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REVIEW

Diagnosis, management and treatment of glucometabolic disorders emerging after kidney transplantation

A position statement from the Nordic Transplantation Societies

Mads Hornum,[1] Jørn P. Lindahl,[2] Bengt von Zur-Mühlen,[3] Trond Jenssen[2,4] and Bo Feldt-Rasmussen[1]

1 Department of Nephrology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
2 Department of Organ Transplantation, Section of Nephrology, Oslo University Hospital Rikshospitalet, Oslo, Norway
3 Department of Transplant Surgery, University Hospital in Uppsala, Uppsala, Sweden
4 Institute of Clinical Medicine, University of Tromsø, Tromsø, Norway

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Correspondence
Mads Hornum MD, PhD, Department of Nephrology, Copenhagen University Hospital Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
Tel.: +45 3545 1762;
fax: +45 3545 2607;
e-mail: mads.hornum@gmail.com

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Summary

After successful solid organ transplantation, new-onset diabetes (NODAT) is reported to develop in about 15–40% of the patients. The variation in incidence may partly depend on differences in the populations that have been studied and partly depend on the different definitions of NODAT that have been used. The diagnosis was often based on 'the use of insulin postoperatively', 'oral agents used', random glucose monitoring and a fasting glucose value between 7 and 13 mmol/l (126–234 mg/dl). Only few have used a 2-h glucose tolerance test performed before transplantation. There is a huge variation in the literature regarding risk factors for developing NODAT. They can be divided into factors related to glucose metabolism or to patient demographics and the latter into modifiable and nonmodifiable. Screening for risk factors should start early and be re-evaluated while being on the waitlist. Patients on the waiting list for renal transplantation and transplanted patients share many characteristics in having hyperglycaemia, disturbed insulin secretion and increased insulin resistance. We present guidelines for early risk factor assessment and a screening/treatment strategy for disturbed glucose metabolism, both before and after transplantation. The aim was to avoid the increased cardiovascular disease and mortality rates associated with NODAT.

Diabetes and transplantation

Diabetes emerging after organ transplantation is called new-onset diabetes (NODAT). It is diagnosed according to the World Health Organization (WHO) definition of diabetes as previously described in guidelines for diagnosis and treatment of NODAT published in 2004 [1] and 2005 [2]. NODAT has a significant impact on allograft and patient survival, quality of life and health care costs [3–6]. Furthermore, even moderately elevated fasting or postchallenge glucose concentrations predict future development of diabetes as shown in two studies demonstrating that 15% of renal transplant patients with impaired glucose tolerance (IGT) developed NODAT after 1 year [7] and 27% after 6 years [8]. For these reasons, more focus should be placed on diagnosing and treating NODAT and therefore the transplantation societies in Denmark, Norway and Sweden have endorsed new guidelines as presented in the following.

Diagnosis of diabetes and the prediabetic conditions

The diagnosis of NODAT is made when fasting plasma glucose (FPG) is $\geq$7 mmol/l (126 mg/dl) and/or 2-h plasma glucose is $\geq$11.1 mmol/l (200 mg/dl) after a 75-g oral tolerance test (OGTT) measured on at least two occasions [WHO and American Diabetes Association (ADA) guidelines] [9,10].

Haemoglobin A1c (HbA1c) is today also used for diagnosing diabetes [10], but HbA1c as a diagnostic criterion of

NODAT raises several problems [11]. In fact, at a glomerular filtration rate (GFR) of <50 ml/min, nonglycaemic mechanisms may affect some HbA1c assays. More importantly, with more advanced renal failure, HbA1c may read spuriously low levels because of a shift from older to younger red blood cells. Conversely, increased levels of HbA1c can also be seen in renal failure, because of increased glycation with oxidative stress [12]. Finally, HbA1c may be increased with metabolic acidosis [13]. Despite these methodological problems, it has been suggested that HbA1c may to some extent be used in diagnosing NODAT. This was based on a study with renal transplant patients, where HbA1c was used to detect the subclinical onset of diabetes [14]. A threshold of 5.8% at 10 weeks identified 83% of the NODAT patients and only 49% of the total population required a confirmatory OGTT for diagnosis [15]. Some consider OGTT a complicated examination, but the importance of diagnosing diabetes outweighs this. We therefore suggest that an OGTT should be performed in all patients if FPG is 5.1–6.9 mmol/l (92–124 mg/dl). Prior to surgery, this would discover 90% of all unknown cases of diabetes and almost all cases of IGT by testing only 50% of the patients [16].

