

## Donors at risk: obesity

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### GUIDELINES

No recommendations possible based on Level I or II evidence

### SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- A combination of waist circumference and body mass index (BMI) is recommended for the clinical assessment of overweight and obesity.<sup>1</sup> Consideration of differential risk according to ethnicity should be undertaken.
- Obesity (BMI > 30 kg/m<sup>2</sup>) should be considered a relative contraindication to donation.
- Potential donors who are obese should be very carefully assessed for risk factors associated with chronic kidney disease (CKD) (i.e. impaired glucose tolerance, hypertension, proteinuria). The presence of obesity and a second risk factor should be considered as a contraindication to donation.
- Age of the donor should be taken into consideration in determining donor suitability as obesity precedes the development of risk factors for future kidney disease. Additional markers of increased risk include family history of diabetes, history of gestational diabetes or high-risk ethnic group.
- The obese donor should be counselled regarding the:
  - increased risk of perioperative morbidity, and
  - absence of long-term safety data.
- Acceptance for donor nephrectomy will require a careful consideration of donor and recipient circumstances and involve acceptance by the donor of probable but unquantifiable future risk.
- Obese donors should be carefully followed up and data submitted to the live donor registry.

### IMPLEMENTATION AND AUDIT

1. Survey Australian and New Zealand renal units to determine current practice in terms of acceptance of obese donors.
2. Have mandatory reporting (ANZDATA) of all cases of end-stage kidney disease (ESKD) in patients who have been previous living kidney donors. This would also include patients with ESKD who chose conservative therapy, recognizing that this would be incomplete when compared with patients requiring dialysis or transplantation. Analyse baseline characteristics to determine the impact of baseline BMI and other comorbidity.

### BACKGROUND

The aim of this guideline is to examine the consequences of obesity on short- and long-term donor outcomes following nephrectomy for purposes of living donor transplantation. Due to the increasing prevalence of obesity in the general population, an increasing percentage of donors coming forward for assessment are overweight and obese. They are often young or middle aged, frequently with no current medical issues and have a projected life expectancy of many decades. The assessment involves consideration of future risk, which is often difficult to quantitate *versus* the more immediate and tangible benefit to the recipient.

Areas of concern relating to obesity are as follows:

- it is a risk factor for perioperative morbidity
- it is a risk factor for future kidney disease as a significant predictor of the development of Type 2 diabetes, hypertension and cardiovascular disease (CVD)
- it may be an independent risk factor for CKD and may be associated with more rapid loss of kidney function in patients with CKD, and
- although a modifiable risk factor, long-term success rates for weight loss interventions are low.

Therefore, the consideration of the impact of nephrectomy in this group is a significant issue for which there is a paucity of long-term data from which to draw firm conclusions.

### Definition of obesity and implications of ethnicity

A number of techniques are available for the assessment of adiposity. BMI (kg/m<sup>2</sup>) is easy to use and reproducible and has been consistently associated with increased risk of mortality, development of CVD and diabetes. However, BMI does not take into account variability of fat distribution or proportion of weight related to muscle or changes associated with aging. Excess intra-abdominal fat is associated with a greater CVD risk than overall adiposity. Alternative measurements of waist circumference and waist-to-hip ratio (WHR) have been proposed as alternatives to BMI and have been shown to be good simple measures of intra-abdominal fat mass and have stronger associations with hypertension and other CVD risk factors. Measurement

error is higher for waist circumference and WHR, particularly at increasing levels of BMI and adds little to the assessment of risk if the BMI is greater than 35. In the literature on living kidney donors, BMI is used almost exclusively.

The National Health and Medical Research Council Clinical Practice Guideline for the Management of Overweight and Obesity in Adults recommends the following definitions of overweight and obesity in adults:<sup>1</sup>

- overweight – BMI > 25 kg/m<sup>2</sup> or a waist circumference above 80 cm in women or 94 cm in men
- obese – BMI > 30 kg/m<sup>2</sup> or a waist circumference above 88 cm in women or 102 cm in men.

It is important to note that these cut-offs have been derived in predominantly Caucasian populations and are likely to vary between different ethnic groups. A recent systematic review,<sup>2</sup> demonstrated that at any given level of obesity, irrespective of the measure used, Asians have a higher absolute risk of diabetes and hypertension compared with Caucasians. Percentage body fat is higher for a given BMI in South Asians and visceral adipose tissue is higher for a given waist circumference in both Chinese and South Asians.<sup>3</sup> There has been a great deal of debate regarding the adoption of appropriate definitions for Asian populations and the WHO expert consultation group published recommendations that a BMI of greater than 23 kg/m<sup>2</sup> represents increased risk and greater than 27.5 kg/m<sup>2</sup> represents high risk in Asian populations.<sup>4</sup> The Hong Kong meeting of WHO/IASO/IOTF recommended a definition of obesity for the Asian population of waist circumference greater than 80 cm in women and 85 cm in men. There are obvious limitations given the great diversity of populations within this group, but in general, increased risk of future diabetes, hypertension and CVD should be assumed at lower levels of obesity.

