

# Impact of Posttransplant Diabetes Mellitus on Outcome After Transplantation

Mariarosaria Campise

U.O di Nefrologia e Dialisi – Pad. Croff, Fondazione Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, IRCCS Milan, Italy

## Abstract

*New-onset diabetes mellitus or glucose intolerance may develop frequently after kidney transplantation. Patients of African American or Hispanic ethnicity, recipients with polycystic disease, hepatitis C virus carriers, cadaver transplant recipients, older patients, and those with pretransplant glucose abnormalities are more susceptible to posttransplant diabetes mellitus. Also, immunosuppressive therapy is a strong factor for the development of post-transplant diabetes mellitus. Calcineurin inhibitors, anti-mammalian target of rapamycin agents and corticosteroids can all predispose to diabetes with different mechanisms. There is a mass of evidence that posttransplant diabetes mellitus is a main risk factor for cardiovascular events. The morbidity and mortality are increased when posttransplant diabetes mellitus is associated with one or more traditional risk factors. However, in transplant patients a number of other factors may also increase the risk for cardiovascular morbidity. Of particular relevance are the donor source, the metabolic syndrome, the life style, and anemia. Posttransplant diabetes mellitus not only is a main cause of cardiac complications, but it can also affect graft survival, particularly in the long term. Measures to prevent post-transplant diabetes mellitus and its consequences include early diagnosis of diabetes mellitus and of cardiovascular complications, tailored immunosuppression, and dietetic-hygienic recommendations, particularly in obese and elderly patients. (Trends in Transplant. 2007;1:104-12)*

Corresponding author: Mariarosaria Campise, [campise@policlinico.mi.it](mailto:campise@policlinico.mi.it)

## Key words

**Posttransplant diabetes mellitus. Cardiovascular risk. Outcome.**

### Correspondence to:

Mariarosaria Campise  
U.O di Nefrologia e Dialisi – Pad. Croff  
Fondazione Ospedale Maggiore Policlinico  
Via della Commenda,15  
20122 Milan, Italy  
E-mail: [campise@policlinico.mi.it](mailto:campise@policlinico.mi.it)

## **Introduction**

Transplantation confers the highest survival benefit among the different renal replacement therapies<sup>1,2</sup>, but renal transplant recipients have a high mortality rate mainly due to cardiovascular (CV) complications<sup>3</sup> secondary to accelerated atherosclerosis<sup>4</sup>. Risk factors for cardiovascular disease (CVD) in the general population, such as hypertension, hyperlipidemia, and cigarette smoking, are predictive of increased CV risk also among transplanted patients; in addition, the development of new onset diabetes mellitus (DM) dramatically elevates this risk<sup>5-7</sup>. The incidence, risk factors, and clinical relevance of posttransplant diabetes mellitus (PTDM) vary among reports<sup>7</sup>. Variation in the incidence may be explained partially by differences in the definition, follow-up times, race, age, and immunosuppressive therapy. However, according to the American Diabetes Association (ADA) criteria for diagnosis of DM<sup>8,9</sup>, up to 25% of renal transplant recipients can develop diabetes in the first few years after transplantation<sup>7</sup> and the incidence progressively increases with the duration of the follow-up<sup>10</sup>. Risk factors for development of PTDM include: African American and Hispanic ethnicity, age at transplantation, deceased kidney donor, hepatitis C infection, autosomal dominant polycystic kidney disease, abnormal glucose metabolism before transplantation<sup>11-16</sup>, and the immunosuppressive therapy. Posttransplant diabetes mellitus is caused by the simultaneous presence of insufficient insulin secretion due to the direct toxic effect of most immunosuppressive drugs (calcineurin inhibitors, rapamycin-derived compounds) on the pancreatic  $\beta$ -cells, together with insulin resistance (reduced tissue response with normal insulin levels) favored by specific therapies (corticosteroid, tacrolimus), or as a condition present before transplantation that is worsened by therapy, obesity, or renal insufficiency<sup>17</sup>. After kidney

transplantation, insulin sensitivity increases, but remains significantly lower in patients with PTDM who also have reduced fasting insulin levels when compared to normoglycemic patients<sup>18</sup>.

