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Clinical Transplantation

Review Article

Guidelines for the treatment and management of new-onset diabetes after transplantation[1]

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Abstract: Although graft and patient survival after solid organ transplantation have improved markedly in recent years, transplant recipients continue to experience an increased prevalence of cardiovascular disease (CVD) compared with the general population. A number of factors are known to impact on the increased risk of CVD in this population, including hypertension, dyslipidemia and diabetes mellitus. Of these factors, new-onset diabetes after transplantation has been identified as one of the most important, being associated with reduced graft function and patient survival, and increased risk of graft loss. In 2003, International Consensus Guidelines on New-onset Diabetes after Transplantation were published, which aimed to establish a precise definition and diagnosis of the condition and recommend management strategies to reduce its occurrence and impact. These updated 2004 guidelines, developed in consultation with the International Diabetes Federation (IDF), extend the recommendations of the previous guidelines and encompass new-onset diabetes after kidney, liver and heart transplantation. It is hoped that adoption of these management approaches pre- and post-transplant will reduce individuals' risk of developing new-onset diabetes after transplantation as well as ameliorating the long-term impact of this serious complication.

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[1]These guidelines, formally endorsed by the International Diabetes Federation (IDF), have been produced in association with Prof. Philip Home on behalf of the IDF, Prof. Paul Keown from the International Transplant Society and Prof. Eberhard Standl from the European Association for the Study of Diabetes. The objective of these guidelines is to ameliorate cardiovascular risk for patients undergoing transplantation through the recognition and control of new-onset diabetes following transplantation. They have been produced following a consensus meeting held in Budapest, on 15 December 2003. This initiative has been supported by an unrestricted educational grant from Novartis Pharma AG, Basel, Switzerland.

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Key words: calcineurin inhibitors – cyclosporine – dyslipidemia – hyperglycemia – immunosuppression – impaired glucose tolerance – new-onset diabetes – tacrolimus – transplantation

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New-onset diabetes and impaired glucose tolerance (IGT) have been recognized as complications of solid organ transplantation for many years, though the seriousness of these conditions has only recently been understood. It has now become apparent that the development of diabetes after transplantation has serious consequences for the patient, being associated with reduced graft function and patient survival, and increased risk of graft loss (1). Furthermore, development of the condition is a major determinant of the increased cardiovascular morbidity and mortality seen in transplant recipients (2).

Studies suggest that a number of risk factors exist that may predict the development of new-onset diabetes after transplantation in susceptible patients. In particular, the increased risk of diabetes in transplant recipients may be largely due to the immunosuppressive agents administered to such people. However, the diabetogenicity of these agents varies greatly and thus the choice of immunosuppressive therapy can influence people's risk of developing new-onset diabetes considerably. Early detection and appropriate treatment of transplant recipients who have developed diabetes can also reduce the long-term consequences of the condition.

Until recently, precise guidance on the diagnosis, management and treatment of transplant recipients at risk of developing diabetes was lacking. However, in 2003, International Consensus Guidelines on New-onset Diabetes after Transplantation were published (3). The guidelines aimed to reduce the incidence and impact of new-onset diabetes after transplantation by providing appropriate management strategies for transplant recipients. However, the 2003 guidelines primarily focused on kidney transplant patients, as the majority of the studies were conducted in this population; development of the condition in liver and heart transplant patients was not considered in depth. Consequently, the 2004 guidelines detailed here seek to extend the recommendations and management options for reducing the risk of new-onset diabetes after transplantation, covering recipients of kidney, liver and heart transplants. [An extensive review of the incidence and impact of new-onset diabetes after kidney, liver and heart transplantation will be available on the International Diabetes Federation (IDF) website: http://www.idf.org.] The new guidelines represent recommendations of an International Expert Panel Meeting convened by the IDF. The panel consisted of experts from both the transplant (kidney, liver and heart specialists) and diabetes fields. Representatives from the European Association for the Study of Diabetes (EASD) and International Transplant Society (ITS) were also in attendance. The current guidelines are designed for use by transplant physicians, diabetologists, primary care physicians and other referring physicians, and related healthcare workers.

