the guidelines do not that differ from how one would manage a non-transplant diabetic patient in the general population.

As this was a retrospective study from patient records, the data retrieved was not always complete eg. I could not measure BMI. I did not look at the asssociation of diabetes with: hepatitis C infection which is well described; β-blockers and 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. A further limitation is that because it is a retrospective study, the diagnosis of diabetes was not always true especially if based on a single random blood result.

I recommend a prospective study to address these shortfalls and thereby provide a more detailed evaluation of this condition.

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APPENDIX A

THE INTERNATIONAL DOLLAR

The international dollar is a hypothetical unit of currency that has the same purchasing power that the U.S. dollar has in the United States at a given point in time, i.e. it means the U.S. dollar converted at **purchasing power parity (PPP)** exchange rates. It shows how much a local currency unit is worth within the country's borders. It is used to make comparisons both between countries and over time. For example, comparing per capita **gross domestic product (GDP)** of various countries in international dollars, rather than based simply on exchange rates, provides a more valid measure to compare standards of living.

The term, while not in widespread use, is sometimes used by international organizations such as the World Bank and the International Monetary Fund in their published statistics. Figures expressed in international dollars cannot be converted to another country's currency using current market exchange rates; instead they must be converted using the country's PPP exchange rate used in the study.

APPENDIX B

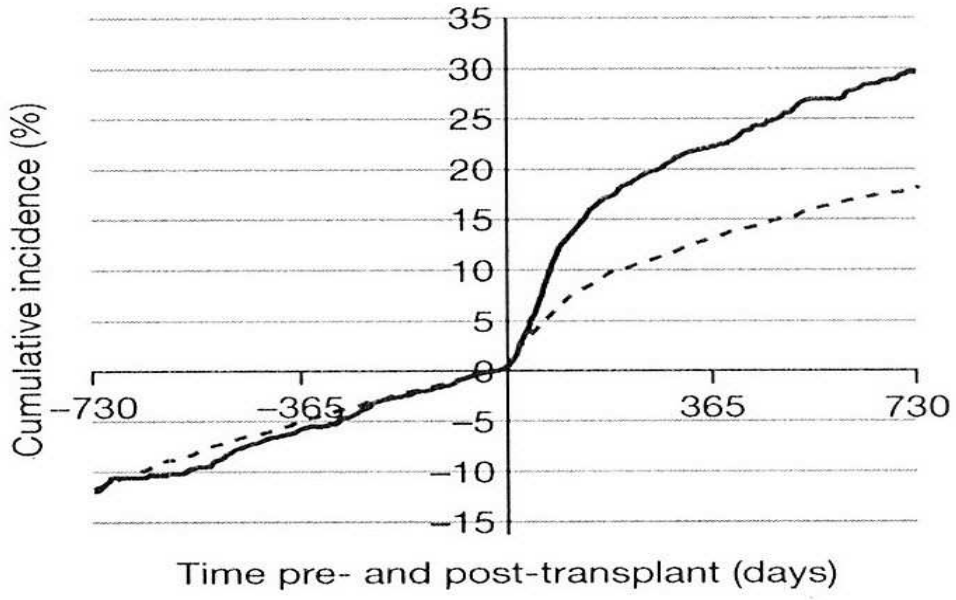


Figure 1— *Incidence of diabetes before and after transplantation in patients receiving tacrolimus (—) or cyclosporine (- - -). At 1 year posttransplant, the incidence of new-onset diabetes was significantly lower in patients receiving cyclosporine than in those receiving tacrolimus (14.1 vs. 22.9%; P < 0.0001). (From Woodward RS, Schnitzler MA, Baty J, et al.: Incidence and cost of new onset diabetes mellitus among U.S. waitlisted and transplanted renal allograft recipients.* Am J Transplant *3:590–598, 2003, with permission from Blackwell Publishing Ltd.)*

APPENDIX C

Table 1—*RR for ischemic heart disease among transplant recipients >1 year after kidney transplantation (8)*

	Men		Women	
Risk factor	Control	Transplant recipient	Control	Transplant recipient
Age (years)	1.05	1.06*	1.40	1.10
Cholesterol (mg/dl)				
<160	0.52	0.00†	0.77	0.00†
160–199	1.00‡	1.00‡	1.00‡	1.00‡
200–239	1.19	2.39	1.23	2.07
240–279	1.66	2.02	1.28	2.44
>280	1.93	2.25	1.71	1.84
Blood pressure (mmHg)				
<120 and <80	1.00	0.25	0.59	0.56
120–129 or 80–84	1.00‡	1.00‡	1.00‡	1.00‡
130–139 or 85–89	1.33	1.05	0.93	1.26
140–159 or 90–99	1.68	1.19	1.30	1.63
≥160 or ≥100	1.86	1.47	1.59	0.31
Diabetes	1.53	2.78*	1.82	5.40*
Smoking	1.69	1.95*	1.34	1.82

A RR of ≥1.00 indicates a higher or lower risk for ischemic heart disease, respectively. Control subjects are from the Framingham Heart Study. *$P < 0.05$ compared with reference risk values for transplant recipients; †too few patients were available to reliably assess this risk; ‡reference risks for cholesterol levels and blood pressure are indicated by 1.00.

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