glomeruli. Since the discovery of nephrin and podocin, several other disease-associated podocyte-specific gene defects have been reported, and, undoubtedly, there will be more to come.

Mutations in different podocyte genes or different mutations in the same gene result in varying phenotypes regarding severity and age of onset of proteinuria, and it is clear that there are likely to be other disease-modifying genes or environmental influences. Moreover, congenital forms of nephrotic syndrome are rare, and a question that intrigues nephrologists and basic scientists alike is whether the more common forms of sporadic, often later onset nephrotic syndrome could also be associated with mutations or polymorphisms in podocyte-specific genes, as predisposing factors or contributors to a complex etiology involving genetic–environmental interactions. If so, then study of these genes could be clinically useful in diagnosis and prognosis, especially concerning the likelihood of corticosteroid responsiveness and the issue of likely recurrence in renal transplants for patients who progress to end-stage renal failure.

The article in this issue of JASN by Hinkes et al.,7 the product of an impressive multinational collaboration, sheds light on these issues. The study amassed 430 patients with steroid-resistant nephrotic syndrome, the vast majority of whom were the only affected family member, although the series did include 23 families with more than one affected member. The patients were screened for mutations in NPHS2 by direct sequencing of all eight exons of the gene. Eighty-two patients (19% of the total) had mutations in NPHS2. In the families with more than one affected member, the proportion with NPHS2 mutations rose to 39%. In patients with two NPHS2 mutations, the authors report that approximately 40% had one truncating (frameshift or nonsense) mutation and an additional 30% had homozygous R1308Q mutations (the “founder” NPHS2 mutation identified by Boute et al.). These two groups of individuals nearly all developed nephrotic syndrome at an early age (<6 yr, with a mean age of onset <2 yr). The remaining 30% of patients with other mutations or variants in NPHS2 had later onset disease without any further specific link between any given genotype and age of onset (although the numbers of patients with each genotype were small). Mutation type did not affect rate of deterioration, time from onset to ESRD being the same in all groups.

Although this represents real progress, even within the groups with early presentation there was still a wide range of age of onset. Also, >80% of the collection with steroid-responsive nephrotic syndrome did not have any abnormality of NPHS2, so their proteinuria remains unexplained; clearly there is more work to be done.

The power of large multinational studies such as this one will be essential if analyses of genotype–phenotype relationships in nephrotic syndrome are to yield informative conclusions. Ideally, genetic analysis should be more widely available as a diagnostic and prognostic aid in patients presenting with nephrotic syndrome; however, at present, clinicians will need further guidance from geneticists about the interpretation of genotype–phenotype relationships. Hinkes et al. are to be congratulated for leading the way.

DISCLOSURES
None.

REFERENCES


The Disadvantage of Being Fat

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doi: 10.1681/ASN.2007121337

Given the epidemic of obesity in the United States, it is not surprising that an increasing fraction of patients who are considered for and receiving kidney transplants are also overweight. Friedman et al.4 found a 41.9% decrease in the fraction
of patients with normal body mass index (BMI) among US patients who received kidney transplants from the 1988 to 2001. During the same period, there was a 32% increase in the number of patients with BMI of 25 to 29.9 and a 116% increase in patients with BMI >30.

Is there a problem with performing transplantations on an increasing fraction of obese patients? Not necessarily. Chang et al.2 found that obesity alone at the time of transplantation was not associated with poorer outcomes among patients who were registered in the Australia and New Zealand Dialysis and Transplant Registry. Gore et al.3 found in United Network for Organ Sharing (UNOS) data that recipient obesity was associated with a 7% higher risk for graft failure and recipient morbidity with a 22% increase, but obesity per se is not associated with a significant difference in the risk for death. BMI may not be the optimal criterion of obesity for transplant candidates. It is widely known that central or visceral obesity rather than hip obesity has the greater impact on cardiovascular outcomes. Waist-to-hip ratio and/or waist circumference may be better measures of obesity than BMI.4

Should obese patients be required to lose weight before kidney transplantation? Probably not. Current approaches to losing weight often fail and may leave transplant candidates in inactive status for prolonged periods with no demonstrable benefits. Indeed, prolonging time on dialysis may decrease later graft survival, so this approach may actually be counterproductive for the obese transplant candidate.5 There are no data confirming that outcomes are superior for patients who succeed in losing weight. Not only do these patients regain weight relatively fast, but also their outcomes are no better than those of patients who do not lose weight before transplantation.6 The experience with bariatric surgery in transplant candidates is still limited, but this approach may be helpful in the future.7 In any case, Glanton et al.8 showed using US Renal Data System data that, just as with nonobese patients, obese patients who received a kidney transplant had better survival than patients who remained on the waiting list. It seems clear that for the otherwise healthy obese patient with ESRD, rapid transplantation remains the best therapeutic option.

