New-Onset Diabetes After Renal Transplantation

Risk assessment and management

LIDIA GHISDAL, MD1
STEVEN VAN LAECHE, MD2
MARC J. ABRAMOWICZ, MD, PHD2
RISK FACTORS

Risk factors shared with type 2 diabetes in the general population

Reports from large databases, such as the United States Renal Data System (USRDS; a national organization that collects, analyzes, and distributes information about ESRD in the U.S.) and the Organ Procurement Transplant Network/United Network of Organ Sharing (OPTN/UNOS; organizations that are collecting medical data on donor and transplant recipients), have identified several independent risk factors associated with NODAT. As observed in type 2 diabetes in the general population, older age is a strong independent risk factor of NODAT. There is a 90% increase of relative risk (RR) in renal transplant patients aged 45–59 and a 160% increase in patients ≥60 (versus 18–44 years as a reference). The RR of NODAT is increased by 32–68% in black patients and by 35% in Hispanic patients in comparison with white patients. Overweight or obese patients have a higher risk of developing NODAT, with an RR of 1.4 for patients with a BMI between 25 and 30 kg/m² and an RR of 1.7–1.8 for patients with a BMI >30 kg/m². The RR of NODAT associated with a positive hepatitis C virus (HCV) infection is similar to that observed in patients on the waiting list (~6% per year) (8). Thus, late-onset cases of NODAT may be difficult to distinguish from genuine cases of type 2 diabetes. The most accurate incidence of NODAT under calcineurin inhibitor (CNI) therapy is provided by the prospective study of Vincenti et al. (9), reporting an incidence of NODAT reaching 20.5% within the first 6 months postrenal transplantation.

Renal transplant recipients with NODAT exhibit similar complications as those seen in the general population with type 2 diabetes, but at an accelerated rate (10). As a consequence, NODAT is associated with worse outcomes after renal transplantation, such as a higher risk of major cardiovascular events, graft failure, death-censored graft failure, and death (11,12). In addition, this metabolic complication substantially increases medical costs (8).
New-onset diabetes after renal transplantation

serology ranges from 1.3 to 1.4 (12,13). While no prospective study has evaluated the impact of pretransplant clearance of HCV on the incidence of NODAT, two retrospective reports suggest that this strategy could be beneficial (14,15).

With regard to cytomegalovirus (CMV), a group showed that both ganciclovir-treated and asymptomatic CMV infection episodes are independent risk factors of NODAT (16,17). These results have not been confirmed by other groups (18,19). Likewise, there is no clear relationship between positive CMV serological status and the risk of type 2 diabetes in the general population (20).

The role of a family history of diabetes in predicting NODAT is unclear, as it has not been evaluated in large registry reports. However, a family history of type 2 diabetes emerged as a significant risk factor associated with NODAT in multivariate analysis of several studies (16,21). Retrospective studies reported a higher incidence of NODAT in patients with a metabolic syndrome at baseline. Patients with an increasing number of criteria are more likely to develop NODAT (74% of patients with five pretransplant criteria developed NODAT) (22,23). The risk of NODAT increases stepwise with pretransplant FPG level (FPG 101–110, odds ratio [OR] 1.5; FPG 110–125, OR 7.6) (24). The 2-h plasma glucose level after an oral glucose tolerance test (OGTT) correlates with the risk of NODAT (OR 1.26 per 1 mmol/L or 18 mg/dL) (25). Pretransplantation hyperglycemia was also shown to correlate with NODAT (26).

