

NATURAL HISTORY, PROGNOSIS, AND MANAGEMENT OF TRANSPLANTATION-INDUCED DIABETES MELLITUS

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SUMMARY - Cardiovascular morbidity and mortality are increased in transplant recipients, and diabetes mellitus is among the main determinants of this increase. This review focuses on the influence of diabetes on survival and functional outcomes in transplant recipients, the prevalences of post-transplantation hyperglycaemia and diabetes, the mechanisms of diabetes in transplant recipients, the respective roles of immunosuppressive drugs, the predictive factors, and the practical implications. Although available studies show that calcineurin inhibitors have diabetogenic effects and that these are more marked with tacrolimus, emphasis should be put on the major diabetogenic role of corticosteroids. This warrants efforts to develop immunosuppressive regimens that eliminate or reduce the need for corticosteroids.

Key-words: transplantation, diabetes mellitus, immunosuppressive drugs, steroids, anticalcineurin inhibitors.

RÉSUMÉ - Histoire naturelle, pronostic et prise en charge du diabète post-transplantation.

La morbi-mortalité d'origine cardiovasculaire est accrue chez les patients transplantés, et le diabète figure parmi les principaux éléments contributifs de l'augmentation de ce risque. Cette revue rappelle l'influence du diabète sur le pronostic fonctionnel et vital du greffé, précise la prévalence de l'hyperglycémie et du diabète post-greffe, en détaille les mécanismes et les risques en fonction du traitement immunosuppresseur, et s'attache à dégager des facteurs prédictifs de diabète post-greffe et une conduite à tenir pratique. Si les études disponibles documentent un effet diabétogène des anti-calcineurines, avec un désavantage pour le tacrolimus, il faut insister sur l'effet diabétogène majeur des stéroïdes. Cela justifie la recherche de protocoles d'immunosuppression permettant d'éviter les corticostéroïdes ou d'en réduire les doses.

Mots-clés : transplantation, diabète, immunosuppresseurs, corticoïdes, anticalcineurines.

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Cardiovascular morbidity and mortality are increased in transplant recipients, and diabetes mellitus is among the main determinants of this increase. The natural history of post-transplantation diabetes shares many similarities with that of type 2 diabetes. This provides a rationale for using data on the epidemiology and management of type 2 diabetes to develop a practical management strategy for patients with post-transplantation diabetes.

■ WHY DO DIABETES AND HYPERGLYCAEMIA EXERT DELETERIOUS EFFECTS ON THE CARDIOVASCULAR SYSTEM?

The absolute risk of cardiovascular disease varies widely across populations and risk factor combinations. However, the relative risk associated with diabetes shows little variation from one population to another [1]. Studies have shown that diabetes increases the cardiovascular risk two- to three-fold in men and three- to five-fold in women, and that the increase is larger in patients with occlusive arterial disease of the lower limbs (relative risk, 4 to 6) or amputation (relative risk, 10 to 20). Finally, excess cardiovascular and overall mortality occurs not only in patients with diabetes but also in those with non-diabetic hyperglycaemia [2-4]. In practice, in patients with diabetes, interventions targeting other risk factors should seek to achieve more than in other patients: in simple terms, the objectives of primary prevention in diabetic patients should be those of secondary prevention in non-diabetic patients [5].

The pathogenesis of diabetic macroangiopathy is multifactorial. It involves not only a direct pathogenic effect of hyperglycaemia related to protein glycation [6] but also increases oxidative stress, endothelial dysfunction, and a procoagulant state. In addition, many patients with type 2 diabetes have other risk factors related to the metabolic syndrome, including central obesity, arterial hypertension, dyslipidaemia, hyperinsulinaemia, decreased fibrinolysis, and endothelial abnormalities.

All these additional risk factors, including total serum cholesterol, LDL-cholesterol, triglycerides, 1/HDL-cholesterol, systolic blood pressure, and body mass index, are present at higher levels in patients with type 2 diabetes than in the population at large, with no significant differences between men and women [7]. This combination of diabetes, atherogenic dyslipidaemia, and hypertension is also found in patients with corticosteroid-induced diabetes.

Non-diabetic hyperglycaemia seems to be another marker for cardiovascular risk and perhaps for the risk of all-cause mortality [8]. Diabetes is preceded by a long silent period characterised by glucose intolerance or non-diabetic hyperglycaemia. This period increases

the duration of exposure to the deleterious effects of the various risk factors seen in metabolic syndrome or syndrome X [9].