Unquestionably, several challenges do arise in performing transplantations on obese patients. It is widely recognized that infections and wound problems are more frequent among obese transplant recipients. Gore et al.3 confirmed an increased risk for delayed graft function, acute rejection, and longer hospitalizations among obese kidney transplant recipients independent of other known risk factors. The tight reimbursement for kidney transplantation rewards transplanting “low-risk” patients. Perhaps partially for these reasons, many transplant centers have a maximum BMI below which they are willing to list patients for kidney transplantation. This approach penalizes many obese patients, because most will not succeed in losing weight to the target BMI.

Because BMI does not enter into the UNOS criteria for kidney allocation, an obese patient, once on an active transplant list, should fare as well in receiving a kidney as a nonobese patient, shouldn’t (s)he? Well, maybe not so. Transplant centers have complete latitude in deciding whether to accept a kidney offered to a given patient, and a potential recipient’s BMI may well enter into this decision. Until recently, the transplant community did not have a good idea of the impact of obesity on a patient’s chance of actually receiving a transplant.

In this issue of JASN, Segev et al.9 report that the decision to accept a kidney is influenced substantially by the obesity of the potential recipient. Reviewing 130,000 transplant candidates listed with UNOS during the period from 1995 to 2006, these investigators determined the chance of a waiting list candidate’s being bypassed for an organ offer and the median time to transplantation for candidates with elevated BMI. The severely obese group had a 4 to 13% higher likelihood and the morbidly obese group a 22 to 23% likelihood of being bypassed compared with patients with a normal BMI. As a consequence, obese, severely obese, and morbidly obese patients had median times to transplantation from listing of 42, 51, and 59 mo, respectively, compared with 39 mo for nonobese patients. It seems that the practice of bypassing obese patients on waiting lists, perhaps hoping for a decrease in BMI, is relatively common in US transplant centers. These analyses may underestimate the impact of obesity on the chance that a patient with ESRD will receive a kidney transplant. Segev et al.9 also report that a sizable fraction of transplant centers did not list a single morbidly obese or severely obese patient during this 11-yr study period (21 and 15% of centers, respectively).

Are there alternative explanations for the increased likelihood of bypassing obese patients when a kidney is offered? Possibly. The UNOS data set lacks information about additional reasons for bypassing a listed transplant candidate. It would be helpful, for example, to have reliable information about severity of comorbidities, such as history of cardiovascular disease and diabetes, that are correlated with obesity. No details are provided on the centers that did not list morbidly or severely obese patients. Although the number of these centers is significant, they may represent a small fraction of US transplants. It is also possible these centers are located in areas with a lower prevalence of obesity. Finally, it is not known whether dialysis center referral rates for transplantation are lower as the BMI increases, but it remains likely that BMI per se plays an important role in the listing and ultimate receipt of transplantation of patients with ESRD. This may not surprise us, but it should serve as a “reality check” on the real impact of elevated BMI in US transplant candidates.

Both the Centers for Medicare and Medicaid Services (CMS) and transplant centers also need to be realistic about the financial realities of offering transplantation to obese candidates. Our mission is to offer the best treatment for the specific patient with ESRD we see, and it seems clear that kidney transplantation is the best option for the obese, too.

Currently, there is no public policy concerning the listing of obese patients for kidney transplantation or accepting kidneys on their behalf; neither are there strong data to support any such policy, yet obesity affects both listing of and performing
transplantation on these patients, possibly in part for economic reasons. The data from Segev et al. should nudge CMS and the transplant community to address this issue with more transparency. Obesity is not the only factor affecting enthusiasm to perform transplants on specific individuals. Similar concerns may be limiting the use of more expanded-criteria donors and donation-after-cardiac-death donors or transplantation for the immunologically high-risk patient. These transplants will incur additional costs. The current reimbursement model of “one size fits all” penalizes centers providing kidney transplantation to the higher risk patient. If there is no modification in the reimbursement system, then it is unlikely that the current practice will change. Obese patients should then be aware that they will likely spend a longer time waiting for a transplant. Whatever the response from CMS and the transplant community is, these issues should be more transparent to the public and the patients on the waiting list.

DISCLOSURES
None.

REFERENCES