## **Assessing the cardiovascular risk**

Although progresses in diagnosis, prevention, and treatment have improved the life expectancy of renal transplant patients with diabetes, the risk of fatal or nonfatal CV events, in particular from cardiac infarct, remains two to three times higher for diabetic than for nondiabetic transplant recipients<sup>7</sup>. Several mechanisms may contribute to accelerated atherosclerosis and CV disease in patients with type 2 diabetes. They include elevated levels of serum triglycerides and very low-density lipoprotein cholesterol, hyperinsulinemia, glycation of lipoproteins, hyperglycemia, and renal dysfunction. On the other hand, not only overt diabetes but also glucose intolerance may contribute to the formation of atherosclerotic plaque by causing glycation of low-density lipoprotein cholesterol and favoring a pro-coagulant state. Silent myocardial infarct is relatively frequent in diabetic transplant patients. Cardiomyopathy may also develop in diabetics with an apparently normal heart and with normal coronarography. Peripheral obliterative arteriopathy is frequent. Apart from CV complications, diabetes may also expose transplant patients to retinopathy, neuropathy, foot ulcers, and infections.

The actual prevention of CV disease relies on the reduction of the overall absolute risk. The traditional CV risk factors derived by Framingham studies are widely used in the general population, but cannot fully explain the increased incidence of CV events among renal transplant recipients. In these patients, the predictive value of this risk calculator can be modified by survival bias or nontraditional risk factors such as hyperho-

mocysteinemia<sup>19</sup>. In a recent study, the predictive value of the Framingham Heart Study calculator<sup>20</sup> proved to be excellent for transplanted patients with a low coronary risk, predicting 11 coronary events for 10 expected, but by contrast it was underestimating the coronary events in high-risk patients: 16 events for seven expected. This may be explained by the impact of nontraditional CV risk factors such as C-reactive protein, fibrinogen, albumin, creatinine clearance and urinary protein excretion in the high-risk patients accounting for the 6.4% incidence of observed CV events versus 2.8% expected<sup>21</sup>. The presence of PTDM was associated with a relative risk (RR) of 1.34 for adverse events in the Cox regression analysis. After adjusting for confounding variables (age, serum C-reactive protein level, and serum high-density lipoprotein concentration), the RR was not significantly modified.

As pointed out before, also the presence of hyperglycemia without an overt diabetic status is related to CVD and mortality<sup>22</sup>. Using the ADA definition for the diagnosis of diabetes, Cosio<sup>23</sup> assessed the incidence of hyperglycemia after transplantation and tried to determine the risk for CV complications in these patients. At the end of the first month after transplantation, impaired fasting glycaemia and PTDM were present in 163 (34%) and 68 (14%) patients, respectively, without changes in the percentages at the end of the first year. Fasting glucose levels > 100 mg/dl were significantly associated with a higher incidence of posttransplant cardiac and peripheral vascular disease events. Since some of the patients with hyperglycemia or PTDM at the first month were no longer hyperglycemic during the follow-up, the incidence of CV events was significantly higher in patients with persistent PTDM but not in those who returned normoglycemic. The incidence of CV events in patients with resolved PTDM was 10%, compared to 11% for normoglycemic patients and 23% for patients with PTDM.

## Donor source

A number of variables may contribute to the deleterious effects of PTDM on CV morbidity. The donor source has a well-known impact on long-term patient and graft survival. Long-term survival of patients receiving a living-donor kidney transplantation is significantly higher than non living-donor recipients<sup>24</sup>. Factors that explain such a favorable outcome are: the quality of the kidney itself, the lower ischemia-reperfusion injury that may reduce the upregulated expression of human leukocyte antigens on endothelial and tubular cell, the avoidance of the cytokine and chemokine storm caused by brain death, and finally, the reduced incidence of acute and chronic rejection. Some organ and recipients characteristics such as younger age, less dialysis time if any, less immunologic complications, lower steroid use, and better adherence to prescriptions may explain the lower incidence of PTDM in living transplantation<sup>25</sup>. In a study on 1349 patients receiving 1400 living-kidney transplants, aimed at evaluating the risk factors for death with a functioning graft, the cumulative incidence of PTDM was 9.6%. Of 131 patients who died with a functioning graft, 30 had PTDM and 20.4% of them died within the first year. At multivariate analysis, PTDM failed to be associated with death. However, deaths due to CV events were analyzed separately without any mention of the causes of death among PTDM patients. One can only assume that other non-referred comorbidities must have played an important role on the outcome<sup>26</sup>.