Early studies evaluating the possible association of NODAT with single nucleotide polymorphisms of various genes are limited by small sample size and the absence of replication cohort, precluding any robust conclusions. After 2007, the association between NODAT and type 2 diabetes–associated genes have been reported in larger cohorts (Table 1). Since the first genome-wide association study (GWAS) in 2007, >40 confirmed loci have been associated with type 2 diabetes in the general population. The effect size of genetic variants so discovered was quite small, however, with an OR ranging from 1.10 to 1.20 for most of them. One of the largest ORs was 1.55 and was observed in non-obese patients with genetic polymorphism rs7903146 (T allele), a common variant in the TCF7L2 (transcription factor 7-like 2) gene (27). This allele has been associated with impaired insulin secretion, incretin effect, and enhanced rate of hepatic glucose production in humans (28). Our group showed that this polymorphism was independently associated with NODAT occurring in the first 6 months posttransplantation, in a large white cohort (N = 1,076) (29). Another group found a significant association with the same variant, in a cohort of 589 Korean transplant recipients (30). TCF7L2 as well as six other genes linked to type 2 diabetes in GWAS are acting through the Wnt signaling pathway involved in pancreas development, islet function, and insulin production and secretion. Wnt ligands might also be involved in the cross-talk between adipocytes and pancreatic β-cells. Investigations of these links should eventually help identify new therapeutic drug targets (31). Currently, TCF7L2 is not routinely genotyped in order to stratify the risk of diabetes and to support personalized medicine. As stated above, the >40 diabetes-predisposing genetic variants discovered as of today only explain 10% of the observed heritability of diabetes, which is of little help in individual prediction (27). Recently, a study showed that the addition of genotypes (20 single nucleotide polymorphisms from GWAS) to phenotype-based risk models yielded only a marginal improvement in accuracy for estimating the absolute risk of type 2 diabetes and that an isolated genetic score was not discriminant (32). Currently, the search is focused on less common variants associated with type 2 diabetes in the general population, which might be more suited to support customized management of patients. Such variants yielding a stronger effect size might also be associated with NODAT in renal transplant patients. Thus, although the association of TCF7L2 with NODAT highlights a major common mechanistic pathway with type 2 diabetes, we do not currently recommend genotyping TCF7L2 for individual risk prediction of NODAT today.

Hypomagnesemia induced by CNIs (more common with tacrolimus) is due to renal magnesium wasting occurring through transcriptional inhibition of the renal magnesium transporter in the distal collecting tubule. Recently, posttransplantation hypomagnesemia was found to be an independent predictor of NODAT in both renal and liver transplant (26,33). This finding is in line with data from the general population where hypomagnesemia might merely represent a surrogate marker or be a consequence of insulin resistance, inflammation, or endothelial dysfunction, which are all risk factors for diabetes in the general population. Although magnesium supplementation has previously demonstrated a beneficial impact on insulin resistance in the general population, randomized, controlled trials assessing the impact of early posttransplantation magnesium supplementation on glucose metabolism, which are ongoing, will hopefully shed light on this still controversial issue (36).

Specific factors related to transplantation

Although the type of donor (deceased versus living) is not an independent risk factor for NODAT, immunosuppression is a major factor contributing to the risk of NODAT. The diabetogenic effect of glucocorticoids, mainly due to insulin resistance, is mediated by both impaired insulin-dependent glucose uptake in the peripheral tissues and enhanced gluconeogenesis in the liver. High-dose glucocorticoid regimens used during the 1970s were associated with a very high incidence of so-called “steroid diabetes,” which declined when cyclosporine was introduced as an immunosuppressant in the 1980s. However, pulse glucocorticoid therapy still given in the context of acute rejection treatment remains an independent risk factor of NODAT (29,37). A recent meta-analysis of 30 randomized controlled trials showed that glucocorticoid withdrawal (discontinuation after some months) was not associated with a reduction of NODAT incidence, whereas avoidance (no steroids at all after transplantation) resulted in less NODAT requiring any treatment. However, both steroid-sparing strategies were associated with higher acute rejection rates and higher risk of graft loss excluding death (38). Therefore, in patients at high risk of NODAT, a glucocorticoid minimization strategy should be balanced with the immunological risk profile to avoid acute rejection and graft loss.

