Should Living Kidney Donor Candidates with Impaired Fasting Glucose Donate?

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Summary

As the kidney transplant waiting list grows, the willingness of transplant centers to accept complex donors increases. Guidelines for the evaluation of living kidney donors exist but do not provide clear guidance when evaluating the complex donor. Although few transplant centers will approve donor candidates with impaired glucose tolerance and most, if not all, will deny candidates with diabetes, many will approve candidates with impaired fasting glucose (IFG). Furthermore, the demographic of living donors has changed in the past 10 years to increasingly include more nonwhite and Hispanic individuals who are at greater risk for future diabetes and hypertension. IFG may be more of a concern in potential donors whose nonwhite and Hispanic ethnicity already places them at greater risk. We review the definition of diabetes, diabetes prediction tools, and transplant guidelines for donor screening and exclusion as it pertains to impaired glucose metabolism, and additional ethnic and nonethnic factors to consider. We offer an algorithm to aid in evaluation of potential living donors with IFG in which ethnicity, age, and features of the metabolic syndrome play a role in the decision making.

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Introduction

Although guidelines for the evaluation of living kidney donors have been created, significant variation in how centers approach isolated medical abnormalities remains (1,2). The demographic of living donors has changed in recent years with more nonwhite and Hispanic populations, at greater risk for diabetes and hypertension, donating than a decade ago (3–5). Furthermore, the willingness of centers to accept donors with potential risk factors for chronic kidney disease (CKD; hypertension, obesity, low GFR) has increased, likely explained by the ever-increasing demand for more kidneys as the transplant waiting list grows (6,7).

Most US centers do not accept donors with diabetes or impaired glucose tolerance (IGT), but several centers accept donors with impaired fasting glucose (IFG) if the 2-hour oral glucose tolerance test (OGTT) is normal (6,7). Several questions arise regarding this practice. If donors with IFG develop diabetes, then would diabetic nephropathy occur earlier or more frequently than in patients who have diabetes and have two kidneys? Are we putting kidney donors with glucose intolerance at more risk for cardiovascular complications because both IFG and reductions in GFR (8,9) are risk factors for cardiovascular disease (CVD)? With the frequency of hypertension and diabetes being higher in African-American, Hispanic, and Native American donors (10), should acceptability of donors with IFG be influenced by ethnicity? Should decisions regarding these issues be influenced by donor age? In this review, we explore these issues, review tools for predicting diabetes, and offer an approach to the donor with IFG based on available data.

Definitions and Pathophysiology of IGT

American Diabetes Association (ADA) definitions of diabetes and glucose intolerance (11) are listed in Table 1. Normal fasting glucose was lowered from 110 to 100 mg/dl in 1997 by an international committee to identify more patients at risk for diabetes despite a normal OGTT (12). More recently, hemoglobin A_{1c} measurement has been added to the diagnostic criteria (Table 1).

The physiology of isolated IFG differs from that of isolated IGT. Isolated IFG is primarily a problem of hepatic insulin resistance with normal peripheral insulin sensitivity, whereas people with isolated IGT have predominantly increased peripheral insulin resistance. Both measurements represent impaired glucose physiologies. A normal fasting glucose can be present without IGT in a 2-hour OGTT, and, conversely, glucose intolerance can be present with a normal fasting glucose (13). The presence of either IFG or IGT increases a person's risk for developing diabetes by 5% to 10% per year, although a number of other variables (ethnicity, weight lipid profile, family history) affect this propensity. Both impaired glucose states are associated with an increase in cardiovascular complications (13).