Definition and diagnosis of new-onset diabetes after transplantation

It is recommended that the definition and diagnosis of new-onset diabetes after transplantation should be based on the definition of diabetes mellitus and IGT described by the World Health Organization (WHO) (4). The diabetes guidelines take into account the fact that impaired fasting glucose (IFG) and IGT are associated with an increased risk for diabetes and cardiovascular disease (CVD). Patients with a fasting plasma glucose (FPG) value of 7.0 mmol/L (126 mg/dL) or above are defined as having diabetes, those with values between 6.1 and 6.9 mmol/L (110 and 125 mg/dL) are defined as having IFG, and those with values below 7.0 mmol/L (126 mg/dL) are defined as having IGT. When the oral glucose tolerance test (OGTT)

is used, a 2-h plasma glucose of between 7.8 and 11.1 mmol/L (140 and 199 mg/dL) is diagnostic of IGT. In each case, in the absence of unequivocal hyperglycemia with acute metabolic decompensation, the criteria should be confirmed by repeat testing on a different day (4).

Pre-transplant management

Pre-transplant baseline evaluation

Screening. A number of risk factors have been identified that appear to predispose patients to the development of diabetes post-transplant, including a family history of diabetes, pre-transplant glucose intolerance and obesity (1, 5–7). Consideration of these factors pre-transplantation may be used to tailor immunosuppressive therapy and reduce individual risk of developing diabetes.

A complete medical and family history, including documentation of glucose history, should be taken from all patients at the pre-transplant consultation and FPG levels tested at regular intervals. Patients with normal FPG levels (<6.1 mmol/L; 110 mg/dL) should then receive an OGTT at both 0 and 2 h post-challenge. Use of this test is recommended for screening purposes as it is more predictive of increased risk of CVD and mortality than FPG testing, particularly in people with IGT (8). Patients identified with IGT prior to transplantation should be particularly closely monitored post-transplant for the development of new-onset diabetes. However, in liver transplant patients, monitoring should take into account the fact that elevated OGTT levels pre-transplant may be due to cirrhosis, and that such patients may become normoglycemic post-transplant. Elevated OGTT levels may also have little predictive value in potential liver transplant patients with uremia, as the condition can cause insulin resistance and IGT; high values should thus be interpreted with caution. It should also be noted that the wait list for potential transplant recipients may be several years and the optimal timing for screening by FPG or OGTT has not been established.

Patients should also be screened for other features of the metabolic syndrome, e.g. blood pressure, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol levels and other CV risk factors (e.g. smoking), as such people have an increased risk of developing diabetes and CVD (4).

Counseling. Patients should receive counseling on weight control, diet and exercise. This is particularly important for those with IGT and abnormal glucose tolerance; such individuals should be referred to a dietician for nutritional advice.

Individualization of immunosuppressive therapy

As there is good evidence that immunosuppressant therapies vary in their diabetogenicity, selection of an appropriate immunosuppressive regimen should take into account people's diabetes risk profile and the relative diabetogenicity and risk for diabetes of each immunosuppressant, balancing minimal diabetes risk with effective immunosuppression. Corticosteroids are associated with the highest risk of new-onset diabetes after transplantation (6, 7, 9). The calcineurin inhibitors (CNIs) cyclosporine and tacrolimus also have diabetogenic effects, though the balance of evidence across all organs suggests that tacrolimus has greater diabetogenicity, particularly in pediatric transplant recipients and those of African descent (1, 10–13). Use of tacrolimus also appears to incur greater healthcare costs than cyclosporine for every patient developing new-onset diabetes after transplantation ($2205 vs. $1137 at 1 yr, respectively, and $3308 vs. $1612 at 2 yr) (10).