CNIs are diabetogenic by inducing a defect in insulin secretion by interfering with the nuclear factor of activated T-cell signaling in pancreatic β-cells. This pathway triggers the expression of genes critical for β-cell function, including at least six genes mutated in hereditary forms of monogenic diabetes (39). Tacrolimus induces a reversible suppression of insulin secretion at the level of insulin mRNA obviously do not prove causality, and hypomagnesemia might merely represent a surrogate marker or be a consequence of insulin resistance, inflammation, or endothelial dysfunction, which are all risk factors for diabetes in the general population.
| Gene (official symbol) | Polymorphism | N   | Reference | Association with NODAT |
|------------------------|--------------|-----|-----------|------------------------|
| Glucokinase (GCK)      | All exons/introns | 58  | Nam et al. (61) | One had one new mutation in exon 5, one had a mutation in intron 7 |
| Apolipoprotein C-III (APOC3) | Ser1 | 110 | Rodrigo et al. (62) | No |
| Apolipoprotein E (APOE)  | e2/e3/e4  | 110 | Rodrigo et al. (62) | No |
| Interferon-gamma (IFNG) | +874 | 278 | Babel et al. (63) | AA genotype is associated with NODAT* |
| Interleukin 10 (IL10)   | −1082 | 278 | Babel et al. (63) | No |
| Vitamin D receptor (VDR) | TaqI | 70  | Numakura et al. (18) | NODAT associated with TaqI |
|                        | Apal |     |           | No |
|                        | BsmI |     |           | No |
|                        | G866A |   |           | No |
| CYP3A5                 | A6986G | 70  | Numakura et al. (18) | No |
| ATP-binding cassette, subfamily B, member 1 (ABCB1, alias MDR1) | C3435T | 70  | Numakura et al. (18) | No |
|                        | G2677(A/T) |   |           | No |
| Uncoupling protein 2 (UCP2) | G866A | 70  | Numakura et al. (18) | No |
| Peroxisome proliferator–activated receptor-gamma (PPARG) | Pro12Ala | 70  | Numakura et al. (18) | No |
| Adiponectin (ADIPOQ)   | T45G | 70  | Numakura et al. (18) | No |
|                        | A349G |    |           | No |
| Angiotensin 1 converting enzyme (ACE) | I/D | 70  | Numakura et al. (18) | No |
| Angiotensinogen (AGT)  | M235T | 42  | Rodriguez-Moreno et al. (64) | TT genotype associated with NODAT* |
| Interleukin 6 (IL6)    | −174 (G>C) | 349 | Bamoulid et al. (65) | CC genotype: decreased risk of NODAT |
|                        | −174 (G>C) | 335 | Sánchez-Velasco et al. (66) | No |
|                        | −174 (G>C) | 278 | Babel et al. (63) | No |
| Tumor necrosis factor (TNF, encoding for TNF-α) | G-238A | 61  | Genço et al. (67) | (AA+GA) genotypes of G-238A: higher fasting insulin level and HOMA-IR* |
|                        | −308 | 278 | Babel et al. (63) | No |
| Transforming growth factor-beta 1 (TGFB1, alias TGF β) | codon10–869 (T/C) | 61  | Genço et al. (67) | No |
| Transcription factor 7-like 2 (TCF7L2) | rs7903146 | 589 | Kang et al. (30) | OR CT genotype: 1.71 |
|                        | 1,076 | Ghisdal et al. (29) | OR CT genotype: 1.7; TT genotype: 2.42 |
|                        | 234  | Kurzawski et al. (68) | No |
|                        | 303  | Yang et al. (69) | No |
| Solute carrier family 30, member 8 (SLC30A8) | rs13266634 | 589 | Kang et al. (30) | OR CC genotype: 1.96 |
| Hematopoietically expressed homeobox (HHEX) | rs1111875 | 589 | Kang et al. (30) | OR CC genotype: 1.81 |
|                        | rs7923837 |     |           | OR GG genotype: 1.84 |
|                        | rs5015480 |     |           | OR CC genotype: 1.97 |
| CDK5 regulatory subunit associated protein 1-like (CDKAL1) | rs10946398 | 589 | Kang et al. (30) | OR CC genotype: 2.02 |
| Cyclin-dependent kinase inhibitor 2A/2B (CDKN2A/B) | rs10811661 | 589 | Kang et al. (30) | OR TT genotype: 1.66 |
| Potassium voltage-gated channel, KQT-like subfamily, member 1 (KCNQ1) | rs2237892 | 589 | Kang et al. (30) | OR TT genotype: 1.61 |
| Calpain 10 (CAPN10) | rs6030952 | 372 | Kurzawski et al. (70) | OR CT genotype: 2.45 |
| Hepatocyte nuclear factor 4 α (HNF4A) | rs2144908 | 303 | Yang et al. (69) | OR AA genotype: 1.96 |
|                        | rs1884614 |     |           | OR TT genotype: 2.44 |
| Insulin receptor substrate 1 (IRS1) | rs1801278 | 303 | Yang et al. (69) | OR AA+AG genotypes: 2.71 |