Tools for Predicting Diabetes

In recent years, a number of screening tools have been developed to allow one to predict the likelihood of developing diabetes given a number of patient

Table 1. Definition of prediabetes and diabetes states (11)

Parameter	Normal	Impaired Glucose State (Prediabetes)	Diabetes
Fasting plasma glucose (mg/dl)[a]	<100	100 to 125 (IFG)	≥126
2-hour 75-g OGTT plasma glucose (mg/dl)	<140	140 to 199 (IGT)	≥200
Hemoglobin A_{1c}	<5.7	5.7 to 6.4	≥6.5
Random glucose (mg/dl)			>200 with classic symptoms of hyperglycemia or hyperglycemic crisis

IFG, impaired fasting glucose; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance. [a]Fasting plasma glucose should be measured after at least 8-hour fast.

variables and can help guide physicians' clinical judgment and patients' informed consent. The Finnish Diabetes Risk Score (FINDRISC) uses age, body mass index (BMI), central obesity, daily exercise, diet, drug-treated hypertension, history of high blood glucose, and family history to calculate risk for diabetes (14). A more comprehensive, sophisticated, and accurate prediction instrument is the Diabetes Personal Health Decisions (PHD) risk assessment tool powered by the Archimedes algorithm (www.diabetesarchive.net/diabetesphd). Unlike FINDRISC, ethnicity is included as a variable. This online model considers the time-dependent interrelationship of each variable and reports 30-year risks for the development of diabetes, myocardial infarction (MI), cerebrovascular accident, and renal failure. It has been validated against 18 clinical trials (15). A more recent validation using the San Antonio Heart Study (SAHS) population confirmed high sensitivity and specificity when compared with the SAHS and Atherosclerosis Risk in Communities (ARIC) prediction models (area under the receiver operating characteristic curve was 0.818) (16). The use of the Diabetes PHD instrument is not often used to exclude donors because there is no consensus as to what constitutes "unacceptable risk." However, these tools can be used to guide donors in the process of informed consent.

Transplant Guidelines for Donor Screening and Exclusion

Guidelines created by the Amsterdam Forum (1) recommend that individuals with diabetes be excluded from donating but do not address donors in the prediabetes state. In their donor evaluation review, Pham *et al.* (17) suggested that IFG or IGT be considered relative contraindications for donation and evaluated on an individual basis. The Asian Pacific Society of Nephrology guidelines make similar recommendations but further suggest that all "at risk" ethnic groups receive an OGTT (18). Review of the evolving US transplant center practices in the past 20 years revealed a trend toward accepting more complex donors with glucose problems (6,7). None of these reports elaborated on an approach to follow in evaluating donors with isolated IFG.

Factors to Consider When Evaluating Donors in the Prediabetes State

The development of diabetes from prediabetes states is more common when associated with other factors that should be considered when evaluating such donors. Similarly, patient age should be added to the equation because younger patients with prediabetes have more time to develop diabetes and its complications.

Gestational Diabetes

Although gestational diabetes can segue into immediate postgestational diabetes, the sugar levels of the vast majority of affected women will normalize after delivery. A recent large, population-based study from Ontario, Canada, found that type 2 diabetes developed within 9 years after the index pregnancy in nearly 19% of women with previous gestational diabetes (the comparable rate for women without gestational diabetes was 2%) (19). Furthermore, although several risk factors, such as maternal age, presence of hypertension, and presence of comorbid conditions, contributed to the development of type 2 diabetes, gestational diabetes imparted the greatest risk (adjusted hazard ratio 37) (19). Accordingly, all female donors should be asked about a history of gestational diabetes and receive an OGTT if positive.

Obesity and the Metabolic Syndrome

Since its inception, the metabolic syndrome has had varying definitions. The American Heart Association and the National Heart, Lung, and Blood Institute reviewed these definitions in 2005 and promoted a revised version of the National Cholesterol Education Program/Adult Treatment Panel (ATP) III (Table 2) (20). The metabolic syndrome has been shown to be a predictor of diabetes in the future (21). Along with obesity itself, the metabolic syndrome is associated with increased morbidity and mortality from CVD (22–24). The role of obesity in enhancing progression of prediabetes to diabetes is best illustrated by studies demonstrating a reduction in this risk with weight loss (25,26). Thus, donor BMI and the presence of the metabolic syndrome should be factored into the risk assessment of living-donor candidates with IFG (5).