■ REVIEW OF IMMUNOSUPPRESSIVE STRATEGIES IN TRANSPLANTATION [10]

All currently available immunosuppressants (*Table I*) act on the same target, namely the T lymphocyte. They inhibit the activation of and cytokine secretion by T cells and/or the clonal expansion of T cells (*Fig. 1*). Conventional immunosuppressive strategies consist of induction therapy followed by maintenance therapy to prevent allograft rejection, with shorter courses of more aggressive treatment for episodes of acute rejection [10].

The treatment of acute rejection relies on antilymphocyte antibodies and high-dose corticosteroids. Consequently, a corticosteroid-sparing effect occurs with recently introduced agents that serve for maintenance therapy and decrease the incidence of acute rejection episodes. These agents include antibodies to the interleukin-2 (IL-2) receptor, mycophenolate mofetil, and sirolimus.

The initial treatment usually consists simply in higher dosages of the maintenance immunosuppressants. However, induction of immunosuppression has relied increasingly on potent anti-T-cell antibodies, particularly since the introduction of humanised antibodies to the T-cell IL-2 receptor. To date, the two preparations currently on the market, daclizumab and basiliximab, have an excellent track record for safety. When added to a conventional dual or triple drug regimen

(cyclosporine + corticosteroids ± azathioprine), these agents have proved capable of reducing the number of acute rejection episodes by 35% in renal transplant recipients.

Optimal maintenance immunosuppressive therapy requires use of several immunosuppressants in combination (*Table II*). The goal of this strategy is to minimise the adverse effects of each drug taken alone by multiplying the sites of impact on the T-cell. In most cases, the combination comprises a corticosteroid, a calcineurin inhibitor (cyclosporine or tacrolimus), and an antiproliferative agent such as azathioprine or mycophenolate mofetil.

Calcineurin inhibitors remain the cornerstone of most immunosuppressive regimens used in transplant recipients. These agents block IL-2 gene transcription and, therefore, IL-2 production by the T cell. The introduction of cyclosporine was a major advance in immunosuppressive therapy, as shown by the 10% increase in 1-year survival of cadaveric renal allogeneic grafts. However, cyclosporine is associated with several major side effects including nephrotoxicity,

TABLE I. Medications used as maintenance immunosuppressive therapy.

Medications	Mechanisms of action	Main side effects
Calcineurin inhibitors Cyclosporine Tacrolimus (FK506)	Inhibits IL-2 production	Nephrotoxicity Alters glucose metabolism Arterial hypertension Dyslipidaemia
Antiproliferative agents Azathioprine Mycophenolate mofetil	Inhibits purine synthesis Selectively inhibits <i>de novo</i> purine synthesis by lymphocytes	Bone marrow aplasia Gastrointestinal/Diarrhoea
Sirolimus or RAD	Inhibit cell cycle progression induced by IL-2	Dyslipidaemia Thrombocytopenia
Corticosteroids	Hinders cytokine gene transcription	Alters glucose metabolism Arterial hypertension Dyslipidaemia Osteoporosis

hypertension, dyslipidaemia, an increased risk of malignancy, and glucose metabolism abnormalities. These effects contribute to increase the cardiovascular risk. The side effects of cyclosporine are dose-dependent.

Tacrolimus (or FK506) is a more recently introduced calcineurin inhibitor. Its side effects are similar to those of cyclosporine, with perhaps an increased

risk of diabetes, but with lower incidences of arterial hypertension and dyslipidaemia.

Antiproliferative agents prevent the expansion of T-cell and B-cell clones activated by the transplantation. Azathioprine, a purine analogue that inhibits DNA synthesis, is the oldest member of this class. It has been superseded by mycophenolate mofetil (MMF), a selective inhibitor of *de novo* purine syn-