N, number of patients included. HOMA-IR, homeostasis model assessment–insulin resistance. *Association significant in univariate analysis only.
transcription, mediated by the binding of the drug to FK506 binding protein-12 and a subsequent inhibition of calcineurin in the β-cells (40). The high level of FK506 binding protein-12 present in pancreatic β-cells might explain why tacrolimus more profoundly inhibits insulin secretion than cyclosporine. Registry analyses, meta-analyses, and the prospective study of Vincenti et al. (9) showed that the risk of NODAT was significantly higher in patients on tacrolimus versus cyclosporine (12,13,41,42). The risk of NODAT related to tacrolimus is dose dependent and high trough levels enhance this risk, in particular during the early posttransplant period (37,43). The impact of the reduction of trough levels has not been evaluated prospectively. Cyclosporine is also diabetogenic but to a lesser extent. Indeed, studies comparing belatacept (a molecule that inhibits T-cell activation) with a cyclosporine-based regimen showed that NODAT developed in 6.7% of patients on cyclosporine versus 3.5% of belatacept patients at 12 months (P = 0.018) (44,45). Based on early studies reporting a high difference of incidence of NODAT between the two available CNIs, we started to switch patients with NODAT under tacrolimus to cyclosporine in our center. We showed that 42% of switched patients experienced a resolution of NODAT, whereas this never occurred in patients remaining on tacrolimus, after a follow-up of 1 year (46). Three other single-center retrospective studies reported, like our group, either a complete resolution or a significant improvement of NODAT after conversion from tacrolimus to cyclosporine in renal allograft recipients (47–49). In this context, we did set up a prospective, randomized, multicenter trial in order to further investigate this strategy (EudraCT no. 2006–001765–42).

There is now strong evidence that m-TOR (mammalian target of rapamycin) inhibitors cause alterations in glucose metabolism. This diabetogenic effect is probably due to a combination of an insulin secretion defect (toxicity to β-cells) and insulin resistance. Sirolimus has been associated with an increased risk of NODAT in large North American and European cohorts. The risk is particularly high when sirolimus is associated with a CNI (50,51). In one study, the discontinuation of CNI with replacement by sirolimus failed to improve glucose metabolism of kidney transplant recipients and was even associated with a worsening of insulin resistance and an inappropriately low insulin response (52). Experimental and clinical data on everolimus, the other m-TOR on the market, are more scant.

**MANAGEMENT OF NODAT**

**Pretransplant evaluation**

Currently, pretransplant risk assessment should be based on the phenotype and the medical history of the patient. The following factors associated with a higher risk of NODAT should be considered: an age >45 years old, a familial history of type 2 diabetes, a personal history of NODAT with previous graft or a gestational diabetes, IFG, impaired glucose tolerance, criteria for metabolic syndrome, a BMI >30 kg/m², and a positive hepatitis C serology. The screening should include an evaluation of the glucose metabolism status by FPG and/or OGTT. A recent large study (N = 889) has underlined the low sensitivity of FPG in detecting pretransplant glucose metabolism abnormalities in patients with ESRD because of insulin resistance. An FPG screening should be performed in all candidates, followed ideally by an OGTT in patients with FPG between 92 and 125 mg/dL (±50% of patients). This should allow the identification of >80% of pretransplant diabetes (53). The use of A1C is not recommended for the screening given the low sensitivity of the test in ESRD patients (53,54). Patients should be screened for risk factors before transplantation in order to prospectively tailor their immunosuppression and minimize the risk of NODAT. Patients at risk should be counseled on the importance of lifestyle intervention, including weight control, diet, and physical activity; as such strategy is efficient in patients at risk for type 2 diabetes. However, it must be acknowledged that we lack robust data showing that immunosuppression tailoring helps to prevent NODAT.

**Posttransplant monitoring of glucose metabolism status**

Recent guidelines recommend screening all kidney transplant recipients with FPG, OGTT, and/or A1C assay at least weekly for 4 weeks, every 3 months for 1 year, and annually thereafter (55). Although these guidelines do not counsel about what screening test to use, a recent large (N = 1,637, mainly white patients) prospective study performing systematic FPG, OGTT, and A1C assay at 10 weeks after renal transplantation provides rationale to use specific cutoff values in this population. NODAT was identified by FPG in only 49% of patients, and by OGTT in the remaining 51% (modified 2003 ADA criteria). Sensitivity analyses showed that performing the OGTT in patients with FPG between 95 and 125 mg/dL or with A1C ≥5.8% allows this test to be limited to 49 and 41% of patients, respectively, while still detecting ≥80% of NODAT. However, the authors did not report the mean hemoglobin level of patients and did not assess the sensitivity of the A1C cutoff value in the subpopulation of recipients with anemia (56). Therefore, screening with FPG levels should be performed at the intervals described above, and an OGTT could be considered in patients with IFG at 3 and 6 months (as the higher risk of NODAT is present during the first 6 months after transplantation). Additionally, A1C could be assessed at 3 and 6 months, and then yearly, to improve NODAT diagnostic accuracy.

NODAT patients should be monitored with A1C assay measured routinely every 3 months and with FPG at each visit. Although there is no study evaluating whether achieving a specific A1C target translates into a better survival, maintaining patients with NODAT <7% is reasonable (1). The cautious interpretation of A1C in patients with anemia should be once more emphasized. Self-monitoring of blood glucose should ideally be performed in patients treated by insulin or oral hypoglycemic agents, as in type 2 diabetic patients (1).

**Management of immunosuppression**

We suggest an algorithm for the management of immunosuppression in order to both minimize the risk of developing NODAT and improve established NODAT, based on published data (see section specific factors related to transplantation) and our own experience (Fig. 1). The choice of immunosuppression should first take into account the immunological risk of the patients in order to avoid acute rejection. In patients with a low immunological risk and a high risk of NODAT, the first choice might be a cyclosporine- or belatacept-based immunosuppressive regimen. In patients with a high immunological risk (see Fig. 1 for definition), tacrolimus is still preferred (57,58). In patients who develop NODAT, a reduction in the exposure to diabetogenic drugs such as CNIs and glucocorticoids should be done carefully and progressively. Likewise, mycophenolic acid (MPA) should be closely monitored to avoid rejection in the context
of glucocorticoid tapering. Area under the curve of MPA should be maintained between 30 and 60 mg·h·L⁻¹ (59). In tacrolimus-treated patients whose diabetes is difficult to control (A1C >7% and/or insulin requirement), a switch to cyclosporine might be considered in cases of high immunological risk, whereas a switch to belatacept might also be considered in cases of low immunological risk. Given the lower MPA exposure under cyclosporine than under tacrolimus, area under the curve of MPA should be closely monitored in switched patients.

Pharmacological management of hyperglycemia
Currently, it is considered that patients with an A1C assay ≥6.5% should start glucose-lowering agents (54). As for type 2 diabetes, a stepwise approach should be adopted. The first step includes hygienodiетetic recommendations (weight control, diet, and exercise). The second step is the initiation of an oral agent in monotherapy. The choice of the drug should take into account the patient-specific factors, graft function (some drugs or active metabolites are eliminated by the kidney), specific side effects, and potential pharmacokinetic interactions with immunosuppressive drugs (mainly interaction with CNI or m-TOR through metabolization by cytochrome P450, family 3, subfamily A, polypeptide 4/5 [CYP3A4/5]). Recommendations for all available glucose-lowering agents (beside insulin) are summarized in Table 2 (1,55,60). Almost all oral agents can be used, except for the first-generation sulfonylureas (because they accumulate and induce hypoglycemic episodes) and biguanides (because they induce lactic acidosis). Biguanides should be avoided if the glomerular filtration rate is <60 mL/min. Gliquidone, the most-prescribed agent for kidney transplants in our institution, is efficient, well tolerated, and has no interaction with immunosuppressive drugs. The third step is a combination of oral agents with different mechanisms of actions. Combination therapy has not been investigated and compared in kidney allograft recipients. The last step is the initiation of insulin with or without oral agents. If individualized goals for glucose control are not achieved within 2–4 months, lifestyle interventions should be reassessed and patients should move to the next step.

CONCLUSIONS—In summary, NODAT and IFG should be defined according to the modified ADA 2003 criteria for the diagnosis of type 2 diabetes. A1C assay is not recommended for the diagnosis. A1C assay should be used for the monitoring of NODAT, with a target <7%. A1C assay should, however, be interpreted with caution in recipients with anemia. NODAT and type 2 diabetes share many risk factors: older age, higher BMI, African or Hispanic ethnicity, family history, presence of a metabolic syndrome feature, positive HCV serology, T-variant of the TCF7L2 gene, and hypomagnesemia. The majority of NODAT cases appear during the first 6 months posttransplantation, when patients...
are treated with high doses of immunosuppression. Thus, immunosuppressive drugs (CNIs, glucocorticoids, and m-TOR inhibitors), by inducing an insulin secretion defect and insulin resistance, probably act as triggers for glucose metabolism abnormalities in patients at risk. The predictive value of a phenotypic score as well as the place of biomarkers like the TCF7L2 polymorphism or the magnesium level remain to be evaluated prospectively. Likewise, interventional strategies that might decrease the risk of NODAT and are focused on modifiable risk factors (BMI, metabolic syndrome components, and immunosuppression mainly) should be prospectively investigated. In patients at risk for NODAT or with confirmed NODAT, exposure to diabetogenic immunosuppressive drugs should be reduced carefully and be balanced with the risk of acute rejection.

Acknowledgments—L.G., M.J.A., and D.A. are supported by the Academic Erasme Fund transdisciplinary grant.

No potential conflicts of interest relevant to this article were reported.

L.G. researched data, wrote and edited the manuscript, and is the guarantor of this article. S.V.L. contributed to discussion and wrote and reviewed the manuscript. M.J.A., R.V., and D.A. contributed to the discussion and reviewed the manuscript.

References
1. Davidson J, Wilkinson A, Dantel J, et al.; International Expert Panel. New-onset diabetes after transplantation: 2003 International Consensus Guidelines. Proceedings of an international expert panel meeting, Barcelona, Spain, 19 February 2003. Transplantation 2003;75(Suppl.):SS3–SS24
2. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003, 26(Suppl.1):S5–S20
3. Genuth S, Alberti KG, Bennett P, et al.; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160–3167
4. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl.1):S62–S69
5. Sharif A, Babooal K. Diagnostic application of the A(1c) assay in renal disease. J Am Soc Nephrol 2010;21:383–385
6. Winkelmayer WC, Chandraker A. Potransplantation anemia: management and rationale. Clin J Am Soc Nephrol 2008;3 (Suppl. 2):S49–S53
7. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–1334
8. Woodward RS, Schnitzler MA, Baty J, et al. Incidence and cost of new onset diabetes mellitus among U.S. wait-listed and transplanted renal allograft recipients. Am J Transplant 2003;3:590–598
9. Vincenti F, Friman S, Scheuermann E, et al.; DIRECT (Diabetes Incidence after Renal Transplantation). Results of an international, randomized, controlled trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant 2007;7:1506–1514
10. Burroughs TE, Swindle J, Takemoto S, et al. Diabetic complications associated with new-onset diabetes mellitus in renal transplant recipients. Transplantation 2007;83:1027–1034
11. Hjelmesaeth J, Hartmann A, Leivestad T, et al. The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. Kidney Int 2006;59:588–595
12. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant 2003;3:178–185
13. Shah T, Kasravi A, Huang E, et al. Risk factors for development of new-onset
diabetes mellitus after kidney transplantation. Transplantation 2006;82:1673–1676

14. Gürsoy M, Güvener N, Köksal R, et al. Impact of HCV infection on development of posttransplantation diabetes mellitus in renal allograft recipients. Transplant Proc 2000;32:561–562

15. Kumar N, Toupane O, Buehler M, et al. Evidence that clearance of hepatitis C virus RNA after alpha-interferon therapy in dialysis patients is sustained after renal transplantation. J Am Soc Nephrol 2003;14:2092–2098

16. Hjelmesaeth J, Hartmann A, Kofstad J, et al. Glucose intolerance after renal transplantation depends upon prednisolone dose and recipient age. Transplantation 1997;64:979–983

17. Hjelmesaeth J, Sagedal S, Hartmann A, et al. Asymptomatic cytomegalovirus infection is associated with increased risk of new-onset diabetes mellitus and impaired insulin release after renal transplantation. Diabetologia 2004;47:1500–1506

18. Numakura K, Satoh S, Tsuchiya N, et al. Clinical and genetic risk factors for posttransplant diabetes mellitus in adult renal transplant recipients treated with tacrolimus. Transplantation 2005;80:1419–1424

19. Sulanc E, Lane JT, Puamula SE, Groggel GC, Wrenshall LE, Stevens RB. New-onset diabetes after kidney transplantation: an application of 2003 International Guidelines. Transplantation 2005;80:945–952

20. Lutsey PL, Pankow JS, Bertoni AG, Szlo M, Folsom AR. Serological evidence of infections and type 2 diabetes: the Multi-Ethnic Study of Atherosclerosis. Diabetes 2009;26:1147–1152

21. Chakkera HA, Hanson RL, Raza SM, et al. Pilot study: association of traditional and genetic risk factors and new-onset diabetes mellitus following kidney transplantation. Transplant Proc 2009;41:4172–4177

22. Porini E, Delgado P, Bigo C, et al. Impact of metabolic syndrome on graft function and survival after cadaveric renal transplantation. Am J Kidney Dis 2006;48:134–142

23. Bayer ND, Cochetti PT, Anil Kumar MS, et al. Association of metabolic syndrome with development of new-onset diabetes after transplantation. Transplantation 2010;90:861–866

24. Cosio FG, Kudva Y, van der Velde M, et al. New onset hyperglycemia and diabetes are associated with increased cardiovascular risk after kidney transplantation. Kidney Int 2005;67:2415–2421

25. Bergrem HA, Valderhaug TG, Hartmann A, Bergrem H, Hjelmesaeth J, Jenssen T. Glucose tolerance before and after renal transplantation. Nephrol Dial Transplant 2010;25:985–992

26. Van Laecke S, Van Biesen W, Verbeke F, De Bacquer D, Peeters P, Vanholder R. Posttransplantation hypogammaglobulinemia and its relation with immunosuppression as predictors of new-onset diabetes after transplantation. Am J Transplant 2009;9:2140–2149

27. Voight BF, Scott LJ, Steinthorsdottir V, et al.; MAGIC investigators; GIANT Consortium. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat Genet 2010;42:579–589

28. Lyssenko V, Lupi R, Marchetti P, et al. Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. J Clin Invest 2007;117:2155–2163

29. Ghisdal L, Baron C, Le Meur Y, et al. TCF7L2 polymorphism associates with new-onset diabetes after transplantation. J Am Soc Nephrol 2009;20:2459–2467

30. Kang ES, Kim MS, Kim CH, et al. Association of common type 2 diabetes risk gene variants and posttransplantation diabetes mellitus in renal allograft recipients in Korea. Transplantation 2009;88:693–698

31. Liu Z, Habener JF. Wnt signaling in pancreatic islets. Adv Exp Med Biol 2010;654:391–419

32. Talmud PJ, Hingorani AD, Cooper JA, et al. Utility of genetic and non-genetic risk factors in prediction of type 2 diabetes: Whitehall II prospective cohort study. BMJ 2010;340:b4838

33. Van Laecke S, Desideri F, Geerts A, et al. Hypogammaglobulinemia and the risk of new-onset diabetes after liver transplantation. Liver Transpl 2010;16:1278–1287

34. Corica F, Corsengo A, Lentile R, et al. Serum ionized magnesium levels in relation to metabolic syndrome in type 2 diabetic patients. J Am Coll Nutr 2006;25:210–215

35. Guerrero-Romero F, Rodriguez-Moran M. Low serum magnesium levels and metabolic syndrome. Acta Diabetol 2002;39:209–213

36. Rodriguez-Moran M, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. Diabetes Care 2003;26:1147–1152

37. Maes BD, Kuypers D, Massiean T, et al. Posttransplantation diabetes mellitus in FK-506-treated renal transplant recipients: analysis of incidence and risk factors. Transplantation 2001;72:1655–1661

38. Pascual J, Zamora J, Galeano C, Royuela A, Quereda C. Steroid avoidance or withdrawal for kidney transplant recipients. Cochrane Database Syst Rev 2009 (1): CD005632

39. Heit JJ, Apelqvist AA, Gu X, et al. Calcineurin/ NFAT signalling regulates pancreatic beta-cell growth and function. Nature 2006;443:345–349

40. Tamura K, Fujimura T, Tsutsui T, et al. Transcriptional inhibition of insulin by FK506 and possible involvement of FK506 binding protein-12 in pancreatic beta-cell. Transplantation 1995;59:1606–1613

41. Heisel O, Heisel R, Balshaw R, Keown P. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. Am J Transplant 2004;4:583–595

42. Webster AC, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. BMJ 2005;331:810

43. Duijnhoven EM, Boots JM, Christiaans MH, Wolfenbuttel BH, Van Hooff JP. Influence of tacrolimus on glucose metabolism before and after renal transplantation: a prospective study. J Am Soc Nephrol 2001;12:583–588

44. Vincenzi F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BELIFT study). Am J Transplant 2010;10:535–546

45. Durrbach A, Festana JM, Pearson T, et al. A phase III study of belatacept versus cyclosporine in kidney transplant patients from extended criteria donors (BELIFT-EXT study). Am J Transplant 2010;10:347–357

46. Ghisdal L, Bouchta NB, Broeders N, et al. Conversion from tacrolimus to cyclosporine A for new-onset diabetes after transplantation: a single-centre experience in renal transplanted patients and review of the literature. Transpl Int 2008;21:146–151

47. Wyzgajal, Oldakowska-Jedynak U, Paczek L, et al. Posttransplantation diabetes mellitus under calcineurin inhibitor. Transplant Proc 2003;35:2216–2218

48. Oberholzer J, Thielle J, Hatipoglu B, Testa G, Sankary HN, Benedetti E. Immediate conversion from tacrolimus to cyclosporine in the treatment of posttransplantation diabetes mellitus. Transplant Proc 2005;37:990–1000

49. Aboujoud MS, Kumar MS, Brayman KL, Emm S, Bynon JS, OLN-452 Study Group. Neonatal rescue therapy in transplant patients with intolerance to tacrolimus. Clin Transplant 2002;16:168–172