Ethnicity

In the United States, nearly 26 million people have diabetes (27). Higher rates exist for racial and ethnic minorities, including African Americans, Hispanics, Native Americans/Alaska Natives, some Asian Americans, and Pacific Islanders (27–29). A large-scale analysis of the development of diabetes in living donors did not show any difference between donors and the expected control rate

Table 2. Definition of the metabolic syndrome according to the National Cholesterol Education Program/Adult Treatment Panel III (20)

1. Abdominal obesity Waist circumference in men >102 cm (40 in) Waist circumference in women >88 cm (35 in)
2. Serum triglycerides ≥150 mg/dl or drug treatment for hypertriglyceridemia
3. Serum HDL cholesterol ≤40 mg/dl in men ≤50 mg/dl in women Drug treatment to improve lipid profile
4. BP ≥130/85 mmHg or drug treatment for hypertension
5. Fasting plasma glucose ≥100 mg/dl or drug treatment for elevated glucose
Three of five features must be present to fulfill criteria for the metabolic syndrome.

but was based on a population of mostly white donors from Minnesota and may not be generalizable to high-risk minority donors (30). A recent review of follow-up data from black and Hispanic donors in the United States revealed not only an increased risk for drug-treated diabetes after donation but also a higher risk for hypertension and CKD compared with white donors (10). Similarly, assessment of indigenous (Aboriginal) living donors in Canada, followed for a mean of 14 years, demonstrated higher rates of hypertension and diabetes compared with white donors (31). In all of these studies, rates of diabetes and hypertension were not significantly different from the rate observed in the general minority population. The presence of obesity, more common in these ethnic minorities, may contribute to these findings (5).

Age and Donor Risk

Age is another factor to consider. A 20-year-old white man has approximately a 26% lifetime risk for developing diabetes; by age 60, this risk is down to 16% (32). The residual lifetime risk for developing diabetes increases when the person is black, Hispanic, or female (32). On the basis of cohort studies, ESRD in living donors, a rare event, occurs a median of 20 years after donation (33); therefore, the younger the candidate donor with IFG, the greater the cumulative risk for developing diabetes and resultant complications.

Are Donors with IFG or Diabetes More Susceptible to Diabetic Nephropathy?

Hyperfiltration plays a pivotal role in progression of diabetic nephropathy (34), and studies of animals with diabetes showed that renal disease progresses after nephrectomy (35,36). Furthermore, data from the Framingham study revealed higher rates of the development of CKD in patients with IFG and IGT (37). Several studies addressed the issue of accelerated kidney damage in patients who have single kidneys and develop diabetes. Silveiro *et al.* (38) showed that nephrectomy might increase the risk for albuminuria and accelerate diabetic nephropathy in patients with type 2 diabetes. In contrast, Chang *et al.* (39) found no difference in the development of kidney damage when comparing patients who had type 1 diabetes and received a transplant (one kidney) with matched patients with type 1 diabetes (two kidneys). However, the absence of hyperfiltration as a result of the use of cyclosporine in the transplant recipients makes the findings of this latter study difficult to interpret. In Japan, where patients who have diabetes and do not have mircoalbuminuria are allowed to donate, Okamoto *et al.* (40) followed 27 donors with well-controlled diabetes at the time of donation and 44 donors with IGT. None of these donors developed ESRD during the 88 months of follow-up. In a long-term follow-up of 3698 kidney donors followed mainly through questionnaires, Ibrahim *et al.* (41) reported a greater frequency of hypertension and proteinuria in donors (predominantly white) who developed type 2 diabetes compared with those who did not, but estimated GFR (eGFR) was similar in both groups. None of the 11 donors who developed ESRD (0.29%) had diabetic nephropathy. Thus, although we would anticipate that hyperfiltration would cause donors who develop diabetic nephropathy to accelerate to ESRD more rapidly than patients with two kidneys, there is no evidence to date in donors who develop diabetes to prove that hypothesis. Such donors with diabetes, however, do have more proteinuria and hypertension (41). Clearly, longer follow-up is needed as well as more data in ethnic minorities to clarify this issue.

Are Donors with IFG or Diabetes More Susceptible to CVD?