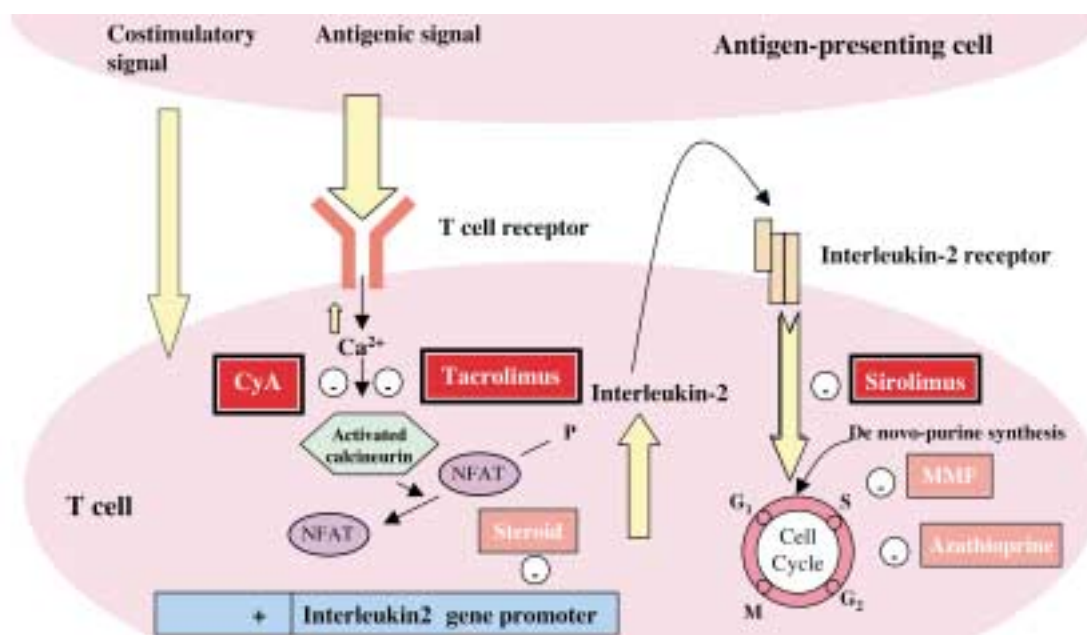


FIG. 1. Stages of T cell activation: multiple targets for immunosuppressive agents.

TABLE II. Examples of immunosuppressive regimens used for maintenance treatment.

Regimens	Comments
Conventional	
Cyclosporine + azathioprine or MMF + corticosteroids	MMF reduces the incidence of acute rejection episodes
Tacrolimus + azathioprine + corticosteroids	Alternative to the above-described protocol
Novel	
Antibodies to the IL-2 receptor + MMF + corticosteroids	Antibodies to the IL-2 receptor are used only during the immediate post-transplantation period but can obviate the need for calcineurin inhibitor therapy
Tacrolimus + MMF + corticosteroids	Low incidence of acute rejection episodes. Corticosteroids used in lower dosages
Sirolimus or RAD ± cyclosporine or tacrolimus ± corticosteroids	With sirolimus or RAD, calcineurin inhibitors and corticosteroids can be given in reduced dosages or even discontinued

MMF: mycophenolate mofetil

thesis by lymphocytes, which ensures more selective and more potent inhibition of B and T cells. Sirolimus (rapamycin) and its derivative RAD are the most recent members of this family. They impair T-cell responses to IL-2 by inhibiting the second messengers downstream from the binding of IL-2 to its receptor, thus hindering progression of T cells to the S phase of the cell cycle. With sirolimus or RAD, corticosteroids are unnecessary or can be stopped early, and the calcineurin inhibitor can be used in lower dosages. These agents do not induce diabetes, although sirolimus and RAD often induce or worsen dyslipidaemia.

Corticosteroids are non-specific antiinflammatory agents. They inhibit cytokine production by T cells and macrophages, thus blocking T-cell activation and the non-specific deleterious effects of macrophages on tissues. The side effects of corticosteroids are both numerous and well documented. They include arterial hypertension, dyslipidaemia, and alterations in glucose metabolism, which also occur with calcineurin inhibitors. Given that cardiovascular disorders are the leading cause of death among transplant recipients, one of the current objectives is to develop immunosuppressant regimens that reduce the risks of acute and chronic rejection as effectively as do conventional regimens but that allow elimination or early discontinuation of corticosteroids and use of lower calcineurin inhibitor dosages (Table II). In the more distant future, the ultimate goal is to inhibit only those T cells that are specific for the donor antigens, thus inducing specific donor-tolerance without having to give prolonged immunosuppressive therapy.

■ HOW DOES DIABETES AFFECT SURVIVAL AND FUNCTIONAL OUTCOMES IN TRANSPLANT RECIPIENTS?

Mortality

Several studies have established that diabetes diagnosed prior to or shortly after transplantation significantly increases the mortality rate, chiefly by increasing the number of deaths caused by cardiovascular disease or infection [11-12].