In Aboriginal Australians, there is a strong linear association between BMI and the age-adjusted prevalence of impaired glucose tolerance and diabetes. Metabolic disturbances increase when the BMI rises above 22 kg/m<sup>2</sup> and this may represent an upper end of a healthy weight range in this population.<sup>5</sup> Compared with a BMI less than 22 kg/m<sup>2</sup>, the age-adjusted odds ratio (OR) for diabetes for a BMI of 25–29.9 kg/m<sup>2</sup> was 3.0 (95% confidence interval (CI): 1.9–4.7) in men and 4.0 (95% CI: 2.3–7.2) in women. Aboriginal Australians have significantly different body fat distribution when compared with Caucasians, with an increased tendency to central adiposity and a higher fat mass for any given BMI.<sup>6,7</sup> In studies by Wang *et al.* the risk of diabetes, CVD and hypertension increased with increasing body size as assessed by any measure but was most closely associated with measures of central obesity (waist circumference or waist : hip or waist : height) in both genders.<sup>8–10</sup> From an analysis of the AusDiab population, Aboriginal people had a higher predicted probability of diabetes at lower levels of body size.

There are currently no firm recommendations regarding the definition of obesity in the Aboriginal and Torres Strait Islander population, however, based on the available data, a BMI of greater than 22 kg/m<sup>2</sup> and/or central obesity is associated with sharply rising prevalence of diabetes and CVD.<sup>8,11</sup>

In contrast, Maori and Pacific Islander peoples have a lower percentage body fat at any given BMI.<sup>12,13</sup> Comparable percentage body fat was associated with a BMI 2–3 units greater in men and up to 4 units greater in women of the Pacific Islander population compared with Caucasians.<sup>13,14</sup> There is no evidence that this is protective and the prevalence of diabetes and CVD are high in the Maori and Pacific Islander population and associated with BMI. In data extracted from the 1997 National Nutrition survey, there were very significant increases in age-standardized attributable mortality for diabetes (10-fold increase), ischaemic heart disease (threefold increase) and stroke (twofold increase) in the higher than optimum BMI category (>21 kg/m<sup>2</sup>) for Maori as compared with non-Maori.<sup>15</sup> A small study by McAuley *et al.*<sup>16</sup> demonstrated that for any given BMI, Maori women are more insulin resistant than Caucasian controls. Therefore, there is no indication that using higher cut-offs to define obesity is justified in the Maori and Pacific Islander population and standard criteria should apply.<sup>17</sup>

## 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 obesity and morbid obesity. The search was carried out in Medline (1950–July Week 3, 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?

### Health hazards associated with obesity

Large epidemiological studies have demonstrated an association between obesity and mortality. In a subset of individuals aged 50 years who had never smoked, and were followed for 10 years, there was a two- to threefold increase in mortality for those with a BMI > 30 kg/m<sup>2</sup>.<sup>18</sup> Obesity is strongly linked to Type 2 diabetes, hypertension, CVD, some cancers and arthritis, which each contribute to the increase in mortality. The mechanism for this relationship may be related to insulin resistance and hyperinsulinaemia, with subsequent increases in impaired glucose tolerance, increased sympathetic activity, renal sodium retention and vascular tone. In spite of increased use of risk-modifying therapies such as lipid-lowering drugs and antihypertensives, there is no evidence of a reduction in the population risk associated with obesity over time.<sup>19</sup>

Cardiorespiratory fitness may modify this risk.<sup>20–22</sup> A prospective observational study of 25 714 predominantly Caucasian men<sup>22</sup> demonstrated that low fitness was common in obese men and an independent predictor of cardiovascular and all-cause mortality and increased the relative risk of mortality to a similar degree as does diabetes. A second important finding in this study was that for each risk factor

studied (i.e. diabetes, high cholesterol, hypertension, current smoker and low cardiorespiratory fitness), increasing adiposity was associated with a stepwise increase in mortality risk. That is, for every risk factor examined, the presence of obesity increased the risk.

In the Australian population,<sup>23</sup> more than 75% of obese males and 65% of obese females had at least one comorbidity (hypertension, dyslipidaemia or diabetes) and 7–10% had all three. The AusDiab 2005 report demonstrated that compared with those with a normal BMI at baseline, the overweight and obese have a 2- to 4-fold increase in the annual incidence of diabetes and hypertension (see Table 1). For example, the annual incidence of hypertension in obese patients was 5% and for diabetes it was 1.6%. These data are derived from a 5-year follow-up study<sup>24</sup> and further information is required to determine the relationship between baseline BMI and the incidence of hypertension and diabetes over time. However, this is of particular relevance to living kidney donors in whom the average age at nephrectomy is 48 years<sup>25</sup> and who have a life expectancy of many more decades.

The impact of obesity on risk of diabetes and hypertension is even more pronounced in Aboriginal Australians. Compared with the AusDiab population, the OR (95% CI) for diabetes among normal, overweight and obese (by waist circumference) remote living aboriginal women were 2.6 (0.6–11.5), 13.1 (6.7–25.7) and 6.1 (4.6–8.0), respectively.<sup>8</sup> The risk for diabetes in aboriginal men was 6-fold higher in each of the weight categories. Similar increased prevalence of obesity, diabetes, hypertension and cardiovascular risk were also described in a cohort of urban indigenous people from Perth.<sup>26</sup> The adjusted relative risk for the incidence of newly diagnosed diabetes in an 8-year follow-up study was 3- to 4 fold higher for BMI > 25 kg/m<sup>2</sup> compared with those with a lean BMI.<sup>11</sup> In summary, indigenous Australians have a significantly increased risk of diabetes, hypertension, cardiovascular and kidney disease, which is further magnified even at low levels of adiposity.