To reduce diabetogenic risk, management should plan to reduce the dose of corticosteroids as early as possible post-transplant and a reduction in CNI dosage should also be considered, particularly for high-risk individuals. When choosing an immunosuppressive regimen, the risk of developing diabetes after transplantation should be weighed against the risk of acute rejection for each individual patient. Steroid-sparing regimens, e.g. induction antibody adjunct treatment, should be considered to allow rapid corticosteroid withdrawal or avoidance.

Post-transplant management

Ongoing monitoring of the transplant patient

Blood glucose. All individuals, regardless of diabetic status, should receive regular FPG testing post-transplant to screen for abnormal glucose regulation (Fig. 1). During the first 4 wk post-transplant, patients should receive FPG testing at least once per week. If an intermediate FPG level is detected (6.1–6.9 mmol/L; 110–125 mg/dL), it is recommended that an OGTT be performed to further check for the development of diabetes. After the first month post-transplant, all patients should receive FPG testing at 3, 6 and 12 months, then annually thereafter. Detection of diabetes should lead to treatment (see later). Detection of IGT and abnormal lipid profiles should lead to the

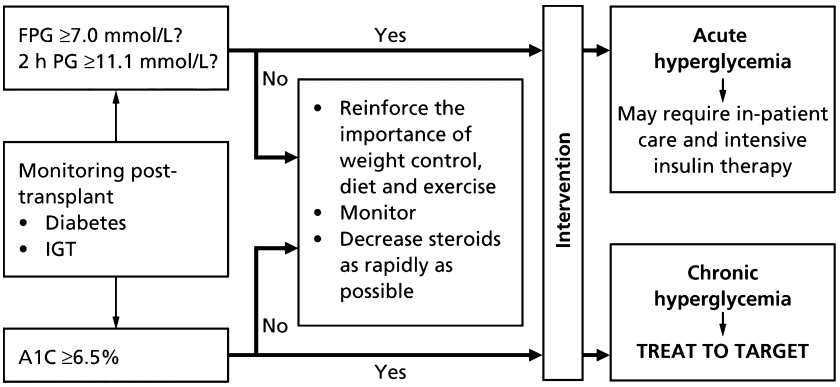

Fig. 1. Post-transplant management: blood glucose control. PG, plasma glucose; IGT, impaired glucose tolerance; FPG, fasting plasma glucose.

implementation of intensive prevention strategies involving weight control, diet, exercise and modification of the immunosuppressive regimen.

A1C (HbA_{1c}; glycated hemoglobin). Use of A1C testing is not recommended before 3 months post-transplant as many people receive blood transfusions at the time of transplantation, rendering the test invalid until new hemoglobin is constituted. However, testing of A1C should form part of the monitoring received by all patients after transplantation for abnormal glucose regulation (Fig. 1). Such testing should be carried out on the same schedule as that required for FPG testing from 3 months post-transplant.

Management of patients with new-onset diabetes after transplantation

Management of immunosuppressive therapy. The type of immunosuppressant received has been shown to explain 74% of the variability in the incidence of new-onset diabetes observed in transplant recipients (14). Consequently, modification of the immunosuppressive regimens of patients developing the condition should be central to their management. Evidence suggests that corticosteroids carry the highest risk for new-onset diabetes after transplantation and thus rapid dose reduction of these agents post-transplant is recommended (Fig. 1). Further consideration may also be given to the use of steroid-free regimens as recent studies suggest that steroid-sparing regimens may be safe in recipients of kidney (15), liver (16) and heart (17) transplants. Nevertheless, use of steroid-sparing and steroid-free regimens remains controversial and requires further investigation. Any reduction in corticosteroid dose should thus be balanced against the possible increased risk of rejection associated with such treatment.