In allogeneic renal transplant recipients, the excess mortality in patients with diabetes diagnosed prior to transplantation is not surprising since transplantation occurs after a long disease duration, at a time when advanced vascular complications are present. An important issue is whether a possible increase in deleterious metabolic effects related to the immunosuppressive therapy can precipitate the occurrence of cardiovascular events. A US study compared mortality rates in 15,188 diabetic patients awaiting renal transplantation and in 7,262 diabetic renal transplant recipients [13]. The results clearly established the benefits associated with renal transplantation in terms of mortality: between 1991 and 1997, mortality was 10.8% patient-years among patients awaiting transplantation and 5.6% patient-years among transplant recipients [13]. Another key issue in diabetic patients who have not yet received a transplant is the development of strategies for detecting atheroma of the coronary and lower limb arteries, which long remains silent in diabetic patients. In a prospective study of

105 diabetic patients awaiting renal transplantation, evidence of clinically silent coronary artery disease was found in 36% of patients by selective coronary angiography, that was not detected clinically nor by electrocardiography in half of the patients [14]. Similarly, distal blood pressure measurements in 129 patients awaiting renal transplantation showed lower limb occlusive arterial disease in 32% of diabetic and 16% of non-diabetic patients [15]. Classically, latent lower limb ischemia causes clinical symptoms in the leg on the same side as the renal transplant.

A five-year retrospective study of patients in whom diabetes was diagnosed after renal transplantation showed that patient and graft survival rates were 87% and 70%, respectively, as compared to 93% and 90% in non-diabetic controls with a similar incidence of rejection and similar dosages of corticosteroids and cyclosporine [16]. In another retrospective study, the mortality rate was increased 2.5-fold among patients younger than 55 years who had post-transplantation diabetes as compared to non-diabetic controls [17].

In allogeneic liver transplant recipients, the incidence of acute rejection and the mortality rate within the first two years are significantly higher in patients with post-transplantation diabetes [18, 19]. However, whether post-transplantation diabetes is causally related to early mortality remains unclear given that rejection episodes are treated by corticosteroid boluses, which contribute substantially to the occurrence of post-transplantation diabetes.

Morbidity

Diabetes is among the main risk factors for coronary heart disease, cerebrovascular disease, and peripheral occlusive arterial disease in renal transplant recipients [20].

Several studies in patients with diabetes prior to transplantation found a 20% risk of amputation within the first five years after transplantation [21].

In patients with post-transplantation diabetes, development of coronary heart disease has been reported in nearly 10% of patients within 29 months of renal transplantation [22]. A prospective single-centre study evaluated the impact of post-transplantation diabetes on survival and functional outcomes in 40 renal graft recipients given Sandimmun® (cyclosporine) and in a group of non-diabetic controls. Although 12-year survival was similar in these two groups (71% and 74%), the rate of infection-related mortality was higher in the diabetic group (46% vs 12%). Furthermore, graft survival was significantly decreased in the diabetic group (48% vs 70%), as was five-year renal function, and diabetes was an independent predictor of graft loss together with age, sex, and ethnicity. Finally, morbidity related to post-transplantation diabetes was similar to that in the overall population of diabetic patients, with both acute metabolic complications (ke-

toacidosis and hyperosmolality) and chronic complications (neuropathy) [23].

It has been established clearly that diabetic nephropathy can affect allogeneic renal transplants, therapy modifying the prognosis of transplantation [24], and that improving metabolic control, for instance by allogeneic pancreatic transplantation, is associated with long-term improvements in the functional and structural characteristics of renal transplants and of native kidneys [25].

■ WHAT ARE THE PREVALENCES OF POST-TRANSPLANTATION HYPERGLYCAEMIA AND DIABETES?

Data in the literature are difficult to analyse, for several reasons.

- The definition of diabetes varies widely across studies, with criteria ranging from arbitrarily selected and unreliable serum glucose thresholds to a need for insulin therapy;

- The definition of diabetes approved by the WHO in 1997 requires a fasting glucose level greater than 1.26 g/L and/or a serum glucose level two hours after the beginning of a meal or an oral glucose load greater than 2 g/L. Fasting serum glucose levels lower than 1.10 g/L and 2-h serum glucose levels lower than 1.40 g/L are considered normal. Intermediate values indicate glucose intolerance or non-diabetic hyperglycaemia. In contrast, before 1997, diabetes was defined as a fasting serum glucose level greater than 1.40 g/L;

- The serum glucose level used to define diabetes was selected based on the risk of microangiopathy, particularly retinopathy. However, as mentioned above, the main risk in transplant recipients is related to macroangiopathy, and both glucose intolerance and non-diabetic hyperglycaemia are associated with excess overall and cardiovascular mortality;

- The prevalence of post-transplantation diabetes varies over time because the higher steroid doses used during the first year are associated with an increased risk of diabetes, a disease that can resolve subsequently;

- Finally, immunosuppressive regimens with lower corticosteroid dosages or no corticosteroids at all have been used increasingly in recent years (*Table II*). This trend can be expected to affect the prevalence of post-transplantation diabetes. Conversely, the current increase in the prevalence of diabetes overall and in haemodialysis patients, together with improvements in the management of coronary heart disease, may contribute to increase the number of diabetic patients who are candidates for renal or cardiac transplantation.