The generally accepted prediabetic conditions are: impaired fasting glucose (IFG; FPG $\geq$6.1 mmol/l (110 mg/dl) and <7 mmol/l (126 mg/dl) according to WHO [9] and between 5.6 and 6.9 mmol/l (100–125 mg/dl) ADA [10]) and IGT [FPG <7 (126 mg/dl) mmol/l and 2-h plasma glucose after an OGTT $\geq$7.8 mmol/l (140 mg/dl) and <11.1 mmol/l (200 mg/dl)].

Incidence and prevalence

The cumulative incidence of NODAT varies considerably between reports, the lowest being 5% and the highest 50% [1,7,17–20]. This can partly be explained by differences in the populations (observation time after transplantation, age, ethnicity, confounding diseases, immunosuppression and other medications). In many studies, the glucometabolic state before transplantation was determined from hospital records after transplantation which explains a major part of differences observed. Different diagnostic criteria have also been used. In some studies, use of insulin or oral hypoglycaemic agents has been the sole diagnostic criterion to define diabetes. In other studies, FPG has been used as a criterion, and only a few studies have had the opportunity to use an OGTT to define diabetes, OGTT-based data being the state-of-the-art criterion [1,9]. In a large Caucasian population being admitted to the wait list for renal transplantation, a diagnostic OGTT was undertaken in all patients without the diagnosis of diabetes prior to transplantation (n = 889) [16]. Of these, 330 (37%) had prediabetes (IFG or IGT), and another 72 patients (8%) had diabetes with a fasting or 2-h blood sugar not acknowledged by the remitting nephrologist [16]. Taken together, it is fair to say that about 50% of the nondiabetic patients on the wait list for renal transplantation already have unrecognized diabetes [7,15] or are at a risk of developing NODAT after transplantation.

Some data indicate that the cumulative incidence of NODAT is declining; others do not [21]. At one centre, using OGTT data 10 weeks after renal transplantation, the incidence of NODAT had dropped from 20% to 13% between 1995 and 2005 [22], even though the patients in 1995 were older and more obese. The explanation could be the use of lower doses of CNIs and prednisolone, and newer immunosuppressive protocols with fewer rejections in the latest cohorts [22].

Risk factors

Risk factors can be divided into measurements of glucose metabolism or patient demographics. The latter can also be divided into modifiable and nonmodifiable risk factors. Screening for risk factors should start before transplantation and be re-evaluated while on the waiting list, and pretransplant risk scores are available [23].

Glucose metabolism

Impaired glucose tolerance and impaired fasting glucose

Impaired glucose tolerance and IFG are risk factors for NODAT [24] and both are measured during an OGTT.

Metabolic syndrome and obesity

The presence of metabolic syndrome (impaired glucose metabolism, hypertension, central obesity with, waist hip ratio >0.9 for men and 0.85 for women or BMI >30 kg/m^2, dyslipidaemia and microalbuminuria) pretransplant is an independent predictor of NODAT, and the risk increases with the number of abnormal components of the metabolic syndrome [25].

Along with age, obesity is one of the most consistent risk factors for NODAT. In the general population obesity, often defined as a BMI >30 kg/m^2, is one of the major risk factors for development of insulin resistance and type 2 diabetes. The weight gain often seen after transplantation is associated with reduced graft- and patient survival [3]. Obesity is also recognized as an independent risk factor for developing chronic kidney disease (CKD) [26].

Nonmodifiable risk factors

Age

Old age is the strongest and the most consistent risk factor for NODAT. A study of over 11 000 patients in the US

Renal Data System (USRDS) who received a kidney transplant between 1996 and 2000 demonstrated that the relative risk for NODAT increases with higher recipient age. Compared with the reference age 18–44 years, recipients between 45 and 59 had a relative risk of 1.9 and those older than 60 years had a relative risk of 2.09 [5]. Other studies confirm this increased risk [7,21,24]. In liver transplantation, the results are not as clear, and in one study, there was no correlation between age and the risk for NODAT [27].

Family history

A positive family history of diabetes among first-degree relatives has been associated with NODAT in all types of solid organ transplantation and in a Spanish multicentre cross-sectional study, the odds ratio for NODAT was 1.51 with a history of diabetes in the closest family [28].