Use of CNIs is also associated with an increased risk of developing new-onset diabetes after transplantation, with evidence suggesting that tacrolimus is more diabetogenic than cyclosporine, particularly in high-risk patients (1, 10–13, 18). Development of the condition in CNI-treated patients should be managed initially by a reduction in the exposure of these agents. It should be noted, however, that no clear relationship exists between tacrolimus drug doses and adverse events and dose titration may not be successful in all patients, necessitating a switch in therapy (19). Indeed, some studies have reported that switching tacrolimus-treated patients who developed new-onset diabetes after kidney (20, 21) or liver (22) transplantation to cyclosporine may improve glucose regulation. Thus, if hyperglycemia persists, a switch from tacrolimus to cyclosporine should be considered; in such cases, patients should receive individualized dose titration of both agents and careful blood monitoring to ensure optimum immunosuppression. If glycemic control cannot be established, CNI discontinuation involving a mycophenolic acid derivative- or proliferation signal inhibitor-based regimen may be considered, though the diabetogenic effects of such regimens are not well studied. The timing of CNI discontinuation, and the strategy used, may result in an increased risk of rejection; thus, if undertaken, patients should be monitored closely.

Monitoring of patients with new-onset diabetes after transplantation

Self-monitoring of blood glucose. Patient monitoring of blood glucose should form an essential component of the therapeutic plan of people with new-onset diabetes after transplantation who are taking oral agents or insulin. Self-monitoring may also be useful for people whose diabetes is controlled by diet therapy alone (23). The frequency of such testing will vary from individual to individual but should be sufficient to provide the feedback needed to optimize therapy. Patient education on self-monitoring of blood glucose should also include advice about detection, prevention and treatment

Table 1. Blood lipid control assessment levels [mmol/L (mg/dL)] for people with type 2 diabetes. Adapted from International Diabetes Federation (24)

Risk of CHD	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides
High risk	>6.5 (>230)	>4.0 (>155)	<1.0 (<39)	>2.2 (>200)
At risk	4.8–6.0 (185–230)	3.0–4.0 (115–155)	1.0–1.2 (39–46)	1.7–2.2 (150–200)
Low risk	<4.8 (<185)	<3.0 (<115)	>1.2 (>46)	<1.7 (<150)

LDL, low-density lipoprotein; HDL, high-density lipoprotein; CHD, coronary heart disease.

of hypoglycemia, with ongoing management undertaken by an endocrinologist.

Lipid levels. In line with the recommendations of the IDF and the American Diabetes Association (ADA), levels of LDL cholesterol, HDL cholesterol, total cholesterol and triglycerides should be measured annually in people with new-onset diabetes after transplantation (24, 25). The categories of coronary heart disease (CHD) risk by lipoprotein levels in patients with type 2 diabetes patients are shown in Table 1. Variation from these target levels requires an increased frequency of monitoring (2–6 monthly), patient reassessment and readjustment of therapy (24).

A1C levels. Individuals with new-onset diabetes after transplantation should receive A1C tests every 3 months to determine appropriate therapy and ascertain if blood glucose control is improving. The A1C assay standardized in the Diabetes Control and Complications Trial should be used in all cases (26). An A1C of 6.5% or higher should indicate therapeutic intervention (Fig. 1). A1C levels should be interpreted with caution in patients with anemia or kidney impairment as such conditions can interfere with the assay rendering the results inaccurate. A1C assay results from patients with high erythrocyte turnover are also invalid.

Diabetic complications. All individuals diagnosed with new-onset diabetes after transplantation should receive annual screening for diabetic complications, including an eye test and a foot check-up (3). People should also be advised to inspect their feet daily and to report any hard skin, corns, cuts, ulcers or infections. Monitoring for the presence of microalbuminuria may be useful in transplant recipients with new-onset diabetes after transplantation to prevent the progression of nephropathy. However, the validity of microalbuminuria screening has not been verified in this population. Indeed, many people with a functioning transplant already have low creatinine clearance necessitating tight blood pressure control. Furthermore, transplant recipients with renal insufficiency may have proteinuria without diabetes and microalbuminuria levels may also be difficult to interpret in kidney transplant recipients with early chronic allograft nephropathy.

Management of new-onset diabetes after transplantation: treat to target

It is recommended that the management of individuals with new-onset diabetes after transplantation should aim toward tight glycemic control, as there is good evidence from the general population that this strategy can substantially lower the overall morbidity associated with diabetes (26, 27).