Keeping these caveats in mind, the data published before the revision of diagnostic criteria for diabetes indicate that 16%, 18%, and 27% of patients become diabetic within one year after receiving a heart, kid-

ney, or liver transplant, respectively [26-28]. In addition, about 10% of kidney or liver transplant recipients are diabetic before the transplantation, indicating that about 20% to 30% of transplant recipients have diabetes. Finally, glucose intolerance as defined before 1997 has been reported in 31% of renal transplant recipients, suggesting that about 50% of these patients may have atherogenic hyperglycaemia [26].

■ WHAT IS THE MECHANISM UNDERLYING POST-TRANSPLANTATION HYPERGLYCAEMIA AND DIABETES?

A classic but simplistic statement is that the rate of occurrence of post-transplantation diabetes fell from 20% to 10% when corticosteroid- and azathioprine-based immunosuppressive regimens were replaced by cyclosporine-based regimens with lower dosages of corticosteroids. Studies have shown that eliminating or reducing the use of corticosteroids is associated with a decrease in the rate of occurrence of diabetes in patients with transplants of any type [24, 28, 29]. For instance, a prospective, randomised, single-centre study evaluated the impact of early corticosteroid discontinuation, on day 14, in allogeneic liver transplant recipients taking MMF + tacrolimus or MMF + Neoral® (cyclosporine). Outcomes were evaluated after six months. None of the patients on Neoral® and only one of the patients on tacrolimus became diabetic; (interestingly, glucose metabolism returned to normal in four of the eight Neoral® patients who had diabetes prior to the liver transplantation) [30].

These data support a major role for corticosteroid therapy in the occurrence of post-transplantation diabetes. The hyperglycaemic effect of corticosteroids is primarily related to induction of insulin resistance, which manifests as an increase in glucose production by the liver with a decrease in glucose uptake by the peripheral tissues, i.e., muscle and fat, which are the targets of insulin effects. In addition to this diabetogenic effect, corticosteroids induce blood pressure and serum lipid changes that contribute to increase the cardiovascular risk and explain why post-transplantation diabetes is similar to type 2 diabetes.

A less prominent target of corticosteroids is the insulin-secreting β cell. This cell is the main target involved in the diabetogenic effect of calcineurin inhibitors, which reversibly decrease the synthesis and secretion of insulin. Morphologic and structural studies of β -cell islets in allogeneic pancreas transplant recipients have shown various β -cell abnormalities (oedema and vacuolisation of the cytoplasm) [31]. Although these abnormalities were more severe with tacrolimus, the difference with cyclosporine was not statistically significant [31]. In this study, the intensity of anatomic abnormalities was dependent on the re-

sidual calcineurin inhibitor concentration, whereas hyperglycaemia was also dependent on the corticosteroid dosage. Finally, examination of serial biopsies in this study established that the histological lesions can resolve after discontinuation of the calcineurin inhibitor (tacrolimus in this study).

In practice, the concomitant use of corticosteroids in most immunosuppressive regimens and the persistence of diabetogenic effects long after corticosteroid discontinuation complicate the interpretation of diabetogenic effects in patients taking tacrolimus or cyclosporine. Numerous controlled studies support the conclusion that abnormalities in glucose metabolism and, above all, in lipid metabolism seen with either of these calcineurin inhibitors depend in large part on the concomitant corticosteroid therapy and diminish markedly when the corticosteroids are discontinued [32-34]. For instance, in a randomised study of switching from cyclosporine-prednisone to cyclosporine azathioprine six months after renal transplantation, improvements occurred in both blood pressure and serum lipid concentrations [35]. A prospective randomised study conducted in The Netherlands to evaluate corticosteroid discontinuation one year after renal transplantation in 84 patients followed up for 14 months showed improvements in glucose metabolism and diabetes in the patients taken off corticosteroids [33]. However, acute rejection precluded corticosteroid discontinuation in 26% of patients. Furthermore, other studies suggest that longer-term beneficial effects on diabetes may be less compelling and that there may be a risk of chronic rejection.