In New Zealand, the prevalence of obesity is increased in Maori and Pacific Islander peoples compared with the Caucasian population (BMI ≥ 31 kg/m<sup>2</sup> 63%, 69% and 26%, respectively).<sup>27</sup> Similarly, the prevalence of diabetes is at least 3-fold higher in the Maori and Pacific Islanders and occurs at a younger age (typically between 5 and 10 years younger than Caucasians).<sup>28</sup> The relationship between fasting insulin and BMI was independent of ethnicity, suggesting that the high prevalence of diabetes was related to obesity. Hypertension is also increased in the Maori and Pacific Islander population<sup>29</sup> and in a large church-based survey, BMI was positively associated with blood pressure (BP), with a 14 mmHg difference in systolic BP between the lowest and highest quartile of BMI in men and 9 mmHg in women.<sup>30</sup>

At any given level of obesity, the absolute risk of diabetes is consistently higher in Asians, for both men and women. For example, for men with a BMI of 24 kg/m<sup>2</sup>, the prevalence of diabetes was 5% in Asians *versus* 2% in Caucasians, and the prevalence of hypertension was 32% in Asians and 17% in Caucasians.<sup>31</sup> There is a continuous positive asso-

ciation between baseline BMI and risk of future diabetes, which is stronger in Asians than Caucasian cohorts.<sup>32</sup> In the Nurses Health study,<sup>33</sup> for each 5-unit increase in BMI, the adjusted relative risk of incident diabetes in Asians was 2.36 (95% CI: 1.83–3.04) and for Caucasians was 1.96 (95% CI: 1.93–2.00). The impact of weight gain from baseline was also a significant factor; in Asians, each 5 kg weight gain was associated with an increase in risk of incident diabetes by 84% (95% CI: 58–114) and 37% (95% CI: 35–38) in Caucasians.

### Obesity as a risk factor for CKD

There are several mechanisms by which obesity may be expected to have a detrimental effect on the kidney. Obesity increases single-nephron glomerular filtration rate (GFR), increases activation of the sympathetic nervous and renin-angiotensin systems, promotes salt resorption in the proximal tubule<sup>34</sup> and has been associated with specific histological changes including glomerulomegaly and focal segmental sclerosing lesions.<sup>35</sup> Obesity is associated with and often precedes multiple factors associated with development of kidney dysfunction – hypertension, diabetes and atherosclerosis but data from longitudinal cohort studies suggest that obesity may also be an independent risk factor for the development of CKD and ESKD<sup>36–41</sup> (see Table 2).

- Analysis of the Kaiser Permanente cohort<sup>40</sup> demonstrated that there is a progressive increase in risk of ESKD associated with obesity, independent of age, gender, race, smoking, previous myocardial infarct, baseline cholesterol, proteinuria and serum creatinine. Compared with normal BMI, the adjusted relative risk for ESKD was 1.87 for overweight and 3.57 for BMI between 30 and 34.9 kg/m<sup>2</sup> and 6.12 for BMI between 34 and 39.9 kg/m<sup>2</sup> and 7.07 for BMI > 40 kg/m<sup>2</sup>. Adjustment for baseline BP and presence of diabetes attenuated the risk slightly but the associations remained strong.
- Preliminary data from the AusDiab follow-up study, on the annual incidence of both de novo eGFR < 60 mL/min per 1.73 m<sup>2</sup> and albuminuria, demonstrates a stepped increase in risk for each weight category. For the obese, the risk approaches 1% per year and is roughly increased by 50% above the risk of the normal weight participants (personal communication, Steven Chadban). The increase in risk is independent of diabetes.
- The Framingham Offspring study<sup>39,42</sup> involving 2676 participants with normal baseline kidney function who were followed for a median of 18.5 years, demonstrated an increased risk of stage 3 CKD in obese participants but in a subsequent publication, this was accounted for by the higher prevalence of diabetes and hypertension. There was a 56% increase in risk of proteinuria (>1+ dipstick) in the obese participants, which was independent of hypertension and diabetes.
- Pooled data from two community-based longitudinal studies (Atherosclerosis Risk in Communities and the Cardiovascular Health Study with a median follow up of 9.3 years,<sup>43</sup> demonstrated that the relationship between

obesity and incident CKD was best determined by WHR rather than BMI. Univariate analysis demonstrated a strong relationship between WHR and CKD, but this was no longer significant after adjustment for multiple risk factors. Of note, this study involved an older population (mean baseline age 57 years) in whom most of the comorbidities that associate with obesity, would likely have developed by the time of enrolment. WHR was also associated with an increased risk of the composite end-point of mortality and CKD, whereas increased BMI was protective of this outcome.

- The Physicians Health Study<sup>38</sup> demonstrated that in healthy men followed for 14 years, higher baseline BMI was associated with an increased risk for CKD following adjustment for potential confounders. In addition, men who had a greater than 10% weight gain, also substantially increased their risk of CKD. This study was flawed by the possible inclusion of men with CKD at baseline.

- Analysis of the Hypertension Detection and Follow-up Program<sup>37</sup> cohort demonstrated that in the presence of hypertension, overweight and obesity significantly increased the risk of CKD compared with normal BMI. In patients who were not diabetic at baseline, the adjusted OR for CKD at 5 years in the overweight group was 1.22 and for the obese group it was 1.38. This study was conducted in the 1970s and it is not known if lower BP targets and newer antihypertensive agents attenuate the risk. CKD was defined as proteinuria 1+ on dipstick and/or eGFR < 60 mL/min.

