A potential living kidney donor with prediabetes

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CASE PRESENTATION
A 54-year-old Caucasian man wished to donate a kidney to his adult daughter, who reportedly had end-stage renal disease secondary to a glomerulonephritis of unknown origin inherited through her mother, thus ruling out any potential donors from the maternal side. As the donor and recipient transplant teams were located in separate centers, all information pertaining to the recipient was collected from the potential kidney donor himself. As a child, his daughter had received a deceased donor renal transplant, which failed for unknown reasons after 3.5 years. He was previously turned down as a donor 7 years before presentation for unknown reasons. His past medical history was significant for hyperlipidemia controlled with a statin, hypothyroidism treated with L-thyroxine, and removal of three colonic polyps 12 years before presentation. Surgical history was significant for cholecystectomy and laser-assisted in situ keratomileusis surgery. He was a nonsmoker and ingested two alcoholic drinks per day. His mother had type 2 diabetes mellitus (T2DM) and died of congestive heart failure in her eighties. On examination, body mass index was 30 kg/m² and blood pressure was 126/85. The remainder of the examination was within normal limits. Laboratory values, shown in Table 1, were consistent with the diagnosis of impaired fasting glucose (IFG). Repeat testing showed persistence of the IFG. On the basis of this diagnosis alone, his risk of future T2DM was estimated at approximately 25% in the next 3–5 years.¹ Additional diabetes risk factors included the following: obese with abdominal obesity; type 2 diabetes in first-degree relative; sedentary lifestyle.

Although they technically did not meet the American Diabetes Association criteria for diabetes risk factors, the following were also highly suggestive of increased diabetes risk: hypertriglyceridemia, elevated diastolic blood pressure.

Despite his increased risk of developing T2DM, the potential donor stated that he ‘understood the risks, but felt that his potential ability to help his daughter far outweighed this’ and that ‘there was no one else available to donate.’ He was ‘willing to do anything’ to ensure that he was able to proceed with donation. Owing to the lack of data regarding long-term risks in recommending living kidney donation in the donor with ‘prediabetes,’ the transplant team expressed concern that proceeding with donation may not be in the donor’s best health interests. However, there was an appreciation that the willingness of a parent to bear a greater risk to help his/her child cannot, and should not, be undervalued. As such, a consult was obtained from the medical bioethics service to determine the ethics of allowing this man to proceed with living kidney donation. As part of the assessment, the potential donor first explained to the ethics team his incontrovertible wish to donate a kidney to his daughter. He stated that he was fully aware that he was at risk of developing T2DM and thus potentially diabetic kidney disease, progression of which may be exacerbated by having a single kidney. He outlined his willingness to modify his lifestyle to decrease this risk, as he felt the importance of donating to his daughter far outweighed any risk to himself. He emphasized that he had made repeated visits to the clinic at the request of the transplant team to discuss the issue of prediabetes in great detail, and felt that he was in an excellent position to give informed consent with regard to the issue of donation. The transplant team then outlined the limited evidence and uncertainty surrounding proceeding with donation in a donor with IFG. The ethics team cited the principles of autonomy, beneficence, and maleficence in assessing this case and in their opinion ‘…just as the patient’s autonomous judgment must be respected, so too must the educated judgment of the renal team be respected.’ It was

Using the American Diabetes Association Diabetes Personal Health Decisions calculator² to incorporate the potential donor’s personal and family history, his 10- and 30-year risk of developing T2DM were estimated at 75 and 81%, respectively.