Autosomal dominant polycystic kidney disease

Approximately 7.5–15% of the kidney transplant population is affected by autosomal dominant polycystic kidney disease (ADPKD). A retrospective multivariate study showed that ADPKD was a strong risk factor for the development of NODAT with an odds ratio of 2.41 [29].

Genotype and ethnicity

In the transplanted population, some HLA phenotypes have been associated with a higher incidence of diabetes, but the results are contradictory and certain HLA phenotypes should therefore not be considered as risk factors for NODAT [1,30].

African Americans and patients of Hispanic origin are at higher risk of developing type 2 diabetes or NODAT after transplantation [5]. The differences in the pharmacokinetics of diabetogenic immunosuppressive drugs could explain the differences between African American and Caucasian patients [31].

Modifiable risk factors

Low physical activity

Physical activity level is low in end-stage renal disease patients and most patients increase their level after transplantation, but fitness compared with the general population remains low. In a prospective study of 540 renal transplant recipients, low physical activity was strongly associated with increased risk for cardiovascular and all-cause mortality [32] and active lifestyle improves glucose tolerance in hyperglycaemic renal-transplanted patients [33].

Hepatitis C

Hepatitis C virus (HCV) infection is associated with the occurrence of type 2 diabetes in the general population. The mechanisms are not clarified, but include impaired hepatic glucose uptake and increased gluconeogenesis, increased insulin resistance and direct negative viral effects on the pancreatic β cells [34,35]. The prevalence of HCV infection is higher in the transplant population than in the general population and HCV increases the risk for NODAT after liver and kidney transplantation [36–38]. The current advice is that hepatitis C infection should be treated prior to transplantation [39].

Cytomegalovirus

Cytomegalovirus (CMV) infection has been shown to be an independent risk factor for NODAT [40]. In a study with 160 nondiabetic renal transplant recipients, CMV was monitored 3 months following transplantation. Even asymptomatic CMV infection was associated with a four-fold increased relative risk of NODAT. Impaired insulin release from the pancreatic β-cells was shown in this study [41]. It is, however, currently unknown whether preemptive treatment of CMV infection may decrease the incidence of NODAT.

Planning of immunosuppression to prevent or treat NODAT

The risk of developing NODAT should be weighed against the risk for acute rejection. Higher doses of CNIs may be necessary when the risk of organ rejection is high. Withdrawal of prednisolone increases risk for acute rejections with marginal effects on glucose control [42], and is generally not recommended. We recommend a low-dose maintenance dose of 5 mg/day, as this does not seem to impair insulin sensitivity significantly, at least in renal transplant patients [43]. Complete withdrawal of prednisolone should only be considered in patients at low immunological risk.

It has been argued that switching from tacrolimus to CsA might help improving glucose control. Evidence in the USRDS database suggested, however, that tacrolimus protected against rejections over CsA among renal transplant patients, despite higher incidence rates of NODAT [5]. The DIRECT study compared *de novo* renal transplant patients with CsA versus tacrolimus-based regimens, and found no significant difference in acute rejections, but a slightly lower incidence rate of NODAT on the expense of higher cholesterol levels and lower GFR [44]. Trough levels of both regimens were rather high in this study.

There are no consistent long-term data on benefits in switching from tacrolimus to CsA. An alternative would be to taper tacrolimus trough levels to the low therapeutic range, as this increases the insulin response [45].

A recent meta-analysis suggests that CNI-sparing strategies are associated with less NODAT [46]. Recently, it was reported that the IL-2 receptor antagonist basiliximab was associated with the development of NODAT 3 months post-transplant [47]. So far, azathioprine and

mycophenolate mofetil (MMF) have not been related to the development of NODAT in clinical studies.

Switching from CNI to mTOR-based therapy has no benefits in this context. The majority of mTOR-based clinical trials addressing NODAT as an end-point has so far been performed with sirolimus [48,49]. When occurrence of diabetes was assessed with either an OGTT [50] or fasting glucose measurements [51], the risk of developing NODAT with sirolimus in renal transplant patients was clearly increased compared with CNI [50,51].

Also, insulin release and insulin sensitivity are impaired after conversion to sirolimus [50]. The decrease in insulin sensitivity is proportional to a concurrent increase in plasma triglycerides [50]. High cholesterol levels are also seen with mTOR inhibition [50,52]. Most likely, mTOR inhibition induces changes in the insulin signalling pathway with increased hepatic synthesis of triglycerides and increased secretion of VLDL cholesterol [50]. Just recently, USRDS data were published confirming that the risk of NODAT increased with sirolimus, either when used together with a CNI or with an antiproliferative agent (MMF or azathioprine) [53].