- A Swedish case control study<sup>36</sup> showed that overweight BMI at age 20, was associated with a 3-fold increase in the risk of CKD and was independent of diabetes and hypertension. Patients were stratified for cause of kidney disease and although the influence of overweight at 20 years was greatest for diabetic nephropathy (5-fold increase), overweight patients also had a 3-fold increase in risk of nephrosclerosis and glomerulonephritis.

- Other earlier studies have not demonstrated an independent association between obesity and subsequent ESKD. The study by Perry *et al.*<sup>44</sup> involved a high-risk group cohort of hypertensive veterans, of whom 45% died during follow up and the degree to which CKD contributed to their death was not examined. Iseki *et al.*<sup>45</sup> found an association between BMI and ESKD in men that was explained by diabetes.

It is important to note that while there is a fairly consistent increase in relative risk between obesity and kidney disease, the absolute risk of ESKD for an individual is small. Using the Kaiser Permanente population as an example, the adjusted rate of ESKD is 10 per 100 000 person years for normal BMI and 46 per 100 000 person years for BMI 30–34.9 kg/m<sup>2</sup>. In terms that patients are more likely to comprehend, this equates to a risk of ESKD over 10 years of 1 in every 1000 normal BMI patients, compared with 4.6 in every 1000 obese patients.

The associations between obesity and incident CKD, are to a variable degree dependent on the associated comorbidities of hypertension and diabetes. This is of relevance when assessing donors who have been carefully screened for these risk factors, and the risk associated with obesity in the

absence of these is likely to be small. However, these assurances can't be assumed in the young donor in whom they may not yet be manifest.

Obesity may be a greater risk factor for loss of GFR in patients who already have impaired kidney function. This is analogous to the greater impact of hypertension in causing progressive disease in patients with CKD when compared with those with normal kidney function. There are some data ( $n = 162$ ) to suggest that obesity promotes more rapid loss of renal function in patients with IgA nephropathy.<sup>46</sup> Patients who were overweight had heavier proteinuria at time of biopsy, were more likely to be hypertensive, have more severe tubulointerstitial changes on biopsy and to subsequently develop hypertension and renal impairment.

### Other associations

Gestational diabetes: a systematic review<sup>47</sup> demonstrated that gestational diabetes is associated with a 17–63% increase in risk of Type 2 diabetes within 5–16 years of pregnancy. The highest risk occurs in the first 5 years after pregnancy and then appears to plateau. BMI > 30 kg/m<sup>2</sup> was identified to further increase risk associated with gestational diabetes in most but not all studies.

Renal cell carcinoma (RCC): although RCC only accounts for 2.8% of cancers in Australia (Cancer in Australia, 2001), it is of particular relevance to potential donors. A systematic review<sup>48</sup> of 22 small studies demonstrated an increase in the relative risk of RCC of 1.07 (95% CI: 1.05–1.09) per unit increase in BMI and the risk was equivalent in men and women. Therefore, the relative risk for patients with a BMI of 30 kg/m<sup>2</sup> is 1.35. Subsequent large cohort studies have been consistent with this finding<sup>49,50</sup> although others have failed to find an association between obesity and RCC in men.<sup>51,52</sup> There is a biologically plausible link between obesity and RCC as increasing BMI is associated with elevated levels of fasting serum insulin-like growth factor,<sup>53</sup> which has been shown to increase cellular proliferation in RCC in animal models.

Kidney stones: analysis of data from the Nurse's Health Study I and II and the Health Professionals Follow-up Study<sup>54,55</sup> demonstrated that prevalence and incidence of new stone disease was directly associated with BMI, with a stronger relationship evident in women. The age-adjusted prevalence OR for women with a BMI  $\geq 32$  kg/m<sup>2</sup> compared with 21–22.9 kg/m<sup>2</sup> was 1.76 (95% CI: 1.50–2.07), and 1.38 (1.51–2.36) for the same analysis in men. For incident stone formation in women, the OR was 1.89 (1.51–2.36) in women, but not significantly different in men.

### The acceptance of obese donors is increasing

Increases in rates of donor obesity have occurred over the past decade and demonstrate regional variation. In a survey of UK transplant centres published in 1999,<sup>56</sup> only one centre was identified as accepting patients with a BMI greater than 30 kg/m<sup>2</sup> or a weight greater than 20% above ideal. Results of a survey of US centres, published in 1995,

reported that only 16% of centres would exclude a donor with moderate obesity.<sup>57</sup> The same centres were surveyed in 2005<sup>58</sup> and the following cut-offs were described – 10% of centres would exclude a donor if BMI > 30 kg/m<sup>2</sup>, 52% if BMI > 35 kg/m<sup>2</sup> and 20% if BMI > 40 kg/m<sup>2</sup>. Subsequent publications<sup>59,60</sup> from the US demonstrate that, in some centres, 20–30% of donors have a BMI > 30 kg/m<sup>2</sup> and data from the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) registry suggest that from 7/2004 to 12/2005, 13% of US donors had a BMI > 30 kg/m<sup>2</sup>.

There are data to suggest that acceptance of obese donors is also increasing in Australia.<sup>61</sup> Preliminary data from the ANZ live donor registry presented in 2007 at the ANZSN ASM, suggest that 16% of donors from 2004–2006 had a BMI of between 30 and 35 kg/m<sup>2</sup> and 2.3% had a BMI > 35 kg/m<sup>2</sup>.

### The impact of nephrectomy in obese patients

Assessment of living donors involves both the assessment of early risk associated with perioperative morbidity and mortality and long-term risk, predominantly associated with the risk of future kidney disease.