In sum, the marked improvement in diabetes seen after corticosteroid discontinuation is a major argument in favour of a central role for corticosteroid therapy in the development of post-transplantation diabetes. Recent progress in islet transplantation achieved with an immunosuppressive regimen that is free of corticosteroids also supports this conclusion [36].

■ WHAT IS THE RISK OF DIABETES WITH EACH OF THE AVAILABLE CALCINEURIN INHIBITORS?

Several studies sought to compare the diabetogenic potentials of cyclosporine and tacrolimus. They were hampered by a number of obstacles:

– Several studies of tacrolimus (FK506) initially used dosages above the therapeutic range. Thus, a study demonstrating an increase in the incidence of post-transplantation diabetes since the introduction of tacrolimus used dosages above the currently recommended range [37];

– The reports of several comparative studies fail to specify which cyclosporine formulation was used (Sandimmun® or Neoral®); the pharmacokinetic pro-

file of Neoral® is associated with less variability of cyclosporine blood levels;

- The concomitant corticosteroid therapy given as part of the immunosuppressive protocols complicates the interpretation of diabetogenic effects seen in patients taking cyclosporine or tacrolimus;

- Similarly, it has been speculated that, despite a greater diabetogenic effect, tacrolimus may ultimately exert beneficial effects in terms of diabetes by reducing the risk of acute rejection, thereby diminishing the patient's exposure to corticosteroids. This hypothesis remains to be proven. On the other hand, higher serum lipid levels have been reported with cyclosporine as compared to tacrolimus, but the corticosteroid dosages were higher in the cyclosporine groups;

- The genetic background of the study population probably has a key influence on the risk of diabetes related to use of a calcineurin inhibitor. This risk is higher in African-Americans and in Hispanic Americans, two groups in which the prevalence of type 2 diabetes is high under "basal" conditions.

A meta-analysis of four studies in 1037 allogeneic renal transplant recipients found that the prevalence of post-transplantation diabetes was significantly higher with tacrolimus than with cyclosporine (odds ratio, 5.03; CI, 2.04-12.36) [38]. However, a more recent study showed no significant difference in the incidence of diabetes between the group given tacrolimus + MMF and the group given Neoral® + MMF [39]. In a prospective randomised study in 120 patients, the incidence of hyperglycaemia requiring insulin therapy was 25.4% with tacrolimus and 5.0% with Sandimmun® [40]. A prospective randomised study conducted in the US to compare tacrolimus and cyclosporine in 412 patients found that one-year patient and graft survival rates were similar but that the incidence of post-transplantation diabetes was higher with tacrolimus, both in African-Americans (36.6% vs 8.3%) and in Caucasians (12.2% vs 1.1%) [41]. In the overall population, the five-year risk of diabetes was five times higher in the tacrolimus group (19.9%) than in the Sandimmun® group (4%) [42]. A similar European study in 448 patients showed that the prevalence of hyperglycaemia after one year was 16.2% with tacrolimus and 6.9% with cyclosporine and that the incidence of newly diagnosed diabetes was 8.3% and 2.2% in these two groups, respectively [43].

A prospective randomised study of 530 allogeneic liver transplant recipients followed up for five years showed no significant differences between tacrolimus and Sandimmun® in terms of patient or graft survival, morbidity, toxicity, or diabetes incidence, although there were non-significant trends towards higher rates of hyperglycaemia and of insulin use with tacrolimus [44]. A similar European study in 101 patients found no differences in glucose metabolism abnormalities between tacrolimus and Sandimmun® after two years

[45]. In a prospective randomised single-centre study in 63 liver transplant recipients, the incidence of hyperglycaemia was similar in the group given tacrolimus and low-dose corticosteroids and in the group given Sandimmun® and high-dose corticosteroids [46]. Finally, another study collected more detailed metabolic data, including oral glucose tolerance tests (OGTTs) conducted eight months after transplantation and at least six weeks after corticosteroid discontinuation [47]. This study included only 20 liver transplant recipients, who were assigned at random to Sandimmun® or tacrolimus. Serum glucose levels were higher in both groups than in healthy controls, particularly two hours after the oral glucose load, and serum insulin levels were also higher. Glucose intolerance was present in 40% of patients in both groups and patent diabetes in 30% of the tacrolimus patients. However, although the corticosteroids were discontinued, it is unclear whether the patients were free of the residual diabetogenic effects of these drugs at the time of testing.