Patients with diabetes and prediabetes are at an increased risk for CVD (9,37,42). Furthermore, there is a widely known relationship between a decline in eGFR and increasing risk for CVD in patients with CKD (43). It is not known whether donors with a reduced GFR as a result of donor nephrectomy carry the same risk. Because donors who develop type 2 diabetes have more hypertension and proteinuria (41), both predictors of CVD, they could be at more risk for CVD. Only one study from Canada has addressed this question directly, and no increase in mortality or CVD in donors with diabetes was observed. In that study, mean follow-up was only 6 years, and 92% of donors were white (44). With studies showing an increase in hypertension, diabetes, and CKD in black and Hispanic donors (10) as well as a significant decreases in GFR after donation in African American donors (45), it gives one pause to consider whether, in contrast to white donors, minority donors who develop diabetes may be at greater risk for CVD after donor nephrectomy. This issue can be resolved only with more outcome studies in these populations.

Case Discussion

To illustrate use of these concepts in a potential donor with IFG, we present a case (Table 3). The approach we follow is depicted in Figure 1. First, it should be emphasized that donors with microalbuminuria are excluded from donation. Screening with OGTT is based on ADA guidelines (46). In our evaluation, we consider ethnicity and age, as well as features of the metabolic syndrome, in the decision making for patients with isolated IFG. Despite this patient's normal OGTT, her IFG, along with her high

Table 3. Case of donor with impaired fasting glucose

Donor candidate (husband is the intended recipient)
Hispanic woman, age 47 years
Pertinent history
no history of kidney disease, diabetes, or hypertension
hyperlipidemia treated with atorvastatin
daily tobacco use (8 pack-year history); limited daily exercise
family history of diabetes (parents, three siblings) and coronary artery disease
Pertinent physical examination and laboratory values
BP in the office is 116/74 mmHg; BMI 28 kg/m^2
fasting glucose 108; 105 mg/dl
estimated GFR 88 ml/min per 1.73 m^2
albumin/creatinine ratio <3 mg/g
LDL is 118 mg/dl, HDL is 39 mg/dl, and triglycerides are 80 mg/dl
glucose after 2-hour OGTT 128 mg/dl

BMI, body mass index; OGTT, oral glucose tolerance test.

BMI, ethnicity, strong positive family history, lipid profile (low HDL), and smoking, put her at increased risk for diabetes. According to the PHD calculator (15), her risk for diabetes and MI by age 60 are 45% and 14%, respectively. These risks would be higher if she were younger and had more features of the metabolic syndrome. They would be lower if she were older, white, without features of metabolic syndrome, and absent a positive family history. Lifestyle modifications, when followed, can have a significant effect on altering the predicted risks (25,26,47). For our candidate, with light exercise, smoking cessation for 1 year, and diet to achieve a weight reduction of 20 lb as well as an alteration in her lipid profile (to achieve a total cholesterol of 171; HDL 55, LDL 100), her risk for diabetes and MI could be reduced to 4.3% and 0.9%, respectively. As part of the informed consent process, we presented these data to her. Acknowledging these risks and uncertainties, she elected to proceed with the donation. Given the lack of long-term outcome data in minority donors, we cautiously agreed.

Conclusion

Although studies to date have reported no increase in diabetic nephropathy or CVD in living donors, these studies have looked at predominately white donors whose