### Short term risks associated with obesity

Retrospective analysis of a US healthcare registry<sup>62</sup> using discharge data for 3074 patients from 28 centres identified comorbidities and complications using ICD-9-CM coding data. Obesity was associated with an increased risk of overall complication rate (OR 1.92, 95% CI 1.06–3.46), however, numbers were too small to assess the impact of obesity on the incidence of major complications, and the study was not able to discriminate between open and laparoscopic nephrectomy. Similar results have been reported from a number of single centre studies, demonstrating an increase in minor complications in obese donors for both open and laparoscopic nephrectomy (see Table 3).<sup>59,63,64</sup> Complications are predominantly wound related and include wound infection, seroma and hernias. The rates of wound infection approach 10% in the obese compared with 2% in normal weight donors. Operative time is longer in obese patients – with increases ranging from 10 to 41 min, but no increase in length of hospital stay is reported.<sup>59,63,65,66</sup> Nor is there any reported increase in delayed graft function in the recipient. Numbers are small and results relating to conversion from laparoscopic to open procedure are mixed, with some studies reporting no difference<sup>59,67</sup> and others<sup>66</sup> reporting increased conversion in obese men. They also commented that the perinephric distribution of fat in obese men increased the technical difficulty. There is a consistent pattern of greater blood loss and increased transfusion requirements in obese patients, which is not significant in each of the single centre studies due to small numbers.<sup>63,66–69</sup> In addition, laparoscopic donor nephrectomy has been a relatively new technique and there may have been an increased complication rate in the more technically challenging obese patients as part of the

learning curve. Rhabdomyolysis is a rare complication of donor nephrectomy. Sporadic case reports of rhabdomyolysis in donors are characterized by the following risk factors – long operative time, laparoscopic procedure and high BMI.<sup>68,70–73</sup>

Does nephrectomy increase the risk of future renal disease in obese patients? Studies in which baseline BMI has been reported are outlined in Table 4.

There are limited data from which to address this issue. The often quoted follow-up studies of living donors are limited by several significant methodological flaws, studies are retrospective, predominantly Caucasian and the rate of loss to follow up is high. Baseline BMI has not been reported in many of the older studies and obese patients are almost certainly under-represented in the long term follow-up statistics used to educate prospective donors regarding the risks of nephrectomy.

Studies reporting baseline characteristics of obese donors suggest that they are at higher risk of future kidney disease.<sup>59,63,74,75</sup> A study from a centre<sup>59</sup> with a high use of obese donors, in which 31% of donors had a BMI > 30 kg/m<sup>2</sup> gives a detailed analysis of the baseline characteristics of obese donors. Obese donors had a significantly higher pre-nephrectomy BP (137/79 vs 126/73 mmHg), increased history of donor hypertension (14% vs 4%), more adverse lipid profiles, higher fasting glucose levels (although within the normal range) and had a family history of diabetes (47% vs 33%), when compared with donors with a BMI < 25 kg/m<sup>2</sup>. Data are available at 1 year for approximately 60% of donors in this study, and demonstrates that BP and fasting glucose remained higher, albeit in the acceptable range, and did not incrementally increase post nephrectomy. The post-nephrectomy GFR and rates of microalbuminuria were not different in the obese, within this short timeframe.

Donors who are overweight or obese are more likely to gain weight post donation than those of normal weight.<sup>76</sup>

There is a probable relationship between BMI and subsequent hypertension.<sup>74,76–78</sup> Obese patients are more likely to have higher BP at the time of donation and it is unknown if nephrectomy alters the age of onset or severity of hypertension. A German study of 152 donors, with 93% followed for a mean of 11 years and with pre-nephrectomy BMI of 26 ± 4 kg/m<sup>2</sup>, demonstrated that baseline BMI was correlated with mean arterial pressure but not change in BP post donation.<sup>78</sup>

There is no evidence of association between the baseline BMI and development of proteinuria or decline in GFR post donation in predominantly Caucasian populations.<sup>78,79</sup> However, the number of donors who were obese at baseline is too small to be able to determine this with any certainty. The study from the Mayo Clinic<sup>79</sup> had long-term follow up on 73% of donors with a median follow up of 12 years. Only data on weight are available and is not differentiated for gender. Median weight at donation was 70 kg and weight gain at follow up was 7.5 kg. Baseline weight, change in weight and relative weight (measured/ideal weight) was not a significant predictor of current serum creatinine or change in creatinine. The flaws are use of creatinine rather than GFR and the number of patients who were obese at baseline is unknown.

The most detailed study, examining the impact of obesity is from Pakistan.<sup>80</sup> The study was large (736 patients) with a mean follow up of 3 years (range: 6 months to 18 years). At last follow up, 11.5% of patients were obese and obesity was more common in women (17% vs 6%). Obese donors, when compared with the non-obese donors, had significantly higher rates of diabetes (13.5% vs 3%) and hypertension (24% vs 10%). There was a non-significant trend to lower GFR (<60 mL/min) and a higher prevalence of proteinuria in obese donors. This data are concerning and the median follow-up time is short. There is limited detail given in terms of screening donors for diabetes, or presence of family history for diabetes and baseline BMI. There are cultural reasons cited for the high rate of weight gain post donation, and the population studied is one that is ethnically more at risk of developing diabetes.