Acute hyperglycemia. Development of acute hyperglycemia necessitates immediate intervention to avoid serious consequences for the patient and graft. This is particularly important in the perioperative period when acute hyperglycemia can lead to death from multiple organ failure. To avoid such problems, people who develop acute hyperglycemia with blood glucose levels above 20 mmol/L (360 mg/dL) may require in-patient care and intensive insulin therapy (Fig. 1). When the condition has stabilized, a 'treat to target' approach to therapy should be adopted (see below). The current guidelines do not include individuals with diabetic ketoacidosis or hyperglycemic hyperosmolar nonketotic syndrome. If these conditions are present, emergency management must follow local protocols, with particular attention being paid to marked insulin insensitivity for those receiving high-dose steroids.

Chronic hyperglycemia. In general, management of new-onset diabetes after transplantation should follow the guidelines outlined by the ADA for the treatment of individuals with type 2 diabetes (23). The physician should set blood glucose targets for each individual patient who develops new-onset diabetes after transplantation or abnormal glucose regulation and adjust therapy according to a 'treat to target' approach (Fig. 1; Table 2). Management of such individuals may involve non-pharmacologic therapy, oral glucose-lowering agent monotherapy or combination therapy and/or insulin. If the desired level of control is not achieved with initial therapy, then a more aggressive approach

Table 2. Recommendations of 'treat to target' approach to management of people with diabetes

Recommendations
Set individual blood glucose targets for each patient
Adopt a 'treat to target' approach and adjust therapy accordingly
The precise intervention required to achieve optimum blood glucose control will vary with each individual patient
Non-pharmacologic therapy
Lifestyle modification
Education
Oral agent monotherapy
Choice of agent should be tailored to the individual patient
Alpha-glucosidase inhibitor
Biguanide
Meglitinide derivatives
Sulfonylurea
Thiazolidinedione
Oral combination therapy
Use of a combination of two or three glucose-lowering agents could be considered. Choice of agents should be tailored to the individual patient[a]
Insulin ± oral agents
Insulin can be in the form of a single injection of intermediate-acting insulin at bedtime, and may be given concomitantly with oral agents as above
Better glucose control may be achieved with a lower insulin dose plus oral agent
If the desired level of control is not achieved with initial therapy, then a more aggressive approach will be needed

[a]No data exists on the use of oral glucose-lowering agent combination therapy in transplant patients. Thus, no recommendations of particular combinations can be made.

will be needed. Patients should be referred to a diabetologist if hyperglycemia persists.

Little information exists on the use of oral glucose-lowering agents in transplant patients, particularly when used in combination, and no comparative trials of these agents have been conducted in post-transplant patients to date. Thus, no precise recommendations for particular agents can be made. The use of different types of glucose-lowering agent is associated with specific advantages and disadvantages. Of particular note is the possibility of life-threatening lactic acidosis associated with the biguanide, metformin, particularly in people with renal failure, sepsis or cardiovascular compromise. In all cases, the choice of the particular agent used should depend upon the individual characteristics of each patient. The features of common oral glucose-lowering agents are reviewed in depth in the literature (3).

Treatment of dyslipidemia. All individuals with new-onset diabetes after transplantation should receive aggressive lipid-lowering therapy based on the belief that aggressive therapy of diabetic dyslipidemia will probably reduce the risk of CHD in individuals with diabetes in the general population (25) and that all people with new-onset diabetes after transplantation have a high risk of CHD. The lipid assessment levels detailed in Table 1 should be used to set individual blood lipid targets, depending on patients' overall risk; appropriate therapy is detailed in Fig. 2. Studies indicate that statin therapy may be beneficial for people with low LDL cholesterol levels who have a history of CVD (28, 29). Furthermore, statin therapy has been shown to confer survival benefits in recipients of organ transplants (30, 31) and their use may be beneficial for all transplant recipients with new-onset diabetes after transplantation. However, the CNIs and most statins are metabolized by cytochrome p450 3A and thus a pharmacological interaction between these agents is possible. Thus,