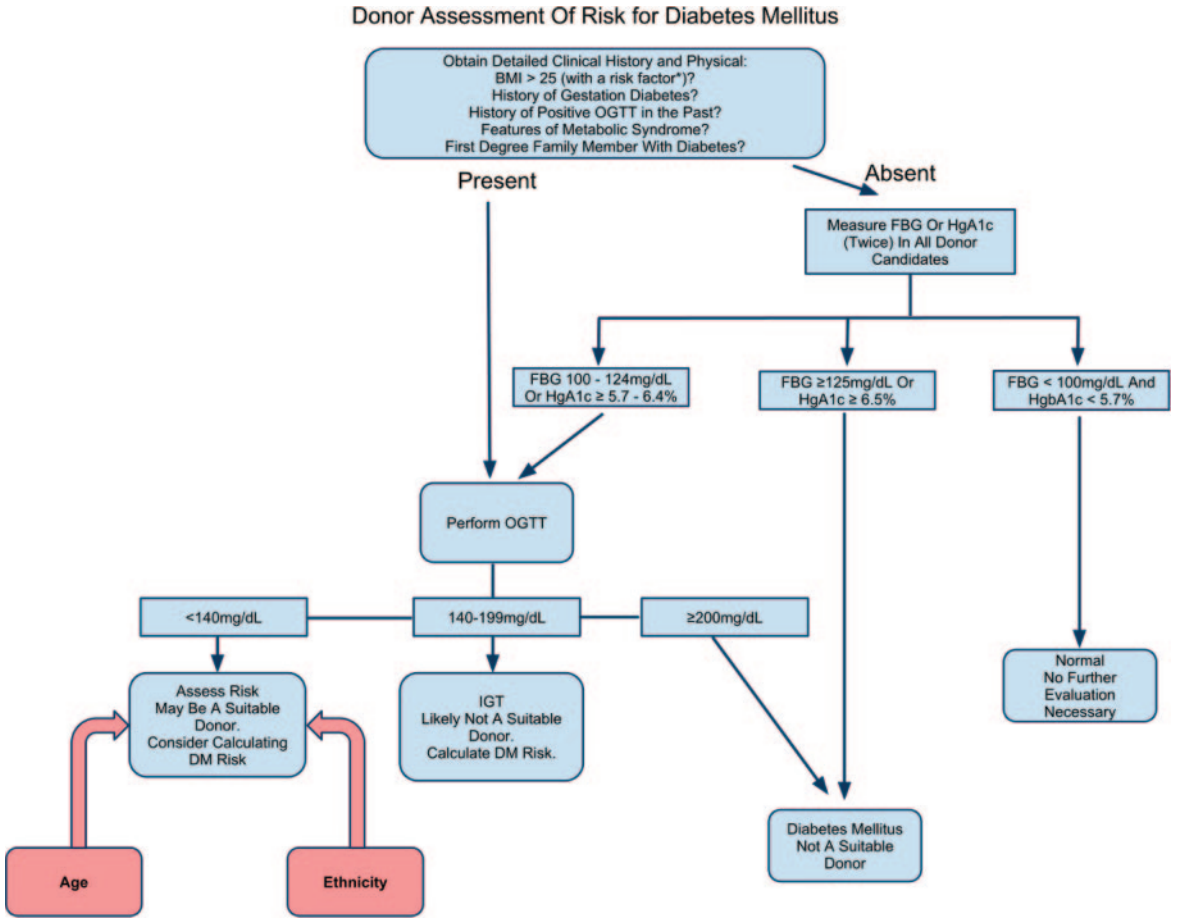

Figure 1. | Algorithm for assessment of living kidney donor candidates with impaired fasting glucose. If IGT (impaired glucose tolerance) accompanies impaired fasting glucose, then the donor is likely not a suitable candidate. If IGT is absent, then the patient may be an acceptable donor candidate, but age, ethnicity, and the presence of features of the metabolic syndrome should contribute to this decision. BMI, body mass index; FBG, fasting blood glucose; OGTT, oral glucose tolerance test.

risks for these complications are less than in minority populations. Risk for ESRD in any donor who develops diabetes is probably low, but the risk for CKD might be higher in donors from minority groups, which, together with their diabetes, could put them at greater risk for cardiovascular complications. This risk has a longer time to unfold in younger donors. Longer follow-up, especially in minority populations, is needed to address this question as has been called for by others (5,10,48). Our intention is not to discourage donation from minority potential donors but rather to explore the issues to be considered in weighing the risks in which ethnicity might be a factor. We offer an algorithm for an approach to donors with isolated IFG in which age and ethnicity, in addition to features of the metabolic syndrome, are important factors to consider when estimating the risks for these donor candidates.

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Disclosures

None.

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