This study highlights that the safety data drawn from predominantly Caucasian populations, do not necessarily hold true for populations with a greater risk of diabetes and/or kidney disease. A report from the OPTN/UNOS registry<sup>81</sup> records 102 individuals as waiting for transplant who have previously been living donors, in which African Americans are over-represented. There is no information on the prevalence of obesity in the group or other identifiable risk factors that may have been present at donation, however, hypertension and diabetes are listed as the cause of ESKD in roughly one third.

The histology of implantation biopsies in obese living donors is subtly different from non-obese donors.<sup>82</sup> Increased glomerular planar surface area (GPSA), glomerulomegaly and minor tubular abnormalities are more common in obese donors and there is a trend to increased arterial hyalinosis. There was no difference in the number of segmental sclerotic lesions or degree of interstitial fibrosis. GPSA was correlated with albuminuria, although all donors had 24 h urinary albumins that were within the normal range. Donor follow up was less than 1 year and no difference in serum creatinine was seen between obese and non-obese donors.

A retrospective analysis of 73 patients examined the outcome of unilateral nephrectomy done for clinical indication (i.e. not donors).<sup>83</sup> At the time of nephrectomy, patients had normal creatinine and urinalysis, no multi-system disease such as diabetes and no morphological abnormality of the remaining kidney examined by ultrasound. Median follow up was 13.6 years (range: 18 months to 35 years). Twenty of 73 patients developed abnormalities of renal function (proteinuria  $\pm$  renal insufficiency). Average time to proteinuria was  $10 \pm 6$  years and was slowly progressive in most patients. Thirteen of 73 patients developed renal impairment (serum creatinine > 1.4 mg/dL and creatinine clearance < 70 mL/min per 1.73 m<sup>2</sup>). Time between development of proteinuria and onset of renal impairment was  $4.1 \pm 4.3$  years. Renal impairment was progressive and two patients were biopsied with histology revealing glomerulomegaly and focal segmental glomerulosclerosis. At time of nephrectomy, BP, age and renal function were similar between those that did and did not develop CKD. There were, however, significant differences in BMI at the time of nephrectomy (BMI 24.9 kg/m<sup>2</sup> in normal function

group, compared with 33.7 kg/m<sup>2</sup> in the abnormal renal function group). BMI was independently associated with proteinuria/renal dysfunction on multivariate analysis (OR 1.34, 95% CI: 1.03–1.76). At 10 years following nephrectomy, the probability of negative proteinuria and normal renal function was 40% and 70%, respectively, in the obese group and 93% and 98%, respectively, for the non-obese patients. It is important not to overinterpret this study, which is retrospective, has small numbers, is subject to ascertainment bias and involved patients who may have had undiagnosed abnormalities of the remaining kidney. However, it does raise some uncertainty about the long-term safety of nephrectomy in obese donors.

### Utility of weight loss

In attempting to modify the risks associated with nephrectomy, it is a logical step to advise obese donors to lose weight prior to donation. In many cases, the perceived benefits of living donation for the recipient will be a strong motivating force. However, the success of sustained weight loss in the general population is low and there are no data on the long-term success rate of pre-donation weight loss.<sup>84,85</sup>

## SUMMARY OF THE EVIDENCE

It is likely that obesity is associated with an increase in perioperative complications, such as wound infections and transfusion requirements. There are limited data on which to base recommendations for long-term safety of the procedure for patients with a BMI > 30 kg/m<sup>2</sup> and none for patients with a BMI > 35 kg/m<sup>2</sup>. Most studies show that obese donors do have more adverse risk profiles, in particular a higher pre-donation BP and it is likely that there is a greater risk of donor hypertension. It is not known whether nephrectomy alters the risk of developing kidney disease or changes the rate of progression. Further studies need to be carried out to define risk.

## WHAT DO THE OTHER GUIDELINES SAY?

### INTERNATIONAL GUIDELINES:

#### The Amsterdam Forum on the Care of the Living Kidney Donor (2006)<sup>86</sup>

- All living donors should have BMI determined at baseline evaluation and obesity should be considered an increased risk for renal disease, acknowledging that there are no data on which to base a firm recommendation.
- Patients with a BMI > 35 kg/m<sup>2</sup> should be discouraged from donating, especially when other comorbid conditions are present.
- Obese patients should be encouraged to lose weight prior to kidney donation and should be advised not to donate if they have other associated comorbid conditions.
- Obese patients should be informed of both acute and long-term risks, especially when other comorbid conditions are present.

- Healthy lifestyle education should be available to all living donors.

#### The Canadian Council for Donation and Transplantation (2006)<sup>87</sup>

There is debate regarding the eligibility of those with . . . donor BMI > 35. Little is known about either the long-term risks to such donors or the long-term outcome of kidneys from such donors.

#### European Renal Association-European Dialysis and Transplant Association (2000)

No recommendation.

#### UK Guidelines for Living Donor Kidney Transplantation (2005)<sup>88</sup>

A BMI of more than 35 kg/m<sup>2</sup> should be regarded as an absolute contraindication to kidney donation and a BMI of more than 30 kg/m<sup>2</sup> is a relative contraindication. Obese patients with a BMI greater than 30 kg/m<sup>2</sup> should undergo careful pre-operative evaluation to exclude cardiovascular, respiratory and renal disease. They should be counselled regarding the increased perioperative risk and potential long-term risk of renal disease and advised to lose weight prior to donation and encouraged to achieve their ideal weight following donation.

#### American Society of Transplantation Position Statement on the Medical Evaluation of Living Kidney Donors (2007)<sup>89</sup>

Morbid obesity is an exclusion criterion.