## The metabolic syndrome

Overt diabetes and glucose intolerance are often associated with the metabolic syndrome (MS). The concept of MS was introduced in 1988 by Reaven, et al.<sup>27,28</sup>. The diagnosis of MS requires the presence of three or more of the following criteria: vis-

ceral obesity (waist circumference > 102 cm for men and > 88 cm for women), hypertension (blood pressure > 130/80 or use of antihypertensive medication), dyslipidemia (serum triglycerides > 1.70 mmol/l, serum high-density lipoprotein cholesterol < 103 mmol/l in men and 129 in women) and abnormal fasting glucose levels (> 6.1 mmol/l), with insulin resistance as the common abnormality. Several studies linked the MS with CV risk and diabetes to the general population and to the presence of renal disease<sup>29-31</sup>. In a recent study, transplant patient survival was significantly lower in the presence of MS. Patients with MS were significantly older, received an older donor kidney, and had a longer follow-up<sup>32</sup>. A limitation of this study is that the definition of MS did not include high-density lipoprotein cholesterol<sup>33</sup>, thus leading to an underestimation of the prevalence of the MS among this cohort of patients. The second point that needs to be taken into account is the limited number of events (a total of eight deaths), which precluded a multivariate analysis of patient survival. Nevertheless, although retrospective, the study has the importance of evidencing MS as a cluster of potentially modifiable risk factors for PTDM, chronic graft dysfunction, and graft loss in renal transplant recipients.

## **Lifestyle**

Unhealthy, modifiable lifestyle practices can increase the CV risk. In a population of 214 patients with a 10% incidence of PTDM, the overall 16% prevalence of CV events was higher in the PTDM group: 33% compared with 19% for the pretransplant DM. The pretransplant DM patients had a higher hemoglobin A1c and a higher pretransplant body mass index than the PTDM group. The PTDM patients, instead, were smokers (36 vs. 0%) and this sole significant difference seems to explain the increased CV events in the PTDM group, possibly

through the increase of microinflammation markers and the increased need for antihypertensive and hypolipidemic drugs<sup>34</sup>.

## **Anemia**

Anemia may also contribute with PTDM to CVD. In a European cross-sectional survey involving 4263 transplanted patients in 16 countries, anemia (defined as hemoglobin levels < 13 g/dl for men and < 12 g/dl for women) is reported with a prevalence of 38.6%. Although 8.5% of patients were severely anemic, treatment was given only to 17.8% of them<sup>35</sup>. In other studies using different thresholds and times of measurement, anemia after transplantation ranged between 20 and nearly 40%, being very common especially among African American patients<sup>36,37</sup>. There is a strong association between hemoglobin levels and poor graft function, but additional transplant-associated factors also contribute to anemia development. Among them, bone marrow suppression, either drug-related (angiotensin converting enzyme inhibitors/angiotensin receptor blockers, mofetil mycophenolate, azathioprine, sirolimus) or infection-related (parvovirus B19), female sex, folate and vitamin B<sub>12</sub> deficiency, malignancy, erythropoietin resistance, and absolute (mainly blood loss) or functional (uremia or chronic inflammation) iron deficiency<sup>38</sup>. Low ferritin (< 100 ng/ml) has been detected in 50% of transplanted anemic patients with chronic kidney disease (CKD) stage 3-5 but not in stage 1<sup>39</sup>. Anemia develops earlier, more frequently, and more severely in patients with diabetic kidney disease<sup>40</sup>. Reduced hemoglobin levels independently identify patients with increased CV morbidity and mortality, hypertension, and microvascular complication. However, anemia is not a risk factor for any outcome in diabetic patients, but becomes a risk factor for adverse outcome if CKD is present. The association CKD/anemia has a hazard ratio

(HR) of 1.7 for composite outcome (myocardial infarction/fatal coronary heart disease), 1.81 for stroke, and 1.88 for all-cause mortality<sup>41</sup>. To the best of our knowledge, there is no study making the same correlation with PTDM patients. But as PTDM is similar to type 2 DM, we can reasonably assume that the appearance of anemia in patients with PTDM may have the same unfavorable impact in the presence of kidney graft dysfunction. In a recent, single-centre, five-year prospective study designed as a follow-up of 503 patients with type 2 diabetes, in addition to standard management, a full blood count was obtained at each routine visit<sup>42</sup>. No intervention was undertaken to modify hemoglobin levels. At baseline, 12% of patients had anemia, and 13% developed anemia during follow-up. Overall hemoglobin levels decreased by  $0.07 \pm 0.01$  g/dl/year. In patients with anemia managed conservatively, hemoglobin levels decreased by  $0.09 \pm 0.03$  g/dl/year and this decrease was associated with hemoglobin A1c levels, but not with renal function. The greatest decreases in hemoglobin levels were seen in patients with microalbuminuria, renal impairment, or established macrovascular disease at baseline. Patients with an estimated glomerular filtration rate  $> 90$  ml/min/1.73 m<sup>2</sup> or normal albuminuria had stable hemoglobin levels during the five-year follow-up. The authors conclude that anemia is the endpoint of a process that begins with the initiation of vascular damage. These studies show that anemia is an important nontraditional risk factor for increasing CV events in high-risk populations such as PTDM patients. Prospective studies are needed to establish if early anemia correction can achieve a reduction of CV events in transplant recipient.