Everolimus is less investigated, but has also been associated with NODAT [54].

The fusion protein and co-stimulation blocker belatacept has been introduced in recent years and has been shown to be associated with less metabolic risk profile including less development of NODAT compared with CsA [55].

NODAT and cardiovascular risk

Cardiovascular events are frequent in NODAT patients [4,5,56–59]. Some studies even show that NODAT is associated with a two- to threefold increased risk of cardiovascular disease (CVD) and death [5,56,58,59]. NODAT is defined by blood sugar criteria, but it carries important additional cardiovascular risk factors of modifiable and nonmodifiable nature, such as age, overweight, hypertension and dyslipidaemia [57]. However, even after correction for these risk factors, NODAT remains an independent risk factor for cardiovascular events.

Hypertension

The prevalence of hypertension is increased after kidney transplantation. After the introduction of CNI, up to 50–90% of kidney transplant recipients are hypertensive [60].

The target of blood pressure after kidney transplantation should be <130/80 mmHg consistent with the recommendations for patients with a high risk for CVD [61]. The high incidence of hypertension and its role as a major risk factor for CVD motivates measurement of blood pressure at every clinic visit after transplantation. Ambulatory, seated, standing and self-measured blood pressures are useful tools to monitor the blood pressure and achieve better treatment results. In renal dysfunction, antihypertensive treatment also aims to lower the degree of proteinuria, if present. To reach the target blood pressure, the treatment includes lifestyle management. Pharmacological monotherapy achieves blood pressure target only in a limited number of patients. Consequently, a combination of multiple drugs is most often required. There is no consensus about first-line therapy, and the most widely used drugs are diuretics, calcium channel blockers, beta-blockers, ACE-inhibitors and angiotensin II receptor blockers. The use of renin-angiotensin system blockade is shown to be reno- and cardioprotective in a diabetic population and the use of these agents in transplantation is now more frequent than in the past [62].

Dyslipidaemia

In the general population, large randomized controlled trials have shown strong evidence that reduction in low-density lipoprotein (LDL) cholesterol decreases CVD. In the transplant population, the prevalence of hyperlipidaemia is high, partly because of immunosuppressive medication. Both corticosteroids and CNI contribute to dyslipidaemia and mTOR inhibition causes an even more profound elevation [63]. In the extension of the ALERT study, 1 652 renal transplant recipients who initially were randomized to fluvastatin showed, after a mean total follow-up of 6.7 years, a reduced risk of major adverse cardiac events, but no difference in total mortality or graft loss [64].

The Kidney Disease Outcomes and Quality Initiative (K/DOQI) has published guidelines for the diagnosis and treatment of dyslipidaemia in patients with CKD, including transplant patients. One key feature is that CKD and kidney transplant patients are not to be managed differently from other patients. For the treatment of LDL cholesterol, the first-line drug is a statin in combination with therapeutic lifestyle changes including a healthy diet, weight reduction, exercise and smoking cessation. Patients treated with CyA need a dose reduction of the statin because of interaction in the metabolism of the two drugs. The target for total cholesterol should be <200 mg/dl (5.2 mmol/l), LDL cholesterol <100 mg/dl (2.6 mmol/l) and triglycerides <150 mg/dl (1.7 mmol/l) [65]. If statins are insufficient or not tolerated, other lipid-modifying agents, i.e. fibrates, niacin or the cholesterol absorption inhibitor, ezetimibe are used. Bile acid sequestrants interfere with the absorption of immunosuppressive agents and are not recommended.

Smoking

A retrospective cohort study of 41 705 renal transplant recipients showed that smokers had an increased risk of allograft loss (adjusted HR 1.46) and death (adjusted HR

2.26) [66]. Smoking cessation could improve renal survival [67]. The ADA recommends all patients not to smoke, and smoking cessation counselling should be a routine component of diabetes care.

Aspirin

In the nontransplanted population, several guidelines recommend the use of low-dose aspirin (75–160 mg) for patients at high risk (>40 years of age with additional risk factors, i.e., family history of CVD, hypertension, diabetes, smoking, dyslipidaemia or albuminuria unless aspirin is contraindicated [68]. In a small retrospective study, low-dose aspirin improved allograft function and survival [69]. To minimize the risk of haemorrhagic stroke, antiplatelet treatment should be started after the blood pressure control has been optimized [70].