### SUGGESTIONS FOR FUTURE RESEARCH

1. Longitudinal assessment of the impact of obesity on the incidence of diabetes, hypertension and kidney disease in donors from ethnically diverse backgrounds. It is important that the appropriate control population be studied as donors should be healthier than the general population. Given that the life expectancy of most donors is greater than 20 years, it would be important that such a study be carried out for an extended period of time (i.e. >20 years).
2. Utility of advising on pre-donation weight loss in terms of long-term post-donation success in weight control and modification of associated risk factors for hypertension, diabetes and kidney disease.

### CONFLICT OF INTEREST

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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## APPENDICES

**Table 1** Annual incidence of diabetes and hypertension according to baseline body mass index: AusDiab<sup>24</sup>

	Diabetes (%)			Hypertension (%)		
	Males	Females	All	Males	Females	All
Normal	0.4	0.4	0.4	2.4	1.5	1.8
Overweight	0.8	0.7	0.8	3.5	3.4	3.5
Obese	1.8	1.4	1.6	5.2	5.6	5.4

**Table 2** Studies examining the association between obesity and incident kidney disease

Author, year	Cohort	Study type	N	Mean age (years)	Follow up (years)	Outcome	Outcome prevalence	Result <sup>a</sup>
White <i>et al.</i> <sup>b</sup> (2007) <sup>41</sup>	AusDiab (Australia)	Observational cohort	6 537	5	eGFR < 60 mL/min per 1.73 m <sup>2</sup>	Non-diabetics BMI <25 kg/m <sup>2</sup> ≥30 kg/m <sup>2</sup> Waist circumference <94 cm (M) and <80 cm (F) ≥102 cm (M) and ≥88 cm (F)	1.00 (referent) 1.61 (1.09–2.97) 1.00 (referent) 1.88 (1.35–2.65)	
Fox <i>et al.</i> (2004) <sup>42</sup>	Framingham Offspring (USA)	Observational cohort	2 585	43	18.5 Men eGFR < 64 mL/min per 1.73 m <sup>2</sup> Women eGFR < 59 mL/min per 1.73 m <sup>2</sup>	9.4%	<sup>c</sup> BMI 1.23 per 1 standard deviation (1.08–1.41)	
Foster <i>et al.</i> (2008) <sup>39</sup>	Framingham Offspring (USA)	Observational cohort	2 676	43	18.5 Men eGFR < 64 mL/min per 1.73 m <sup>2</sup> Women eGFR < 59 mL/min per 1.73 m <sup>2</sup>	7.9%	<sup>d</sup> Ideal BMI Overweight Obese	
Elsayed <i>et al.</i> (2008) <sup>43</sup>	Atherosclerosis Risk in Communities and Cardiovascular Health Study (USA)	Observational cohort	13 324	57.4	9.3 eGFR decrease > 15 mL/min per 1.73 m <sup>2</sup> and final eGFR < 60 mL/min per 1.73 m <sup>2</sup>	5.5%	<sup>e</sup> Waist-to-hip ratio 1.17 per unit increase (0.99–1.34) BMI 0.99 per unit increase (0.96–1.03)	
Kramer <i>et al.</i> (2005) <sup>37</sup>	Hypertension Detection and Follow-up Program (USA)	Post hoc analysis of RCT	5 307 Hypertensive non-diabetic	~51	5 1+ protein on dipstick and/or eGFR < 60 mL/min per 1.73 m <sup>2</sup>	Normal 28% Overweight 31% Obese 34%	<sup>f</sup> Ideal BMI Overweight Obese	
Hsu <i>et al.</i> (2006) <sup>40</sup>	Kaiser Permanente cohort (USA)	Historical cohort study	320 252	31–43	8 347 955 person	0.46%	<sup>g</sup> Ideal BMI Overweight Obese Class I Class II Class III	
Tozawa <i>et al.</i> (2002) <sup>90</sup>	Okinawa (Japan)	Observational cohort	5 403	~48	2 Proteinuria 1+ protein on dipstick	5.8%	<sup>h</sup> Obese (BMI > 27 kg/m <sup>2</sup> ) 1.45 (1.13–1.86)	
Perry <i>et al.</i> (1995) <sup>44</sup>	Hypertensive veterans (USA)	Observational cohort	10 222 Hypertensive	na	13.9 ESKD	1.97%	<sup>i</sup> BMI ≤ 24 >24 and ≤26 >26 and ≤30 >30	

Iseki <i>et al.</i> (2004) <sup>45</sup>	Okinawa (Japan)	Observational cohort	100 753	53	17	ESKD	0.4%	<sup>j</sup> BMI Men <21 21–23.1 23.2–25.4 ≥25.5 Women <21 21–23.2 23.2–25.5 ≥25.5	1 1.79 (1.12–2.85) 1.95 (1.23–3.09) 2.39 (1.53–3.74) 1 1.25 (0.78–1.99) 0.88 (0.53–1.44) 0.96 (0.6–1.5)
Ejerblad <i>et al.</i> (2006) <sup>36</sup>	Sweden	Nationwide, population based, case control study	926	na	na	Serum creatinine men > 300 µmol/L Women >250 µmol/L	na	<sup>k</sup> Lifetime highest <sup>k</sup> BMI Men <25 25–29.9 30–34.9 ≥35 Women <25 25–29.9 30–34.9 ≥35	1.0 (referant) 1.4 (1–1.9) 2.7 (1.9–4) 4.4 (2.4–8.2) 1.0 (referant) 1.2 (0.8–2.4) 1.4 (0.8–2.4) 3.1 (1.6–6.1)
Gelber <i>et al.</i> (2005) <sup>38</sup>	Physician's Health study	Post hoc analysis of randomized controlled trial	11 104 men	~53	14	eGFR < 60 mL/min per 1.73 m <sup>2</sup>	12.4%	<sup>l</sup> BMI <25 25–29.9 ≥30	1.0 (referant) 1.32 (0.96–1.8) 1.25 (1.11–1.41)