## Homocysteine

Homocysteine (Hcy) is an atherogenic amino acid that is associated with increased

risk of ischemic heart disease also in general population<sup>43</sup>. The presence of moderate hyperhomocysteinemia is an independent risk factor for CVD among renal transplant recipients. Hyperhomocysteinemia is inversely related to graft function. The increase of 1  $\mu$ mol/l of Hcy increases the risk of CVD by 6%<sup>44</sup>. The mean plasma total Hcy (tHcy) level is usually low or normal in DM patients. However, when nephropathy is present the tHcy levels tend to be higher than in non-DM patients. An independent association with tHcy and CVD was shown in retrospective studies for DM patients. Prospective studies showed an association between elevated tHcy and all-cause mortality in DM patients. In general, the association between elevated levels of tHcy and the outcome was stronger than in non-DM individuals for all types of study<sup>45</sup>. In a prospective study assessing the potential role of PTDM in the development of atherosclerotic adverse events in transplanted patients, the presence of tHcy levels  $> 21$   $\mu$ mol/l was directly associated with adverse events, carrying a relative risk of 4.67<sup>46</sup>. The correction of hyperhomocysteinemia with high vitamin B<sub>12</sub> doses or with folic acid has not yet proven to be associated with a CVD risk reduction. The ongoing FAVORIT (Folic Acid for Vascular Outcome Reduction in Renal Transplantation) trial will probably address this question, but until then there is no evidence that treating moderate hyperhomocysteinemia can be really useful.

## Impact on graft function

The development of PTDM is not devoid of consequences on the allograft outcome. In a series, the 12-year graft-survival rate in diabetic patients was as low as 48% compared to 70% in transplant patients without PTDM. At Cox regression analysis, PTDM was a significant predictor of graft loss, carrying a relative risk of 3.72, independently of age, sex, and race<sup>6</sup>. In another study, glyce-

mic levels one year after transplantation did not significantly relate with graft survival, but were related to higher uncensored graft survival<sup>23</sup>. Porrini, et al.<sup>32</sup> analyzed the prevalence of MS and its evolution to diabetes, influence on graft function, graft and patient survival, and the relevance of each MS component on the outcome. This retrospective analysis was conducted on 230 patients with a minimum follow-up of 18 months beyond one year posttransplant who received a deceased-donor kidney between 1995 and 2001. Metabolic syndrome was diagnosed in 37.7% of patients at baseline and was significantly associated with the development of PTDM during follow-up. Components associated with this complication were higher body mass index and triglyceride levels. Metabolic syndrome was an independent risk factor for decreasing inverse serum creatinine, with a hazard ratio of 2.6 for a 30% decrease in 1/creatinine. Graft survival was significantly lower among patients with MS at univariate analysis as well as at multivariate Cox analysis, with a hazard ratio of 3-4.5 in different models. On the other hand, not all the components of the MS contribute equally to the impaired long-term graft function. In a multivariate analysis conducted by de Vries, et al.<sup>47</sup>, only systolic blood pressure and hypertriglyceridemia were independently associated with impaired renal allograft function beyond one year after transplantation.

## **Preventive measures**

Prevention of any complication is by far the best way to avoid it. However, preventive measures are not always easy to apply, particularly with PTDM in which only a few factors contributing to its development are modifiable. The only potentially successful preventive measure on non-modifiable factors is an early diagnosis and, among the modifiable ones, a tailored immunosuppression in high-risk patients.