Diabetes diagnosed during pretransplant work-up

Pretransplant diabetes newly diagnosed during work-up for the wait list is either classified as type 1 or more often type 2 diabetes (Table 1). Hyperglycaemia, dyslipidaemia and hypertension in these patients have most likely persisted for many years. As the patients suffer from both diabetes and uraemia, they are predisposed to neuropathy and autonomic neuropathy and they may have cardiac disease without clinical symptoms.

Diagnosis of diabetes qualifies the patients to undergo:

1. Cardiac work-up including resting ECG, and a myocardial stress test (e.g. myocardial scintigram or a stress echo test)
2. If ischaemic myocardial disease is discovered, one should perform a coronary angiogram
3. Retinal examination
4. Examination for neuropathy, including autonomic neuropathy

Micro-and macrovascular work-up should be performed every second year while on the wait list.

Table 1. Complete pretransplant medical evaluation.

Medical history	Diabetes in first-degree relatives
	Gestational diabetes
	Steroid diabetes
	Prescription of gout medicine
	Primary renal disease
Measurement of glucose metabolism	FPG
	OGTT
	HbA1c
	C-peptide
Screening for metabolic syndrome and CVD risk factors and preplanned treatments	Age
	BMI
	Waist circumference
	Lipid profile (TG, LDL, HDL, ApoB/ApoA1)
	Blood pressure
	Smoking
	Preplanned steroid treatment post-transplant

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; HbA1c, haemoglobin A1c; BMI, body mass index; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CVD, cardiovascular disease.

After transplantation

Screening for post-transplant hyperglycaemia/NODAT

Blood sugar should be monitored in all newly transplanted patients. There are data suggesting the use of an OGTT or FPG at day 5 as a predictive tool for development of NODAT [71]. FPG should be tested at least once a week in the initial period when steroid dose is high (equivalent to or above 20 mg/day prednisolone) and CNI dose is not in the maintenance level. If FPG is found increased between 6.1 and 6.9 mmol/l (110–124 mg/dl), an OGTT should be considered [72]. If blood sugar levels exceed the threshold of diabetes according to ADA/WHO-criteria [73], treatment should be initiated. One-third of the patients with NODAT have a normal fasting glucose to start with, and can only be diagnosed by the 2-h postload glucose concentration after an OGTT [15]. HbA1c levels may or may not be elevated in this setting. An OGTT is not commonly performed in all patients after renal transplantation. Selecting patients for OGTT according to, e.g., FPG $\geq$5.5 mmol/l (100 mg/dl), would require 40% of the patients to be tested to find 70% of all cases with NODAT [15]. It is probably more convenient to perform an OGTT in those patients who have a FPG $\geq$5.0 mmol/l (90 mg/dl) and HbA1c $\geq$5.7% 10–12 weeks post-transplant. That would detect 80% of all cases with NODAT by testing only 30% of the patients, at least among Caucasian recipients [15]. Although early manipulations pre- or post-transplant may have affected the prevailing HbA1c levels, the HbA1c levels stabilize in most cases within 3 months post-transplant.

In the outpatient clinic, an FPG should be performed every week until 1 month post-transplant and regularly every 1–3 months thereafter [15,24,74,75]. An alternative to OGTT could be a home glucometer preprandial screening for 3 days [76]. One study suggested OGTT testing at 2 and 12 months post-transplant because of the dynamics of glucose metabolism during the first year following transplantation, but this may be too cumbersome to advise as a general recommendation [14,15,72].

Treatment of diabetes after transplantation

There are no solid data on the clinical effects of strict glycaemic control during hospitalization after transplantation in either diabetic or NODAT patients. However, in a pilot

study of 50 patients with early hyperglycaemia after renal transplantation, Hecking *et al.* managed to reduce the occurrence of NODAT after 1 year by early insulin intervention, probably by preserving beta-cell function over time [77]. The incidence of complicating hypoglycaemia was low. The same concept of beta-cell preservation with early insulin treatment has previously been shown also for patients with type 2 diabetes [78]. In other clinical settings, hyperglycaemia has been found associated with various adverse clinical outcomes, including increased risk of postoperative complications, longer hospital stay and higher mortality, both in-hospital and long-term [79–82]. Findings in randomized control trials (RCT) indicate that tight glycaemic control during admission improves these clinical outcomes, reducing both the number of admission days and mortality [83–85]. A more recent RCT [86] and a meta-analysis [87] have, however, not been able to confirm these findings and the NICE-SUGAR Study demonstrated that in critically ill patients, intensive glucose control leads to moderate and severe hypoglycaemia, both of which are associated with an increased risk of death [88]. In the NICE-SUGAR Study, there were more patients in the strict glycaemic control group treated with corticosteroids. The authors declared that the patients treated with corticosteroids were severely ill and the most stated indication for corticosteroid treatment was 'septic shock'. Transplanted patients are not considered 'critically ill' and this is a major difference that may justify advocating a more strict glycaemic control after transplantation despite the potential risk mentioned above. The ADA and the American Association of Clinical Endocrinologists (AACE) recommend that random blood glucose levels should be <10 mmol/l (180 mg/dl) in noncritically ill patients during hospitalization [89].

Treatment of diabetes in the postoperative phase after transplantation

This will depend on the patients' history of diabetes.

Four different settings should be considered:

1. Type 1 diabetes
2. Type 2 diabetes, treated with insulin
3. Type 2 diabetes, treated with diet alone or oral with anti-diabetic agents
4. New-onset diabetes after transplantation

The postoperative treatments are summarized in Table 2. The treatment targets should not be too low as

Table 2. Treatment of diabetes in the postoperative phase after transplantation.

During operation and early postoperative phase
Treatment of any kind of diabetes should follow the local guidelines as defined by the local anaesthesiologists. In most cases, this will include intravenous insulin together with glucose and potassium driven by frequent measurements of blood glucose. When the patient is awake, the treatment will to some extent vary according to the different settings of diabetes
Postoperative insulin treatment of type 1 diabetic patients
As all patients will have received a relatively high dose of i.v. methyl prednisolone prior to transplantation, they will be insulin resistant during the first days after transplantation. If they continue on steroid treatment in tapering doses in the first weeks after transplantation, they will need extra insulin and there are some general rules to be followed:
The preoperative–24 h insulin dose (per 24-h) is the minimum dose that the patients should always receive after transplantation
Because of steroids and postoperative stress, this preoperative dose should be preplanned to be increased by at least 25%
The 24-h dose should be preplanned as four insulin injections per day administered as one dose of intermediate acting insulin late evening and three premeal injections of rapid acting insulin during the day
Plasma glucose should be measured at least four times a day; that is, before the three meals and before night-time
If the plasma glucose is higher than 8 before the meals, the preplanned rapid acting insulin dose should be increased accordingly
Patients with type 2 diabetes on insulin treatment before transplantation
These patients are expected to be even more insulin resistant than the type 1 diabetic patients described above and the supplementing insulin dosages may have to be increased
Type 2 diabetic patients on oral hypoglycaemic agents or diet
After transplantation, they will very often need insulin. Their usual oral anti-diabetic agents may be continued, but they should have blood glucose measured at least four times a day and adjusting insulin dosage should be administered accordingly. The dosages should be aggressively increased to meet the treatment targets discussed above
Each day, the total insulin dose from the previous day should be estimated to rapidly build up a preplanned insulin regimen
Patients with new-onset diabetes
Treatment guidelines as described for patients having type 2 diabetes except that we recommend they should be started out with insulin and not oral agents during the first days. If the insulin dose per 24 h required is modest (below 20 IE per day) indicating a residual capacity of the beta cell, they could be shifted to oral anti-hyperglycaemic agents and encouraged to increase exercise and focus on a low-carbohydrate diet
Treatment targets
During hospitalization, the Scandinavian Post-Transplant Diabetes Expert Group suggest that the treatment targets [89] should be:
Fasting morning plasma glucose 4–7 mmol/l (72–126 mg/dl)
Preprandial plasma glucose 4–10 mmol/l (72–180 mg/dl)
Plasma glucose at night-time 4–10 mmol/l (72–180 mg/dl)

Table 3. Recommendations for the diagnosis, treatment and management of glucometabolic disorders emerging after kidney transplantation.