■ IS POST-TRANSPLANTATION DIABETES REVERSIBLE AFTER THE PATIENT IS SWITCHED TO THE OTHER CALCINEURIN INHIBITOR?

The corollary issue is whether post-transplantation diabetes resolves when the patient is switched to the other calcineurin inhibitor. In a recent study in 70 liver transplant recipients, 15 patients were switched from tacrolimus to Neoral® because of newly diagnosed diabetes. In these patients, reducing the tacrolimus dosage was not associated with a significant improvement in the diabetes; conversely, switching to Neoral® was consistently followed by resolution of the diabetes [48]. An interesting case-report describes hyperacute development of diabetes in a liver transplant patient given tacrolimus, followed by complete resolution of the diabetes after switching to Sandimmun® [49]; however, the determinants of diabetes in this patient probably differed markedly from those seen in the usual pattern of post-transplantation diabetes. Other anecdotal reports in kidney or liver transplant recipients are equivocal, with a suggestion in some cases that diabetes and the other adverse effects of calcineurin inhibitors may be dose-dependent and in large part reversible after dosage reduction. Nevertheless, there are few clinical, anatomic, and molecular data in favour of switching from one calcineurin inhibitor to the other, and it is unfortunate that no controlled studies are available.

■ Can diabetes be predicted? (Table III)

An ability to predict the risk of post-transplantation diabetes would be of considerable assistance in select-

ing the immunosuppressive regimen. However, the predictive value of currently available markers is limited.

Anecdotal reports of acute ketotic diabetes during the immediate post-transplantation period in patients found subsequently to carry susceptibility genes for type 1 diabetes have been published. In first-degree relatives of patients with type 1 diabetes, the presence of autoantibodies against pancreas islet antigens (islet-cell antibodies [ICAs], anti-GAD antibodies, anti-IA-2 antibodies, and anti-insulin antibodies) strongly predicts the development of diabetes, and the risk is even higher in individuals who carry HLA haplotypes conferring susceptibility to diabetes. In the general population, the predictive value of these immunological and genetic markers is less well documented; nevertheless, testing for anti-GAD and anti-IA-2 antibodies can easily be included in the pretransplantation workup and deserves to be evaluated, particularly in patients with a personal or family history of autoimmunity.

No genetic markers for type 2 diabetes have been validated. Functional tests for insulin sensitivity and insulin-secreting capacity have been described and are undergoing evaluation. It might be of interest to investigate whether these tests are useful for predicting post-transplantation diabetes. At present, prediction should probably rely on the following: family history of diabetes; overweight (body mass index $> 25 \text{ kg/m}^2$) with preferential distribution of the fat to the abdominal area; abnormal glucose regulation prior to transplantation, defined as a fasting serum glucose level between 1.10 and 1.26 g/L and/or a postprandial serum glucose level between 1.40 and 2.00 g/L; and presence of other components of metabolic syndrome (hypertriglyceridaemia, hypo-HDLaemia, hypertension, hyperuricaemia), although the failure of the organ to be replaced can complicate the evaluation of their role. In addition, in a recent study, patient age and corticosteroid dosage were the main risk factors for hyperglycaemia, with a 5% risk increase for each 0.01 mg/kg/d increase in the prednisolone dosage [26]. A retrospective US study showed that age, ethnicity (black or Hispanic), and cadaveric kidney as compared to living related donor kidney predicted the

risk of diabetes [16], suggesting that acute rejection episodes may play a pivotal role in the development of diabetes. Another retrospective study investigated 325 renal graft recipients, of whom only 33 developed diabetes [50]. A family history of diabetes, body mass index, ethnicity, HLA status, cyclosporine dosage, and corticosteroid dosage failed to predict the occurrence of post-transplant diabetes, whereas bolus corticosteroid therapy apparently played a critical role [50]. The predictive value of an OGTT done prior to transplantation was investigated in a prospective single-centre study in 18 patients who were subsequently given tacrolimus and corticosteroids. Among the nine patients with normal OGTT results, two required insulin during the post-transplantation period, but only briefly. Insulin-requiring diabetes developed in two of the eight patients with glucose intolerance, and the patient with diabetes prior to transplantation continued to require insulin after transplantation [51]. Finally, a study in allogeneic liver transplant recipients suggests a higher risk of post-transplantation diabetes among patients whose liver failure was related to hepatitis C [46].

■ HOW SHOULD DIABETES BE MANAGED IN TRANSPLANT RECIPIENTS?

