Donors at risk: impaired glucose tolerance

GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **All potential living kidney donors should have a fasting plasma glucose level performed on at least two occasions. If the levels are:**
  – **≥7 mmol/L on both occasions then the potential donor is diabetic and this is an absolute contraindication for living kidney donation,**
  – **6.1–6.9 mmol/L on at least one occasion then this patient should have a 2 h oral glucose tolerance test (OGTT),**
  – **<6.1 mmol/L then this is normal and not a contraindication to donation.**
- **Patients at high risk for the development of type 2 diabetes mellitus (i.e. family history, age > 45 years, Aboriginal or Torres Strait Islander (ATSI) or obesity) should be screened with a 2 h OGTT.**
- **If the 2 h glucose of an OGTT results are:**
  – **≥11.1 mmol/L then the patient is diabetic and this is an absolute contra-indication to living kidney donation,**
  – **7.8–11.0 mmol/L then this patient has impaired glucose tolerance and this is an absolute contraindication to living kidney donation,**
  – **<7.8 mmol/L is normal and not a contraindication to donation.**
- **A past history of gestational diabetes is an absolute contraindication to living kidney donation.**

IMPLEMENTATION AND AUDIT

Short- and long-term living kidney donor outcomes need to be closely monitored.

BACKGROUND

The aim of this guideline is to review the available literature on the potential long-term risks of donating a kidney in the presence of pre-donation impaired glucose tolerance and develop suggestions for the management of these potential donors.

The justification for performing living kidney donation is based on the benefits of the procedure on the recipient's health and on the psyche of the donor through the act of altruism, outweighing the short- and long-term adverse outcomes on the donor. In the medical assessment of the potential donor, a critical estimation is made of their future risk of kidney failure and cardiovascular disease. If the risk is predicted to be too great then the living kidney donation should not proceed.

There is no direct evidence quantifying the outcome of patients with impaired glucose tolerance who proceed to donate a kidney for transplantation. This is primarily related to the traditional practice of not using patients with diabetes mellitus or impaired glucose tolerance as living kidney donors. Many of these recommendations are extrapolated from the documented natural history of patients with impaired glucose tolerance.

The following definitions of impaired glucose tolerance have been proposed:[1,2]

A fasting plasma glucose on two occasions of –
≥7 mmol/L indicates diabetes mellitus
6.1–6.9 mmol/L indicates impaired fasting glucose
<6.1 is normal

A standard 2 h OGTT with a 2 h glucose concentration of –
≥11.1 mmol/L indicates diabetes mellitus
7.8–11.0 mmol/L indicates impaired glucose tolerance
<7.8 mmol/L is normal.

The presence of diabetes mellitus is a contraindication for living kidney donation due to the 25–51% long-term risk of the individual developing diabetic nephropathy.[3,4] Despite the common practice of avoiding people with diabetes mellitus and impaired glucose tolerance as living kidney donors, the development of type 2 diabetes mellitus in living kidney donors is documented. Due to the lack of suitable controls, however, it is unclear if this is at an increased rate compared with normal ageing. In the event that diabetic nephropathy does develop, the reduced renal reserve in a donor will lead to a more rapid onset of end-stage kidney disease.

Chronic kidney disease does increase the risk of cardiovascular events and all cause mortality.[5] It is unclear if a similar increased risk is associated with chronic kidney

disease that has resulted from donor nephrectomy, although a rise in blood pressure seems to occur.[6] Concern would be raised as to the possibility that the chronic kidney disease that results from donor nephrectomy may have an additive or synergistic effect with impaired glucose tolerance or diabetes to increase the cardiovascular risk, adding further weight to avoiding the use of diabetics as living kidney donors.

Patients with impaired glucose tolerance have a 5-year risk of developing type 2 diabetes mellitus of 30% if they have a family history of type 2 diabetes (parent or sibling) and 10% if there is no family history.[7] This risk may be higher with certain ethnic groups (e.g. ATSI, South East Asians).[8] In addition, impaired glucose tolerance induces an increased risk of cardiovascular events even in the absence of overt diabetes mellitus, especially in the context of the metabolic syndrome.[9,10]

Patients with a history of gestational diabetes have a high risk of subsequently developing Type 2 diabetes mellitus and this is therefore a contraindication to living kidney donation.[11]

Patients with a family history of diabetes, age > 45 years, ATSI and obesity are at an increased risk for the future development of diabetes and as such consideration for screening all high-risk patients with a 2 h OGTT rather than just two fasting plasma glucose measurements should be made.[12]

SEARCH STRATEGY

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for living donor and combined with MeSH terms and text words for glucose intolerance. The search was carried out in Medline (1950–July Week 2008). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.
Date of searches: 24 July 2008.

WHAT IS THE EVIDENCE?

Outcome of living kidney donors with pre-donation impaired glucose tolerance

There are no published studies that could be located that quantify the risk to donors with impaired glucose tolerance prior to transplant nephrectomy. This likely reflects the common practice of avoiding these donors.