The impact of early diagnosis on CV disease is not well described. In a prospective observational study, the long-term effects of early diagnosed PTDM on major adverse cardiac events (MACE) and patient survival was investigated. Three months after transplantation and during a period of 16 months, diabetes and CV risk factors were assessed in 201 consecutive kidney transplant recipients. Follow-up data were obtained from the national (Norwegian) registry. The eight-year cumulative incidence of MACE was 7% in recipients without diabetes, 20% in patients with PTDM, and 21% in patients diabetic before transplantation. Proportional hazard regression analyses showed that patients with PTDM had an approximately three-fold increased risk of MACE as compared with nondiabetic patients. Eight-year patient survival was 80% in the nondiabetic group, 63% in the PTDM group, and 29% in the DM group, respectively. Pretransplant diabetes (HR: 5.09), age (HR: 1.03), cytomegalovirus (CMV) infection (HR: 2.66) and creatinine clearance (HR: 0.98), but not PTDM (HR: 1.20), were independent predictors of death in the multiple Cox regression model. Early diagnosed PTDM has been demonstrated to be a predictor of MACE, but not of all-cause mortality in the first eight years after renal transplantation<sup>48</sup>.

Posttransplant DM and its long-term complications have emerged as major adverse effects of immunosuppression, responsible for increased morbidity and mortality among solid-organ transplant patients and particularly kidney transplanted patients<sup>49,50</sup>. The mechanisms through which immunosuppressants exert their diabetogenic effect are different, though. Cyclosporine and tacrolimus cause PTDM, decreasing insulin secretion via a direct toxic effect on the pancreatic  $\beta$ -cells<sup>51,52</sup>. For corticosteroids, the induction of insulin resistance seems to be the predominant factor<sup>53</sup>. Still controversial is the action of rapamycin-derived com-



pounds. Through an immunophilin-mediated, calcineurin-independent mechanism, there would be an initial increase of insulin secretion that would diminish afterwards through the same pathway<sup>54</sup>.

The development of PTDM has also emerged as a major concern among selected populations such as elderly and obese patients who are a growing number in transplant waiting lists and are both already at increased risk of CV disease. A number of modifiable factors have been identified for intervention in these patients. Pretransplantation dietary restriction and exercise to achieve a correct body weight are strongly recommended<sup>55</sup>. After transplantation, tight blood pressure control<sup>56</sup>, early hyperlipidemia treatment<sup>57</sup>, and the choice of an immunosuppressive therapy with minimal effects on glucose metabolism can also reduce the risk of PTDM. Attempts to modify doses and regimens of tacrolimus and corticosteroids, especially when used in combination, or even to avoid them have been successful, but should be considered before transplantation after balancing the therapy against the occurrence of rejection. New-onset DM has decreased from 20 to 1.4% when tacrolimus is used at reduced doses and in monotherapy<sup>58</sup>. The incidence of PTDM with mTOR inhibitor therapy has been reported in some 10% of cases with calcineurin inhibitor (CNI) avoidance immunosuppressive schedules<sup>59</sup>. On the contrary, when conversion treatment is done after CNI avoidance, the effect on glucose metabolism seems to be more detrimental than positive; shift to rapamycin would produce an increased insulin resistance together with a higher number of new-onset diabetes<sup>60</sup>.

## Conclusion

Although patient and graft survival is continuously improving, some degree of

mortality risk remains as a consequence of comorbid conditions that may be present at transplantation or develop thereafter. Among the latter, the new onset of DM brings a negative impact on long-term outcomes. Transplant specialists and patients should both take responsibility in the management if this complication develops. Correction of potentially modifiable factors, early diagnosis, and tight glycemic control are mandatory in ameliorating the overall health status and reducing the risk of late graft failure and mortality.