Recommendation 1

It is well documented that many patients on the waiting list for transplantation have undiagnosed diabetes. They should be characterized annually according to absence or presence of diabetes

Fasting plasma glucose (FPG) should be measured annually

An oral glucose tolerance test (OGTT) should be performed once before transplantation in all patients on the waiting list

Diabetes is diagnosed when FPG $\geq$ 7 mmol/l (126 mg/dl) and/or 2-h plasma glucose $\geq$ 11.1 mmol/l (200 mg/dl) after a 75-g OGTT measured on at least two occasions

Prediabetic conditions are: impaired fasting glucose [IFG; FPG $\geq$ 6.1 mmol/l (110 mg/dl) and <7 mmol/l (126 mg/dl) (according to WHO) and between 5.6 and 6.9 mmol/l (100–125 mg/dl) (according to ADA)] and IGT [FPG <7 (126 mg/dl) mmol/l and 2-h plasma glucose after an OGTT $\geq$ 7.8 mmol/l (140 mg/dl) and <11.1 mmol/l (200 mg/dl)]

Recommendation 2

Before transplantation, risk factors for development of new onset diabetes after transplantation (NODAT) are well documented, and should be identified and treated

Besides age, ethnicity and family history of diabetes, some risk factors are modifiable such as obesity, the metabolic syndrome and glucose intolerance. An appropriate screening should be performed before transplantation to identify patients with higher risk for NODAT. Risk factor intervention should be started already in the period before transplantation directed towards:

Overweight

Sedentary lifestyle (exercise)

Smoking

Hepatitis C infection

Extreme overweight; consider bariatric surgery

Recommendation 3

Patients with diabetes and poor glycaemic control have an increased morbidity and mortality during hospitalization

Plasma glucose should be monitored at least four times daily in diabetic and nondiabetic patients during primary hospitalization after transplantation to diagnose NODAT and provide an overall optimal immunosuppressive and metabolic treatment of known diabetes and NODAT after transplantation. Patients with diabetes, cystic fibrosis or NODAT should be started out with insulin and not oral agents during the first days. If the insulin dose per 24 h required is modest (below 20 IE per day) indicating a residual capacity of the beta cell to increase insulin production, they could be shifted to oral anti-hyperglycaemic agents like the meglitinides and encouraged to increase exercise and focus on a low-carbohydrate diet

Treatment targets

During hospitalization, the treatment targets should be:

Fasting morning plasma glucose 4–7 mmol/l (72–126 mg/dl)

Preprandial plasma glucose 4–10 mmol/l (72–180 mg/dl)

Plasma glucose at night-time 4–10 mmol/l (72–180 mg/dl)

The treatment targets should not be too low and the treatment not too aggressive. The risk of hyperglycaemia should be weighed against the risk of hypoglycaemia [89]

Consider to use a progressive strategy in the supplementation of insulin where the use of steroid is increased, remembering that the usual insulin demand is increased by approximately 40% when treating with a prednisolone dose of 50 mg

Recommendation 4

Use of steroids, calcineurin inhibitors and mTOR inhibitors are known modifiable risk factors of NODAT

In patients with diabetes or NODAT, or high risk of NODAT before transplantation, the immunosuppressive treatment should be tailored to prevent development of diabetes, but not on the expense of rejection episodes. If possible, it should be considered to aim at low-dose steroids, low trough levels of CNI inhibitors and withholding use of mTOR inhibitors

Recommendation 5

Patients with NODAT are at risk of diabetic complications and have a high risk of cardiovascular morbidity and mortality. They should be treated according to current guidelines on treatment of patients with diabetes to the extent these do not have a negative impact on the function and survival of the transplanted organ. Such guidelines include:

Measure FPG annually for a minimum of 5 years, and longer in patients at higher risk of diabetes i.e. cystic fibrosis, to diagnose NODAT

Measure FPG when significant changes in immunosuppressive changes are implemented

Lifestyle advice (weight, smoking habits, exercise)

Antihypertensive treatment to target <130/80 mmHg, including renin–angiotensin blockade if possible. Blood pressure must also be measured in the standing position to disclose orthostatic hypotension

Treating dyslipidaemia to target LDL cholesterol <3.0 mmol/l

Treating glycaemic control to target HbA1c <7% (51 IFCC units) [89]

Close collaboration with endocrinologists and ophthalmologists

ADA, American Diabetes Association; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; HbA1c, Haemoglobin A1c.

set by the department treatment standard and according to ADA and AACE [89]. The risk of hyperglycaemia should always be weighed against the risk of hypoglycaemia. It has recently been shown that very aggressive insulin treatment in the intensive care unit [87], as well as post-transplantation of type 1 diabetic patients [90] is of no benefit to the patients and may in fact be harmful to the patients [87].