KEYWORDS: diabetic nephropathy; ethics; impaired fasting glucose; kidney donation; live donor; prediabetes

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Table 1: Laboratory values

<table>
<thead>
<tr>
<th>Test</th>
<th>Value (reference range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum/blood</strong></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.09 mg/dl (0.7-1.3)</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>6 mg/dl (9-25)</td>
</tr>
<tr>
<td>Fasting total cholesterol</td>
<td>157.6 mg/dl (&lt;200.0)</td>
</tr>
<tr>
<td>Fasting triglycerides</td>
<td>231 mg/dl (150-499)</td>
</tr>
<tr>
<td>Fasting high-density lipoprotein</td>
<td>46.8 mg/dl (40-60)</td>
</tr>
<tr>
<td>Fasting low-density lipoprotein</td>
<td>62.4 mg/dl (100-189)</td>
</tr>
<tr>
<td>Prostate-specific antigen</td>
<td>0.5 ng/ml (0.4-4.0)</td>
</tr>
<tr>
<td>HIV</td>
<td>Negative (negative)</td>
</tr>
<tr>
<td>Hepatitis B surface antigen</td>
<td>Negative (negative)</td>
</tr>
<tr>
<td>Hepatitis C antibody</td>
<td>Negative (negative)</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>120.9 mg per 100 ml (54-118)</td>
</tr>
<tr>
<td>2 h glucose on 75 g OGTT</td>
<td>79 mg per 100 ml (6.7 mmol/l (3.6-6.0))</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>99 ml/min/1.73 m² (&gt;90)</td>
</tr>
<tr>
<td>(99mTc-diethylenetriamine–</td>
<td></td>
</tr>
<tr>
<td>pentaetic acid clearance)</td>
<td></td>
</tr>
<tr>
<td><strong>Unite</strong></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>66 ml/min, repeat 62 ml/min (58-120)</td>
</tr>
</tbody>
</table>

OGTT, oral glucose tolerance test.

decided that to recommend donation was ethically defensible. However, as stated at the Amsterdam Forum on the Care of the Live Kidney Donor,7 obesity should be considered a potential risk factor for renal disease, though long-term data on outcomes of obese donors are lacking.7 Thus, on the advice of the transplant team and in accordance with the current guidelines,3 the patient lost 13.6 kg (30lbs) before donation, decreasing his 10-year risk of T2DM from 75 to 20%.2 The patient then successfully donated his kidney.

‘MEDICALLY COMPLEX’ LIVING DONORS
The global epidemic of end-stage renal disease has resulted in a widening gap between the supply and demand of kidney transplants.5,6 The ever-increasing waiting times for deceased-donor kidneys have focused attention on living donation as a useful way to increase the supply of organs for transplant candidates.7 However, as both living and deceased donor transplant kidneys are in short supply, many renal transplant centers are faced with evaluating potential living donors with risk factors for developing future kidney disease, a group of patients termed ‘medically complex living donors,’8 a group which includes donors with prediabetes. Living kidney donation is performed with the expectation that the risk for short- and long-term harm to the donor is minimal, although it is important to note that most published series have only included low-risk donors. In the case of the medically complex living donor, however, insufficient data about long-term outcomes and lack of consensus regarding important risk factors8–10 force transplant professionals to tailor their decisions regarding suitability for kidney donation to the particular circumstances of each donor.11