## References

1. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999;341:1725-30.
2. Medin C, Elinder GC, Hylander B, et al. Survival of patients who have been on a waiting list for renal transplantation. *Nephrol Dial Transplant* 2000;15:701-4. \**Comparison of survival of all replacement therapy patients accepted for kidney transplantation and either transplanted with cadaver or living donor or remained on chronic dialysis. Transplantation carries better long-term survival.*
3. Briggs JD. Causes of death after renal transplantation. *Nephrol Dial Transplant* 2001;16:1545-9. \**The paper focuses on the causes of death after transplantation using the USRDS and the ERA-EDTA data bases and two single centre European studies. Although there is a decreased mortality particularly in the early post transplant period, cardiovascular disease is the first cause of death among transplanted patients but using adequate preventive measures, the reduction of cardiovascular deaths seems to be feasible at least in the medium term.*
4. Kasiske BL. Ischemic heart disease after renal transplantation. *Kidney Int* 2002;61:356-69. \*\**Very interesting nephrology forum with an emblematic case-report followed by a discussion about traditional and non traditional factors increasing the CV risk among patients with chronic renal failure. The paper also points out the importance of screening before transplantation and the importance of immunosuppression.*
5. Kasiske BL. Epidemiology of cardiovascular disease after renal transplantation. *Transplantation* 2001;72:S5-8.
6. Miles AMV, Sumrani N, Horowitz R, et al. Diabetes mellitus after transplantation: as deleterious as non-transplant-associated diabetes? *Transplantation* 1998;65:380-4.
7. Kasiske B, Snyder J, Gilbertson D, Matas A. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 2003;3:178-85. \*\**Data from USRDS about incidence and consequences of PTDM among patients transplanted between 1996 and 2000. Identification of risk factors including tacrolimus therapy, and importance of tailored immunosuppression particularly in high-risk patients.*
8. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2002;25(Suppl 1):S1-147.
9. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; 20:1183-97.
10. Cosio FG, Pesavento TE, Osei K, Henry LM, Ferguson R. Posttransplant diabetes mellitus: Increasing incidence in renal allograft recipients transplanted in recent years. *Kidney Int* 2001;59:732-7. \*\**Single centre study population paper analysing the incidence, the risk factors and the out-*