It should also be kept in mind that insulin is a universally anabolic hormone. Lack of insulin/hyperglycaemia may increase the risk of infections and prolong wound healing and thereby hospitalization.

Treatment of diabetes after hospitalization/the first weeks after transplantation

With lower doses of steroids and less postoperative stress and infection, the insulin sensitivity will improve. In most cases, type 1 diabetic patients can resume their original insulin dosages as prior to transplantation. Patients with other types of diabetes should be re-evaluated to select an appropriate treatment regimen. Many patients will, in our opinion, probably benefit from insulin treatment for some weeks or perhaps months even though they may be able to return to oral agents or only diet later on. The same will probably be the case for patients with NODAT. In general, the insulin dose at discharge should be estimated by calculating the dosage of insulin per 24 h needed over the last 2 days before discharge from hospital. Further adjustments of insulin or other treatments in the out-patient clinic should preferentially be chosen in collaboration with the diabetologists.

Oral hypoglycaemic agents

There are a number of treatment principles for oral hypoglycaemic agents, but only few are feasible in patients with kidney disease and potential risk of recurrent uraemia.

Those that should be used in the initial phase are the meglitinides, where especially repaglinide is considered relatively safe in kidney-transplanted patients [91] with an emphasis on monitoring the risk of hypoglycaemia. All the other treatments available have potential side effects in renal disease. The Biguanides are cleared by the kidneys and associated with lactate acidosis, especially in combination with ACE-inhibitors and angiotensin II receptor blockers, and at present not sufficiently tested in a renal transplant population. The Sulphonylureas may accumulate, induce hypoglycaemia and weight gain, need dose reduction and may even impair the beta-cell secretion capacity [92]. The Glitazones are associated with fluid retention and an increased cardiovascular risk in some patients. The alphaglucosidase blockers have not been systematically used in kidney patients and the incretin-based therapies (GLP-1 mimetics and enhancers) have not yet been sufficiently tested in patients with NODAT or kidney disease patients with type 2 diabetes. Studies on DPP4-inhibitors in transplanted patients are being conducted, and recently two short-term studies reported that sitagliptin [93] and vildagliptin [94] could be safely used in renal transplant patients. Furthermore, linagliptin can safely be used in ESRD patients and potentially also in transplanted patients without dose reduction, as it is metabolized in the liver [95].

The treatment targets should be as in any patient with diabetes, but hypoglycaemic events should be avoided because of cardiovascular risk. The treatment should be coordinated with the diabetologists.

Conclusions and recommendations

In summary, patients on the waiting list for renal transplantation and transplanted patients share many characteristics in terms of hyperglycaemia, disturbed insulin

Table 4. Available treatment options for hyperglycaemia after transplantation.

Agent	Mechanism of action	Adjustment according to renal allograft function	Comments
Insulin	Exogenous anabolic and primary glycaemia lowering hormone	Reduced according to eGFR and clinical effect	Efficacious glycaemia reduction, risk of hypoglycaemia
Meglitinides	Insulin secretion stimulation	Variable can be used	Possible weight gain, drug cost
DPP-4 inhibitors	Decreases inactivation of incretin hormones	Reduce dose with an eGFR <60 ml/min, except linagliptin	No weight gain, drug cost
GLP-1 agonists	Insulin secretion stimulation and decreased glucagon production	Reduce dose with an eGFR <60 ml/min, avoid when eGFR <30 ml/min	No weight gain, few data available
Sulphonylureas	Insulin secretion stimulation	Reduced according to eGFR	Risk of hypoglycaemia and accumulation in renal failure
Biguanides	Insulin sensitizing	Caution when eGFR<50 ml/min	Risk of lactate acidoses and gastrointestinal side effects

eGFR, estimated glomerular filtration rate; DPP-4, dipeptidase-4; GLP-1, glucagon-like peptide 1.

secretion and increased insulin resistance. Early risk factor assessment and a screening strategy for disturbed glucose metabolism and cardiovascular risk factors both before and after transplantation are important to avoid the increased CVD and mortality rates associated with NODAT.

Early metabolic control after transplantation is mandatory and includes treatment of disturbed blood glucose, lipids and hypertension.

Recommendations for diagnosing and assessing risk factors for diabetes and NODAT, glycaemic control, immunosuppression and cardiovascular risk factors in kidney-transplanted patients are summarized in Tables 3 and 4.

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