Although living donor kidney transplantation yields the best results in terms of recipient and graft survival compared with other renal replacement therapies,9 there are some risks to the donor that may be directly attributable to nephrectomy. Ever since the recognition of hyperfiltration injury in animals undergoing renal ablation,12,13 there has been concern over the renal consequences of living kidney donation.11,14–16 However, the majority of studies on live donors have not found increased risk of end-stage renal disease or mortality.17–25 Several long-term follow-up studies in humans have suggested that hyperfiltration of the remaining kidney after unilateral donor nephrectomy was not associated with increased risks of adverse effects for more than 10 years.15,18,25,26,28,29 although other studies have suggested that the risk of kidney disease is elevated in living renal donors.24,26,28–30 A recent meta-analysis suggests that a 5 mm Hg increase in blood pressure occurs within 5–10 years after donation above that anticipated with normal aging,31 and a second meta-analysis reported a slightly increased risk of proteinuria but no increase in loss of kidney function in living kidney donors,32 although these results could reflect—at least in part—surveillance bias. Most people do well with a single kidney and in fact, donors may even live longer than nondonors, although this observation may simply indicate the careful selection of living donors from among very healthy candidates.33 Of importance, however, is that these studies have not consistently distinguished between ‘medically complex’ and ‘non-medically complex’ living donors, and extrapolation of these results to the case described in our report, a donor with prediabetes, may not be appropriate. Conversely, it is equally important to note that historically the oral glucose tolerance test was not performed as part of the donor work-up, suggesting that some older studies on long-term outcomes of kidney donors may have included donors today who would be defined as ‘prediabetic.’ Although the individual described in this report showed more than one clinical characteristic that may increase his risk of medical sequelae, we have chosen to focus our discussion on the literature surrounding prediabetes. Prediabetes is a common condition, and it is estimated that more than 54 million American adults are affected with IFG.34 Although debate continues over the benefits and harms of screening and then treating adults who have asymptomatic diabetes or prediabetes,34 prediabetes is a significant risk factor for the development of type 2 diabetes, microvascular, and macrovascular disease.35 How best to evaluate and consider the future risk of developing diabetes in live kidney donors is not well defined and varies considerably between programs.36
PREDIABETES AND THE KIDNEY

Although diabetes mellitus has been clearly established as a major risk factor for the development of kidney disease and is the leading cause of end-stage renal disease in North America and other developed countries, there are few studies examining the effects of prediabetes on the kidney. The term ‘prediabetes’ is applied in the setting of impaired glucose tolerance (IGT) or IFG and indicates a relatively high probability for the development of diabetes, microvascular, and macrovascular disease. The natural history of both IFG and IGT is variable, with ~25% progressing to diabetes, 50% remaining in their abnormal glycemic state, and 25% reverting to normal glucose tolerance over an observational period of 3–5 years. However, with longer observation, the majority of individuals with IFG appear to develop T2DM. Glomerular hyperfiltration, the hallmark of the onset of diabetic nephropathy, is positively correlated to fasting plasma glucose and has been observed in renal physiological studies in individuals with IGT, which suggests that the increased renal risk associated with diabetes may also occur in the prediabetic stage. Although no association was found between hyperinsulinemia or IGT and microalbuminuria in a nondiabetic Caucasian population, studies in other populations have reported an association between insulin resistance and an increased risk of microalbuminuria in the absence of diabetes. A large cross-sectional study identified a significant dose–response relationship among insulin resistance, insulin level, and risk of chronic kidney disease among nondiabetic participants, and impaired insulin sensitivity may be involved in the development of renal dysfunction at an early stage, before the onset of diabetes or prediabetic glucose elevations. Although this study was not designed to determine causality, worsening glycemic status has been associated with an increased risk of new renal dysfunction, with IGT or IGT conferring a 65% increased odds of developing chronic kidney disease over a 7-year period compared with normoglycemic individuals.

Worsening of insulin resistance has been found to be a risk factor for renal injury because of greater glomerular capillary and systemic blood pressures in older subjects. In healthy humans, higher insulin levels were associated with increased activity of the intrarenal renin-angiotensin system, activation of which has been implicated in the pathophysiology of diabetic nephropathy. In a study of patients undergoing renal biopsy for proteinuria, isolated diffuse thickening of the glomerular basement membrane was proposed as a renal lesion associated with prediabetes, although a firm relationship between this histological finding and the development of diabetes remains to be proven.

Donor nephrectomy in the case of normal renal function results in functional adaptation, hypertrophy, and hyperfiltration of the remaining kidney. While the first stage of diabetic, and perhaps prediabetic, nephropathy is glomerular hyperfiltration, the increase in glomerular filtration rate in uninephrectomized nondiabetic individuals is due to the increase in renal plasma flow, whereas in diabetic patients, the increase of renal plasma flow accounts for approximately 40% of the increase in glomerular filtration rate. Therefore, the mechanisms of hyperfiltration of nondiabetic single-kidney patients are probably not the same as those of diabetic patients. Although the effects of prediabetes in the setting of a single kidney are not known, a cross-sectional study concluded that glomerular hyperfiltration related to single-kidney status conferred an increased risk of developing renal disease in the presence of diabetes, though few subjects in this study were live kidney donors. However, no definite link between ‘prediabetes’ and the risk of kidney dysfunction has been shown, suggesting that the absolute risk of developing a glycemia-related kidney abnormality in the donor described in this report was probably not high.