## Mariarosaria Campise: Impact of Posttransplant Diabetes Mellitus on Outcome After Transplantation

- come of new onset diabetes mellitus in 2078 patients divided in two groups according to the year of transplantation: before and after 1995. PTDM increases with the time probably because of the changing of patients characteristics and the introduction in 1995 of a better absorbed CsA formulation with consequent higher blood levels and cumulative exposure.
11. Sumrani NB, Delaney V, Ding Z, et al. Diabetes mellitus after renal transplantation in the cyclosporine era—an analysis of risk factors. *Transplantation* 1991;51:343-7.
  12. De Mattos AM, Olyaei AJ, Prater JC, et al. Autosomal-dominant polycystic kidney disease as a risk factor for diabetes mellitus following renal transplantation. *Kidney Int* 2005; 67:714-20.
  13. Ducloux D, Motte G, Vautrin P, et al. Polycystic kidney disease as a risk factor for posttransplant diabetes mellitus. *Nephrol Dial Transplant* 1999;14:1244-6.
  14. Yildiz A, Yazici H, Akkaya V, et al. Association between HCV infection and development of posttransplantation diabetes mellitus in renal transplant recipients. *Transplantation* 2002;74:1109-13.
  15. Bloom RD, Rao V, Weng F, et al. Association of Hepatitis C with posttransplant diabetes in renal transplant patients on tacrolimus. *J Am Soc Nephrol* 2002;13:1374-80.
  16. Sulanc E, Lane JT, Puumala SE, Grogger GC, Wrenshall LE, Stevens B. New-onset diabetes after kidney transplantation: an application of 2003 International guidelines. *Transplantation* 2005;80:945-952.
  17. Markell M. New-onset diabetes mellitus in transplant patients: pathogenesis, complications, and management. *Am J Kidney Dis* 2004;43:953-65.
  18. Nam JH, Mun JL, Kim SL, et al. Beta-cell dysfunction rather than insulin resistance is the main contributing factor for the development of post renal transplantation diabetes mellitus. *Transplantation* 2001;71:1417-23.
  19. Ducloux D, Motte G, Challier B, et al. Serum total homocysteine and cardiovascular disease in chronic stable renal transplant recipients: a prospective study. *J Am Soc Nephrol* 2000;11:134-7. *\*Elevated fasting homocysteine levels are a non traditional risk factor for increased cardiovascular risk. In this prospective, single centre study, the association between atherosclerotic events and homocysteine concentrations was examined. High homocysteine levels are an independent risk factor for the development of cardiovascular events in chronic stable renal transplant recipients.*
  20. Mosterd A, D'Agostino RB, Silbershats H, et al. Trends in the prevalence of hypertension, antihypertensive therapy, and left ventricular hypertrophy from 1959 to 1989 *New Engl J Med* 1999;340:1221-7.
  21. Ducloux D, Kazory A, Chalopin JM predicting coronary heart disease in renal transplant recipients: a prospective study. *Kidney Int* 2004;66:441-7.
  22. The DECODE Study Group: Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and non cardiovascular disease? *Diabetes Care* 2003;26:688-96.
  23. 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;67:2415-21. *\*The paper analyses the implications of developing hyperglycemia of lesser severity than overt diabetes mellitus, and shows that the appearance of fasting glucose levels above 100 mg/dl any time after the first month post-transplant, is associated with increasing cardiovascular risk.*
  24. Cecka JM. The UNOS renal transplant registry. Cecka JM, Terasaki PI, et al. *Clin Transplant* 2000: UCLA Tissue Typing Laboratories, Los Angeles: 2001;1-18.
  25. Kasiske B, Snyder JJ, Matas AJ, et al. Preemptive kidney transplantation: the advantage and the advantaged. *J Am Soc Nephrol* 2002;13:1358-64. *\*Preemptive kidney transplantation is associated with improved patient and graft survival for both cadaver and living donor. These patients are also at lesser risk of short and long term complication such as PTDM.*
  26. El-Agroudy AE, Bakr MA, El-Dein ABS, Ghoneim MA. Death with functioning graft in living donor kidney transplantation: analysis of risk factors. *Am J Nephrol* 2003;23:186-93.
  27. Reaven GM. Banting lecture: Role of insulin resistance in human disease: 1988. *Diabetes* 1988;37:1595-607. *\*\*Important paper that introduces for the first time the concept of metabolic syndrome sustained by insulin resistance.*
  28. Reaven GM. Multiple CHD risk factors in type 2 diabetes: beyond hyperglycemia. *Diabetes Obes Metab* 2002;4: S13-18.
  29. Schillaci G, Pirro M, Vaudo G, et al. Prognostic value of the metabolic syndrome in essential hypertension. *J Am Coll Cardiol* 2004;43:1817-22.
  30. Chen J, Munter P, Hamm L, et al. Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. *J Am Soc Nephrol* 2003;14:469-77.
  31. Zoccali C. Traditional and emerging cardiovascular and renal risk factors: an epidemiologic perspective. *Kidney Int* 2006;70:26-33.
  32. Porrini E, Delgado P, Bigo C, et al. Impact of metabolic syndrome on graft function and survival after cadaveric renal transplantation. *Am J Kid Dis* 2006;48:134-42.
  33. Anonymous. Third report of the national cholesterol educational program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Cholesterol in Adults (Adult Treatment Panel III) Final report. *Circulation* 2002; 106:3143-241.
  34. Diaz JM, Sainz Z, Gich I, et al. Cardiovascular risk factors in diabetic patients with renal transplants. *Transplant Proc* 2005;37:380-4.
  35. Vanrenterghem Y, Ponticelli C, Morales JM, et al. Prevalence and management of anemia in renal transplant recipients: A European survey. *Am J Transplant* 2003;3:835-45. *\*\*The paper documents the prevalence and the management of anemia in kidney transplant patients. Data from 72 transplant centres in 16 countries were screened and it appeared that the incidence of anemia is surprisingly high, reaching almost 40%. Of the 8.5% of patients with severe anemia only 17.8% received treatment.*
  36. Moore LW, Smith SO, Winsett RP, et al. Factors affecting erythropoietin production and correction of anemia in kidney transplant recipients. *Clin Transplant* 1994;8:358-64.
  37. Shibagaki Y, Shetty A. Anemia is common after kidney transplantation, especially among African Americans. *Nephrol Dial transplant* 2004;19:2368-73.
  38. Afzali B, Al-Khoury S, Shah N, Mikhail A, et al. Anemia after renal transplantation *Am J Kidney Dis* 2006;48:519-36. *\*\*Detailed review on anemia after kidney transplantation, aimed at appraising the available literature on the topic and concentrating on etiopathogenesis, effects on morbidity and mortality, and rationale for intervention and treatment.*
  39. Karthikeyan V, Karpinski J, Nair RC, Knoll G. The burden of chronic kidney disease in renal transplant recipients. *Am J Transplant* 2003;4:262-9.
  40. Bosman DR, Winkler AS, Marsden JT, Macdougall IC, Watkins PJ. Anemia with erythropoietin deficiency occurs early in diabetic nephropathy. *Diabetes Care* 2001;24:495-9.
  41. Vlagopoulos PT, Tighiouart H, Weiner DE, et al. Anemia as a risk factor for cardiovascular disease and all-cause mortality in diabetes: the impact of chronic kidney disease. *J Am Soc Nephrol* 2005;16:3403-10.
  42. Thomas MC, Tsalamandris C, Maclsaac RJ, Jerum G. The epidemiology of hemoglobin levels in patients with type 2 diabetes *Am J Kidney Dis* 2006;48:537-45.
  43. Clarke R, Daly L, Robinson K, et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. *N Engl J Med* 1991;324:1149-55. *\*First important paper demonstrating that hyperhomocysteinemia is an independent risk factor for vascular disease, and in most instances, is probably due to cystathionine beta-synthase deficiency.*
  44. Friedman AN, Rosenberg IH, Selhub J et al. Hyperhomocysteinemia in renal transplant recipients. *Am J Transplant* 2002;2:308-13. *\**
  45. Audelin MC, Genest J Jr. Homocysteine and cardiovascular disease in diabetes mellitus. *Atherosclerosis* 2001; 159:497-511.
  46. Ducloux D, Kazory A, Chalopin JM. Posttransplant diabetes mellitus and atherosclerotic events in renal transplant recipients: a prospective study. *Transplantation* 2005; 79:438-43.