50. Johnston O, Rose CL, Webster AC, Gill JS. Sirolimus is associated with new-onset diabetes in kidney transplant recipients. J Am Soc Nephrol 2008;19:1411–1418

51. Flechner SM, Glyda M, Cockfield S, et al. The ORION study: comparison of two sirolimus-based regimens versus tacrolimus and mycophenolate mofetil in renal allograft recipients. Am J Transplant 2011;11:1633–1644

52. Teutonico A, Schena PF, Di Paolo S. Glucose metabolism in renal transplant recipients: effect of calcineurin inhibitor
New-onset diabetes after renal transplantation

withdrawal and conversion to sirolimus. J Am Soc Nephrol 2005;16:3128–3135
53. Bergrem HA, Valderhaug TG, Hartmann A, et al. Undiagnosed diabetes in kidney transplant candidates: a case-finding strategy. Clin J Am Soc Nephrol 2010;5:616–622
54. Wilkinson A, Davidson J, Dotta F, et al. Guidelines for the treatment and management of new-onset diabetes after transplantation. Clin Transplant 2005;19:291–298
55. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9(Suppl. 3):S1–S155
56. Valderhaug TG, Jenssen T, Hartmann A, et al. Fasting plasma glucose and glycosylated hemoglobin in the screening for diabetes mellitus after renal transplantation. Transplantation 2009;88:429–434
57. Ekberg H, Tedesco-Silva H, Demirbas A, et al.; ELITE-Symphony Study. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007;357:2562–2575
58. Noel C, Abramowicz D, Durand D, et al. Daclizumab versus antithymocyte globulin in high-immunological-risk renal transplant recipients. J Am Soc Nephrol 2009;20:1385–1392
59. van Gelder T, Le Meur Y, Shaw LM, et al. Therapeutic drug monitoring of mycophenolate mofetil in transplantation. Ther Drug Monit 2006;28:145–154
60. Lubowsky ND, Siegel R, Pittas AG. Management of glycemia in patients with diabetes mellitus and CKD. Am J Kidney Dis 2007;50:865–879
61. Nam JH, Lee HC, Kim YH, et al. Identification of glucokinase mutation in subjects with post-replantation diabetes mellitus. Diabetes Res Clin Pract 2000;50:169–176
62. Rodrigo E, González-Lamuño D, Ruiz JC, et al. Apolipoprotein C-III and E polymorphisms and cardiovascular syndrome, hyperlipidemia, and insulin resistance in renal transplantation. Am J Transplant 2002;2:343–348
63. Babel N, Cherepnev G, Kowalenko A, Horstrup J, Volk HD, Reinke P. Non-immunologic complications and gene polymorphisms of immunoregulatory cytokines in long-term renal transplants. Kidney Int 2004;66:428–432
64. Rodriguez-Moreno A, Sánchez-Fructuoso AI, Ridao-Cano N, et al. Association of the genetic polymorphisms of the renin-angiotensin system with kidney graft long-term outcome: preliminary results. Transplant Proc 2005;37:3716–3717
65. Bamoulid J, Courvau C, Deschamps M, et al. IL-6 promoter polymorphism -174 is associated with new-onset diabetes after transplantation. J Am Soc Nephrol 2006;17:2333–2340
66. Sánchez-Velasco P, Rodrigo E, Fernández-Fresnedo G, et al. Influence of interleukin-6 promoter polymorphism -174 g/c on kidney graft outcome. Transplant Proc 2010;42:2854–2855
67. Gençtoy G, Kahraman S, Arici M, et al. The role of proinflammatory cytokine gene polymorphisms for development of insulin resistance after renal transplantation. Transplant Proc 2006;38:521–528
68. Kurzawski M, Dziewanowski K, Kedzierska K, Wajda A, Łapczuk J, Droźdżik M. Association of transcription factor 7-like 2 (TCF7L2) gene polymorphism with post-transplant diabetes mellitus in kidney transplant patients medicated with tacrolimus. Pharmacol Rep 2011;63:826–833
69. Yang J, Hutchinson II, Shah T, Min DI. Genetic and clinical risk factors of new-onset diabetes after transplantation in Hispanic kidney transplant recipients. Transplantation 2011;91:1114–1119
70. Kurzawski M, Dziewanowski K, Kedzierska K, Górnik W, Banas A, Droźdżik M. Association of calpain-10 polymorphism and posttransplant diabetes mellitus in kidney transplant patients medicated with tacrolimus. Pharmacogenomics J 2010;10:120–125