As with type 2 diabetes, post-transplantation diabetes is usually asymptomatic and detected by routine tests, although acute metabolic forms with ketoacidosis or hyperosmolarity are not exceedingly rare. However, the management of post-transplantation diabetes includes the therapeutic and preventive steps taken in patients with type 2 diabetes.

Prevention and screening

Evaluation of the various risk markers described above (*Table III*) should, if possible, lead to individual tailoring of the immunosuppressive regimen with, in particular, corticosteroid tapering or discontinuation as early as possible and a reduction in the calcineurin inhibitor dosage. Whenever possible, the patient

TABLE III. Predictors of post-transplantation diabetes.

Family history of diabetes	Ethnicity
Age > 45 years	Cadaver kidney/living donor (kidney)
Central obesity	Specific HLA groups
Glucose intolerance prior to transplantation	Metabolic syndrome (Tg, HDL, hypertension)
Corticosteroid dosage	Hepatitis C (liver transplantation)

should follow an appropriate diet and engage in a higher level of physical activity, the goals being to trim off excess weight and abdominal fat and to improve sensitivity to insulin.

Screening for glucose regulation disorders requires determination of fasting serum glucose levels once a month during the first year and at least once every three months thereafter. However, this test is not sufficient: because glucose levels in patients with steroid-induced diabetes are usually highest between 10 am and 10 pm and fasting serum glucose levels are frequently near normal, the glucose level must be determined two hours after the midday meal. Life-style and dietary interventions should be initiated if the serum glucose level is greater than 1.10 g/L in the fasting state or 1.40 g/L after a meal. None of the available antidiabetic medications have been validated or approved for use during this phase of glucose intolerance, and their use should not be considered until the glucose level exceeds 1.26 g/L in the fasting state or 2 g/L after a meal. Glycosylated haemoglobin A_{1c} (HbA_{1c}) is not yet recommended for screening purposes, although several studies have found that a level greater than 6.1% with a reference method is diagnostic of diabetes.

Treatment

In addition to the primary and secondary goals of reducing the corticosteroid and calcineurin inhibitor dosages, respectively, treatment aimed at improving sensitivity to endogenous insulin should be considered. In two recent studies, it was found almost fortuitously that two agents significantly reduced the incidence of newly diagnosed diabetes: pravastatin in the WOSCOP study [51] and ramipril in the HOPA study [52]. The pharmaceutical companies that market these drugs have not made use of these findings. More specifically, the only insulin-responsiveness enhancing agent approved in France is metformine. Because there is a risk of toxicity in patients with overt renal failure (glomerular filtration rate < 40 ml/min) or liver failure, use of metformine, although not contraindicated, is not reasonable within the first year after transplantation. Metformine therapy is legitimate beyond this period. The thiazolidinediones are a new family of insulin responsiveness-enhancers of which two members, pioglitazone and rosiglitazone, will soon be introduced on the French market. Their role after transplantation remains to be determined. Insulin release-enhancers (sulphonylureas and glinides) are used as second-line therapy in patients with diabetes, with the same caveats regarding renal and hepatic failure, given that the marked binding of these agents to plasma proteins requires closely spaced determinations of blood immunosuppressant levels. If use of oral hypoglycaemic agents is unsafe, or if blood glucose levels do not fall below 1.20 g/L before meals and 1.60 g/L after meals with an HbA_{1c} level lower

than 6.5%, insulin should be given. In this situation, the treatment regimen is often specific of corticosteroid-induced diabetes and different from the usual regimen, with a noticeably higher dose in the morning and at noon than in the evening. Efforts to enhance patient autonomy and prescription of a self-monitoring program with the usual precautions to avoid transmission of hepatitis remain indispensable.

CONCLUSION

The many epidemiological and interventional studies conducted in the 1990s have established that glucose, lipid, and blood pressure abnormalities are not only highly significant markers of cardiovascular risk but also pathogenic factors that are legitimate targets for intervention. Although available studies show that calcineurin inhibitors have diabetogenic effects and that these are more marked with tacrolimus, emphasis should be put on the major diabetogenic role of corticosteroids. This predictable metabolic catastrophe and its well-documented impact on survival and functional outcomes warrant efforts to develop immunosuppressive regimens that eliminate or reduce the need for corticosteroids without jeopardising graft function. Until methods for inducing specific graft tolerance become available, immunosuppressive regimens should be tailored to the individual patient on the basis of predictive criteria, which need to be improved.

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