Incidence of diabetes in 'healthy' living kidney donors

Due to the lack of information on the outcome in living kidney donors with pre-donation impaired glucose tolerance we commenced our review by examining the incidence of type 2 diabetes mellitus in healthy living kidney donors (i.e. normal blood pressure, glomerular filtration rate > 80 mL/min and normal amount of proteinuria pre-donation). There are 11 studies that describe the development of diabetes

mellitus following living kidney donation in donors.[13–23] These studies describe an incidence of 1.5–7.4% with a follow up of more than 20 years in some studies. All of the studies suffer with the following methodological problems:
1. cross-sectional – none were designed to follow donors prospectively from the time of transplant and most examine donors cross-sectionally post transplant,
2. sampling bias – the selection of participants was primarily convenience based rather than random or complete,
3. lack of suitable controls – living donors being a healthy group of people should have better long-term outcomes than the general population and therefore should be compared with an equally healthy group of non-donors, and
4. lack of baseline information – most studies did not provide detailed blood glucose results prior to donor nephrectomy to accurately classify the donor's baseline status.

Fehrman-Ekholm et al. described 348 Swedish living kidney donors at a mean of 12 years post-donation. They represent 87% of the total living donors from Stockholm between 1964 and 1995 who were still alive. Despite normal OGTT for all donors at baseline, six developed type 2 diabetes mellitus.[13]

In another study, the authors were able to obtain information on 33% (256/773) of living kidney donors over 20 years post-donation. Of these, 19 developed type 2 diabetes mellitus, despite the 10 with a positive family history having negative baseline OGTT.[14]

It is unclear the effect donation has on the incidence of developing diabetes mellitus due to the lack of suitable controls.

The risk of developing diabetic nephropathy in patients with diabetes mellitus

Diabetic nephropathy is currently the most common cause of end-stage kidney disease in developed countries. The risk of developing diabetic nephropathy varies between studies, with one study documenting a prevalence of 25.4% for microalbuminuria and <10% for macroalbuminuria or end-stage kidney disease in 27 805 type 1 diabetic patients.[24] A similar prevalence was observed in type 2 diabetes.[3,4,25] The prevalence also seems to differ with ethnicity.[8]

The risk of developing diabetes mellitus in patients with impaired glucose tolerance

In a meta-analysis of six prospective studies, the incidence of type 2 diabetes mellitus in people with impaired glucose tolerance was 57.2 per 1000 person years.[26] The incidence however, varied considerably, depending on the ethnicity of the individual, being increased in Mexican–Americans, Hispanics and Pima Indians. This has been supported by other publications.[27]

Impaired glucose tolerance and risk of cardiovascular disease and mortality

Even in the absence of frank diabetes mellitus, impaired glucose tolerance is associated with an increased risk of

death. In a systematic review and meta-analysis performed using MEDLINE until 1996, the results of 95 783 people were collated. A fasting plasma glucose level of 6.1 mmol/L and a 2 h OGTT glucose level of 7.8 mmol/L was associated with an increased relative risk of cardiovascular events of 1.33 (95% confidence interval (CI): 1.06–1.67) and 1.58 (95% CI: 1.19–2.10), respectively, compared with a fasting plasma glucose level of 4.2 mmol/L.[9]

More recently, the Diabetes Epidemiology: Collabarotive Analysis of Diagnostic Criteria in Europe (DECODE) investigators examined 22 cohorts in Europe, totalling 29 714 people followed up for 11 years.[10] This group demonstrated that elevated fasting plasma glucose levels and 2 h plasma glucose levels were associated with a graded increased risk of mortality.

SUMMARY OF THE EVIDENCE

There is no direct evidence documenting the outcome of people with impaired glucose tolerance who subsequently donate a kidney. Diabetes mellitus is a contraindication to living kidney donation due to the high risk of the development of nephropathy and cardiovascular disease. In line with this logic, impaired glucose tolerance is in addition a contraindication to living kidney donation. This is based on the high risk of the development of diabetes mellitus in people with impaired glucose tolerance and the inherent risk of cardiovascular disease even without the development of diabetes mellitus.

WHAT DO THE OTHER GUIDELINES SAY?

INTERNATIONAL GUIDELINES:
The Amsterdam Forum on the Care of the Living Kidney Donor (2006)
. . . individuals with a history of diabetes or fasting blood glucose ≥ 7 mmol/L on at least two occasions (or 2 h glucose with OGTT ≥ 11.1 mmol/L should not donate.
The Canadian Council for Donation and Transplantation (2006)
We recommend . . . to refer to existing guidelines regarding the assessment and eligibility of potential living kidney donors (e.g. Amsterdam Forum).
European Renal Association-European Dialysis and Transplant Association (2000)
. . . exclusion criteria: . . . Diabetes mellitus . . .
UK Guidelines for Living Donor Kidney Transplantation (2005)
Diabetes mellitus is an absolute contraindication to living donation. Prospective donors with an increased risk of type 2 diabetes mellitus because of family history, ethnicity or obesity should undergo a glucose tolerance test and only be considered further as donors if this is normal.

SUGGESTIONS FOR FUTURE RESEARCH

1. Conduct prospective, controlled studies on long-term living kidney donor outcomes. Include an assessment of the incidence of impaired glucose tolerance and diabetes in donors with normal glucose tolerance pre-donation compared with controls. Assess the effect of impaired glucose tolerance on cardiovascular events, renal outcomes and mortality.
2. Set up a registry for living kidney donors. Include practice patterns of living kidney donors.

CONFLICT OF INTEREST

Neil Boudville has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

Nicole Isbel has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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OUT OF DATE

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