47. De Vries APJ, Bakker SJL, van Son WJ, et al. Metabolic syndrome is associated with impaired long-term renal allograft function; not all component criteria contribute equally. *Am J Transplant* 2004;4:1675-83.
48. Hjelmsaeth J, Hartmann A, Leivestad T, et al. The impact of early-diagnosed new-onset posttransplantation diabetes mellitus on survival and major cardiac events. *Kidney Int* 2006;69:588-95.
49. Cosio FG, Pesavento TE, Sunny K, Osei K, Henry LM, Ferguson R. Patient survival after renal transplantation: IV. Impact of posttransplant diabetes. *Kidney International* 2002;62:1440-6.
50. Jindal RM, Hjelmsaeth J. Impact and management of posttransplant diabetes mellitus. *Transplantation* 2000;70:S58-63.
51. Heisel Olaf, 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;4:583-95. *\*Meta-analysis evaluating the reported incidence of new onset diabetes mellitus after solid-organ transplantation in patients treated with calcineurin inhibitors.*
52. Gillison SL, Bartlett ST, Curry DL. Inhibition by cyclosporine of insulin secretion a beta cell-specific alteration of islet tissue function. *Transplantation* 1991;52:890-5. *\*Important experimental paper demonstrating that cyclosporine inhibits insulin secretion via an alteration of the islet tissue function, specific for insulin release.*
53. Gunnarsson R, Arner P, Lundgren G, et al. Diabetes mellitus a more-common-than- believed complication of renal transplantation. *Transplant Proc* 1979;11:1280-1.
54. Fuhrer DK, Kobayashi M, Jiang H. Insulin release and suppression by tacrolimus, rapamycin and cyclosporin A are through regulation of the ATP-sensitive potassium channel. *Diabetes Obes Metab* 2001;3:393-402.
55. Parikh CR, Klem P, Wong C, et al. Obesity as an independent predictor of posttransplant diabetes mellitus. *Transplant Proc* 2003;35:2922-6. *\*This is a retrospective, single centre, small sample, analysis demonstrating that obesity is and independent predictor of diabetes after transplantation. It is also, among all the risk factors, the only one that can be effectively modified before transplantation*
56. Kasiske BL, Anjum S, Shah R, et al Hypertension after kidney transplantation *Am J Kidney Dis* 2004;43:1071-81.
57. Sahadevan M, Kasiske BL. Hyperlipidemia in kidney disease: causes and consequences *Curr Opin Nephrol Hypertens* 2002;11:323-9. *\*Interesting review on dyslipidemias in chronic kidney disease. Analysis of causes and consequences particularly of the association between dyslipidemia in patients with chronic renal failure and transplantation.*
58. Duclos A, Flechner LM, Faiman C, Flechner SM. Posttransplant diabetes mellitus: risk reduction strategies in the elderly. *Drugs Aging* 2006;23:781-93.
59. Larson TS, Dean PG, Stegall MD, et al. Complete avoidance of calcineurin inhibitors in renal transplantation: a randomized trial comparing sirolimus and tacrolimus. *Am J Transplant* 2006;6:514-22.
60. Teutonico A, Schena PF, Di Paolo S. Glucose metabolism in renal transplant recipients: effect of calcineurin inhibitor withdrawal and conversion to sirolimus. *J Am Soc Nephrol* 2005;16:3128-35.