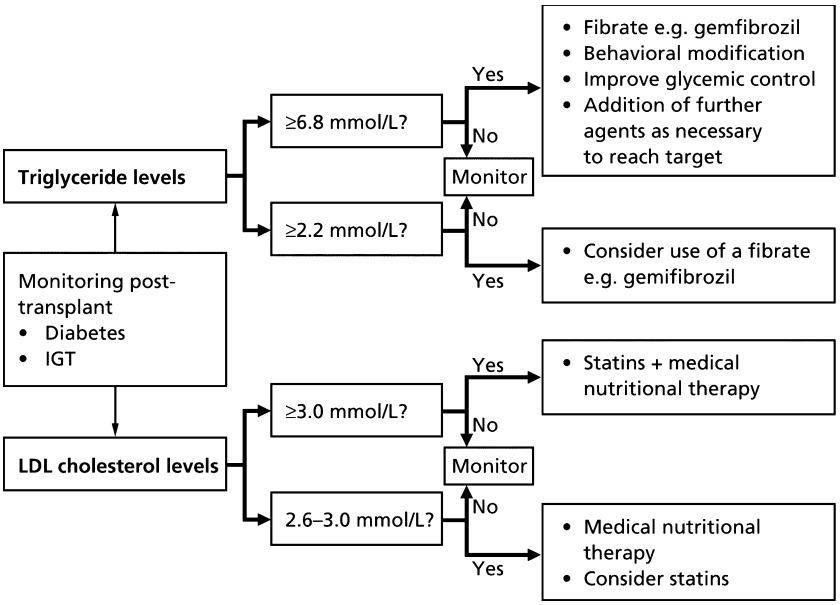

Fig. 2. Post-transplant management: dyslipidemia. IGT, impaired glucose tolerance; LDL, low-density lipoprotein.

the interaction potential of statins should be considered carefully before they are administered to CNI-treated transplant recipients.

Fibrates may be used as primary therapy for people with markedly elevated triglyceride levels (>6.8 mmol/L; 600 mg/dL). However, all fibrates, apart from gemfibrozil, are potentially nephrotoxic and fenofibrate has been shown to reduce blood cyclosporine levels in heart transplant recipients (32); these agents should, therefore, be used with caution in transplant patients, particularly those with renal insufficiency. If LDL cholesterol or triglyceride targets are not achieved with monotherapy, then combination therapy with, for example, cholesterol absorption inhibitors may be considered (33). People receiving combination therapy should be monitored carefully to avoid the risk of toxicity or drug–drug interaction. Use of statins is contraindicated with fibrates and therefore this combination should not be used.

Treatment of hypertension. A blood pressure target of 130/80 mmHg or lower is recommended for all people with new-onset diabetes after transplantation. Antihypertensive therapy in people with new-onset diabetes after transplantation may be initiated with an angiotensin-converting enzyme (ACE) inhibitor and further agent(s) added to reduce blood pressure to the target level as required. Although no antihypertensive agents are currently contraindicated in transplant patients, further studies are required to assess the efficacy of these agents in this population. Particular care should be given to administration of ACE inhibitors and other antihypertensive agents in the first 6 month after transplantation in the setting of high CNI levels or renal artery stenosis. Consideration should be given to the use of aspirin to further reduce the risk of cardiovascular events.

Conclusions

There remain significant gaps in our knowledge of new-onset diabetes after kidney, liver and heart transplantation; however, in each indication, standard immunosuppressive therapies play a significant role in the development of the disease. Furthermore, evidence suggests that identification of predictive factors, early detection and appropriate management can reduce the long-term complications of the condition. The recommendations in these guidelines for the management and treatment of new-onset diabetes after kidney, liver and heart transplantation have been based on the evidence available on the condition to date. It is hoped that adoption of these management approaches pre- and post-transplant will reduce patients' risk of developing the condition, as well as ameliorating the occurrence and impact of its long-term consequences.

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