CURRENT GUIDELINES FOR LIVING KIDNEY DONATION

The person who gives consent to be a live organ donor should be competent, willing to donate, free from coercion, medically and psychosocially suitable, fully informed of the risks and benefits as a donor, and fully informed of the risks, benefits, and alternative treatment available to the recipient. The benefits to both donor and recipient must outweigh the risks associated with the donation and transplantation of the living donor organ. The Amsterdam Forum has set forth a comprehensive list of medical criteria that is now used internationally in the evaluation of potential kidney donors; although a diagnosis of diabetes precludes donation, the presence of prediabetes does not necessarily render a potential donor unacceptable. It should be noted, however, that the purpose of the guidelines is not to replace the individual physician’s medical judgment in deciding to accept (or not) a potential live kidney donor. A recently published report on evaluation of the potential living kidney donor suggests that prediabetes is a relative contraindication to donation, and prospective donors with IFG or IGT should be assessed on an individual basis.

FOLLOW-UP OF CASE PRESENTATION

The donor did not comply with scheduled follow-up at our clinic, opting instead to follow up with his primary care physician. As such, we are not aware of any further outcomes other than a creatinine of 1.4 mg/dl (124 μmol/l) 6 months post-donation. Similarly, we are unaware of the recipient’s current status.

CLINICAL PERSPECTIVE AND CONCLUSIONS

Nephrologists assessing potential candidates for living donation should take into consideration the diagnosis of ‘prediabetes’. The role of the nephrologist assessing a person willing to donate a kidney is to be the advocate of the potential donor, and recommend proceeding with donation if, and only if, the degree of risk with the procedure is acceptable to both the physician and the patient. Although the ethical complexities of living kidney donation are beyond the scope of this article, a thorough discussion between the
two parties of both the short- and long-term potential risks associated with the procedure based on the currently available evidence is of clear importance, as ‘uncertainty is not a stumbling block to informed consent’ if the uncertainty is communicated to the potential donor. In fact, potential donors are more likely than potential recipients and transplant professionals to consider donation acceptable, even when long-term donor risks are uncertain. As the population at risk for diabetes and the ‘need’ for kidneys each continues to increase, the scenario described in this report is more likely to become increasingly common. As sparse data about long-term risk of uninephrectomy in the donor with prediabetes exist, current guidelines suggest that proceeding with kidney donation in the patient with prediabetes is acceptable, provided the potential donor is aware of the possible risks and is thus able to make an informed decision. Nonetheless, prediabetic donors should likely be counseled to engage in activities that reduce their future risk of diabetes (increase physical activity, weight loss, and metformin treatment in some individuals), given the clear association between diabetes and nephropathy.

It was unclear to the transplant team if the potential recipient (who was at a different center) was aware of the possible risks associated with nephrectomy to this particular donor. There are many factors that come into play when sharing with a recipient that a potential donor has a pre-existing medical condition that puts him/her at greater or uncertain long-term risk, the main one being permission from the donor to share his/her personal medical history as it relates to future risks. Potential kidney donors readily accept high long-term risks, whereas potential recipients appear to be the most averse to donor risk. However, it was suggested at the Amsterdam Forum on the Care of the Live Kidney Donor that ‘judgments should generally be made by the one most affected by the outcome—i.e., the prospective donor him/herself.’ Clearly, multicenter, long-term studies of health outcomes for medically complex donors, such as the patient described in this report, are essential to understanding which factors impart risk in a clinically important way, and will allow both physician and potential donor to determine acceptability of proceeding with kidney donation.

DISCLOSURE
All the authors declared no competing interests.

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