<sup>a</sup>Values expressed as OR (95% CI). <sup>b</sup>Abstract publication ANSN ASM 2007. <sup>c</sup>Other significant predictors of chronic kidney disease age, gender, baseline eGFR, smoking, diabetes. <sup>d</sup>Adjusted for age, sex, diabetes, systolic blood pressure, hypertension treatment, current smoking and HDL. <sup>e</sup>Adjusted for age, sex, race, high school graduation, prior cardiovascular disease, diabetes, hypertension, current smoking, alcohol consumption, systolic BP, HDL, total cholesterol, albumin, hematoctrit, baseline kidney function and study of origin. <sup>f</sup>Model adjusted for age, sex, race, diabetes, BP. <sup>g</sup>Model adjusted for age, sex, race, education level, smoking, history of myocardial infarction, serum cholesterol, proteinuria, haematuria, serum creatinine. <sup>h</sup>Model adjusted for age, sex, hypercholesterolaemia, hypertriglyceridaemia, anaemia, hyperuricaemia, alcohol intake, exercise. <sup>i</sup>Other significant predictors current smoking, hypertension, diabetes. <sup>j</sup>Univariate analysis. <sup>k</sup>Adjusted for age, education, smoking, alcohol, use of analgesics. <sup>l</sup>Adjusted for age, smoking status, alcohol consumption, exercise, family history of premature heart disease. BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; F, female; HDL, high density lipoprotein; M, male.

**Table 3** Perioperative complications associated with obesity

Author, year	N	Operation	Comparator	Overall complication rate (%)	Death	Operative time (min)	Conversion (%)	Wound complication (%)	Transfusion (no.)	Length of stay (days)
Pesavento <i>et al.</i> (1999) <sup>63</sup>	223	ON	BMI < 27 vs >27 kg/m <sup>2</sup>	3.4 vs 16.8 ***	Nil	141 vs 151*	na	2 vs 9*	0 vs 4	5.5 vs 5.7
Jacobs <i>et al.</i> (2000) <sup>69</sup>	82	LN	BMI < 30 vs BMI > 35 kg/m <sup>2</sup>	24.3 vs 24.4	Nil	195 vs 237**	0 vs 7.3	na	0 vs 0	2.7 vs 2.7
Kuo <i>et al.</i> (2000) <sup>67</sup>	40	LN	BMI < 31 vs >31 kg/m <sup>2</sup>	na	Nil	165 vs 182	3.6 vs 0	na	na	2.1 vs 2.3
Levanthal <i>et al.</i> (2004) <sup>60</sup>	500	LN	BMI < 30 vs BMI > 30 kg/m <sup>2</sup>	2.56 vs 3.63	Nil	na	1.28 vs 3.63	na	na	1.7 vs 1.7
Mateo <i>et al.</i> (2003) <sup>68</sup>	47	LN	BMI < 30 vs BMI > 30 kg/m <sup>2</sup>	na	Nil	291 vs 307	na	na	0 vs 0	4 vs 4.2
Heimbach <i>et al.</i> (2005) <sup>59</sup>	553	LN	BMI < 25 vs BMI > 35 kg/m <sup>2</sup>	5 vs 16*	Nil	127 vs 146*	1 vs 2	2 vs 9*	na	2.3 vs 2.4

\*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001. BMI, body mass index; LN, laparoscopic nephrectomy; na, not available; ON, open nephrectomy.

**Table 4** Studies of living kidney donors in which BMI is documented as baseline demographic

Author, year	Location	N	Years of donation	Percentage followed up	Death (no.)	Age at donation (years)	BMI at donation (kg/m <sup>2</sup> )	Years since nephrectomy	Outcome
Torres <i>et al.</i> (1986) <sup>76</sup>	USA	100	1963–1973	69%	5	37 ± 12	na	At least 10	Weight at donation is an independent predictor of follow-up BP
Gracida <i>et al.</i> (2002) <sup>75</sup>	Mexico	574	1992–1999	73%	na	33.7 ± 11	17% BMI > 30 kg/m <sup>2</sup>	5 ± 2	Obesity not associated with low GFR
Grossmann <i>et al.</i> (2005) <sup>78</sup>	Germany	152	1973–2001	93%	7	45 ± 11	26 ± 4	11 ± 7	BMI not associated with GFR, proteinuria or rise in BP post nephrectomy
Rizvi <i>et al.</i> (2005) <sup>80</sup>	Pakistan	734	1986–2004	57%	5	36 ± 11	Na	3 ± 3	Obesity associated with hypertension and incident diabetes
Heimbach <i>et al.</i> (2005) <sup>59</sup>	USA	325	1999–2003	59%	0	42 ± 1	Females 27.5 ± 0.3	0.9	Obesity associated with higher pre- and post-nephrectomy BP and glucose.
							Males 28.6 ± 0.3 kg/m <sup>2</sup>		Obesity not associated with serum creatinine or microalbumin.

BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate.