Body mass index and body fat distribution as renal risk factors: a focus on the role of renal haemodynamics

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ABSTRACT

Weight excess and/or central body fat distribution are associated with increased long-term renal risk, not only in subjects with renal disease or renal transplant recipients, but also in the general population. As the prevalence of weight excess is rising worldwide, this may become a main renal risk factor on a population basis, even more so because the risk extends to the overweight range. Understanding the mechanisms of this detrimental effect of weight excess on the kidneys is needed in order to design preventive treatment strategies. The increased risk associated with weight excess is partly attributed to associated comorbid conditions, such as hypertension, dyslipidaemia, insulin resistance and diabetes; however, current evidence supports a direct pathogenetic role for renal haemodynamics as well. Weight excess is associated with an altered renal haemodynamic profile, i.e. an increased glomerular filtration rate relative to effective renal plasma flow, resulting in an increased filtration fraction (FF). This renal haemodynamic profile is considered to reflect glomerular hyperfiltration and glomerular hypertension, resulting from a dysbalance between afferent and efferent arterial vasomotor balance. This unfavorable renal haemodynamic profile was found to be associated with renal outcome in experimental models and in human renal transplant recipients, and is associated with a blunted sodium excretion, and reversible by weight loss, renin-angiotensin-aldosterone system blockade or by dietary sodium restriction. More recent evidence showed that a central body fat distribution is also associated with an increased FF, even independent of overall weight excess. In this review, we provide an overview...
over, a body mass index (BMI) over 25 kg/m² still carries a 2
morbid obesity have a 5-fold increased risk for end-stage renal
distribution, and we will describe the implications for long-
and obesity, including the association with central body fat
progression of chronic renal damage. In this review, we will
studies, where glomerular
response in the remnant nephrons, characterized by glomer-
hypertension, is an important factor in progressive renal
Brenner
association between obesity and progressive renal damage in
subjects with renal disease [1], in renal transplant recipients
Overweight and obesity are well-established risk factors for the
development of renal function loss. Several studies noted an
association between obesity and progressive renal damage in
subjects with renal disease [1], in renal transplant recipients
and even in the general population [5–9]. Subjects with
morbid obesity have a 5-fold increased risk for end-stage renal
disease (ESRD) when compared with lean subjects [7]. More-
over, a body mass index (BMI) over 25 kg/m² still carries a 2
to 3-fold elevated long-term risk of ESRD [7, 8]. Of note, a
central body fat distribution is also associated with a detriment-
long-term renal prognosis [10, 11].

Several factors contribute to the adverse renal effect of
weight excess. Overweight subjects have an increased risk of
developing hypertension, dyslipidaemia, insulin resistance/
diabetes mellitus and cardiovascular complications, all of
which promote chronic kidney disease (CKD). However,
even in the absence of these risks, obesity itself is associated
with the development of CKD and accelerates its progression
[8, 9]. Weight excess and/or a central body fat distribution are associated with an unfavourable renal haemodynamic
profile, which may play a role in the susceptibility and pro-
gression of chronic renal damage. In this review, we will
focus on these renal haemodynamic alterations in overweight
and obesity, including the association with central body fat
distribution, and we will describe the implications for long-
term renal risk.

INTRODUCTION

Experimental data

The role of renal haemodynamics in progressive renal
function loss in obesity has mainly been derived from animal
studies, where glomerular flow and filtration pressure can be
directly measured. The pathogenetic potential of altered
renal haemodynamics was first put forward in the 1980s by
Brenner’s group, who extensively demonstrated that glomer-
ular hyperfiltration, and in particular glomerular capillary
hypertension, is an important factor in progressive renal
function loss in remnant kidney models. The adaptive
response in the remnant nephrons, characterized by glomer-
ular capillary hypertension, serves to preserve glomerular fil-
tration in the short term, but leads to glomerular capillary
damage, glomerular protein leakage and consequent nephron
loss on the long term, thus eliciting a vicious circle of progress-
ive renal damage [12].

Renal haemodynamic alterations resembling those in rem-
nant nephrons have been observed in experimental models of
obesity-associated renal damage, albeit not uniformly. These
include an increased glomerular filtration rate (GFR) relative
to effective renal plasma flow (ERPF), resulting in an
increased glomerular filtration pressure and filtration fraction
(FF), caused by a dilated glomerular afferent arteriole, accom-
panied by a relatively elevated efferent arteriolar vascular tone
[13–15]. However, the evidence for a major pathogenetic role
of glomerular hypertension in obesity-associated models is
not as abundant as in remnant kidney models. Moreover, the
relative contribution of renal haemodynamics to overall renal
damage versus the effects of systemic hypertension, dyslipi-
daemia and insulin resistance in obesity has not been estab-
lished with certainty, and may vary between different obesity
models.

Human data: assessment of renal function and renal
haemodynamics in relation to weight excess

In humans, renal function can only be measured
indirectly and currently relies mainly on creatinine-based
equations for estimated GFR (eGFR) [16–18]. For the assess-
ment of GFR in relation to body dimensions, however, it is
important to be aware that renal function equations are
subject to BMI-associated bias. A recent study in healthy sub-
jects, comparing the Cockcroft–Gault, Modification of Diet
in Renal Disease (MDRD) and CKD-EPI formulas, showed that
the influence of BMI on overestimation of GFR was the
largest for Cockcroft–Gault and least for MDRD and CKD-
EPI [19]. In transplant recipients, the MDRD equation
progressively underestimated Cockcroft–Gault and overesti-
imated true GFR with an increasing BMI [20]. Likewise, in
subjects with native kidney disease, the Cockcroft–Gault
equation underestimated GFR at low BMI, and overestimated
GFR at high BMI [21]. This substantially hampers the interpre-
tation of studies on BMI and renal function by eGFR.
Creatinine clearance using well-collected 24 h urine samples
might be a non-biased alternative to assess renal function in
relation to weight excess. However, Sinkeler et al. [22] re-
cently showed that tubular creatinine secretion is closely
associated with BMI, thus affecting the performance of crea-
tinine clearance. BMI independently determined the overesti-
imation of true GFR (125I-iothalamate) by creatinine
 clearance that ranged from 6% in lean subjects to 15% in
 obese subjects. Thus, the impact of BMI on tubular creatinine
handling needs to be accounted for in the interpretation of
creatinine-based renal function assessment. The association
between BMI and tubular creatinine secretion was confirmed
in renal transplant recipients, supporting the robustness of
the association [23].

The gold standard for the assessment of GFR and ERPF in
humans is by the renal clearance of markers such as inulin,
99mTc diethylene-triamine pentaacetic acid (Tc-DTPA) or
iothalamate and Xenon, para-hippuric acid or hippur-
an, respectively [24]. When GFR and ERPF are measured sim-
ultaneously, FF can be calculated as the ratio from GFR and
ERPF, a helpful parameter to interpret changes in GFR in
terms of the underlying haemodynamic changes. During hy-
perperfusion, GFR will rise in proportion to ERPF with a
stable FF. When a rise in GFR is due to a change in filtration
Table 1: Human studies on the impact of body weight (excess) and body fat distribution on renal haemodynamics

<table>
<thead>
<tr>
<th>References</th>
<th>N</th>
<th>Population</th>
<th>Categorized by increasing BMI (kg/m²)</th>
<th>GFR assessment</th>
<th>ERPF assessment</th>
<th>Renal haemodynamics in obese subjects versus non-obese controls</th>
<th>Indexing measure</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Renal haemodynamics</td>
<td>Indexing measure</td>
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<tr>
<td></td>
<td></td>
<td>Impact of overall body weight (excess) on renal haemodynamics</td>
<td>Subjects without apparent comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[32]</td>
<td>95</td>
<td>Healthy men, all non-obese</td>
<td>23</td>
<td>Iothalamate</td>
<td>Hippurate</td>
<td>↑ FF with higher BMI; all subjects studied during low and high salt diet. GFR and FF positively associated with BMI on a high, but not on a low, salt diet</td>
<td>Unindexed, and indexed for height</td>
</tr>
<tr>
<td>[33]</td>
<td>102</td>
<td>Healthy subjects, all non-obese</td>
<td>24</td>
<td>Iothalamate</td>
<td>Hippurate</td>
<td>↑ FF with higher BMI</td>
<td>Indexed for BSA and height</td>
</tr>
<tr>
<td>[31]</td>
<td>315</td>
<td>Healthy subjects, 35% overweight and 10% obese</td>
<td>25</td>
<td>Iothalamate</td>
<td>Hippurate</td>
<td>↑ FF and ↓ ERPF with higher BMI</td>
<td>Unindexed, and indexed for BSA and height</td>
</tr>
<tr>
<td>[34]</td>
<td>45</td>
<td>Severely overweight subjects</td>
<td>29</td>
<td>–</td>
<td>Xenon</td>
<td>↑ RBF, on low sodium diet only</td>
<td>Unindexed</td>
</tr>
<tr>
<td>[28]</td>
<td>20</td>
<td>Severely obese subjects versus lean/ moderately overweight subjects</td>
<td>47 versus 26</td>
<td>Inulin</td>
<td>Hippurate</td>
<td>No consistent difference in RBF</td>
<td>Unindexed, and indexed for BSA and height</td>
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<td></td>
<td></td>
<td>Subjects with hypertension</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>[35]</td>
<td>42</td>
<td>Obese versus lean subjects, either normo- or hypertensive</td>
<td>31 versus 22</td>
<td>–</td>
<td>Hippurate</td>
<td>↑ RBF in normotensive and hypertensive obese subjects</td>
<td>Unindexed, and indexed for height</td>
</tr>
<tr>
<td>[27]</td>
<td>60</td>
<td>Overweight/obese versus lean subjects, either normo- or hypertensive</td>
<td>32 versus 23</td>
<td>Tc-DTPA</td>
<td>Hippurate</td>
<td>↑ FF in hypertensive obese only, ERPF and GFR in obesity</td>
<td>Unindexed, and indexed for height</td>
</tr>
<tr>
<td>[2]</td>
<td>838</td>
<td>Renal transplant recipients, 13% obese, 72% hypertensive</td>
<td>26</td>
<td>Iothalamate</td>
<td>Hippurate</td>
<td>↑ FF and ↑ GFR with higher BMI, independent of DM</td>
<td>Unindexed, and indexed for height</td>
</tr>
</tbody>
</table>

Continued
pressure, this will be apparent as a rise in FF. An increased FF is assumed to be a pathogenetic factor in long-term renal damage. For these reasons, FF is used as an alternative parameter for glomerular hypertension in the human. However, it must be kept in mind that glomerular pressure cannot be directly assessed in humans. Accordingly, the measurement of an increased FF in humans cannot distinguish between increased glomerular pressure and other causes of a high GFR.

### Table 1: Continued

<table>
<thead>
<tr>
<th>References</th>
<th>N</th>
<th>Population</th>
<th>Categorized by increasing BMI (kg/m²)</th>
<th>GFR assessment</th>
<th>ERPF assessment</th>
<th>Renal haemodynamics in obese subjects versus non-obese controls</th>
<th>Indexing measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>[36]</td>
<td>12</td>
<td>Morbidly obese subjects with insulin resistance versus healthy subjects</td>
<td>44 versus 22</td>
<td>Inulin</td>
<td>Hippurate</td>
<td>↑ FF, ↑ RBF and ↑ GFR in obese subjects with insulin resistance</td>
<td>Unindexed</td>
</tr>
<tr>
<td>[37]</td>
<td>8</td>
<td>Morbidly obese subjects with insulin resistance versus healthy subjects</td>
<td>48 versus 22</td>
<td>Inulin</td>
<td>Hippurate</td>
<td>↑ FF, ↑ RBF and ↑ GFR in obese subjects with insulin resistance; studied before and after weight loss by bariatric surgery</td>
<td>Unindexed</td>
</tr>
</tbody>
</table>

### Impact of body fat distribution on renal haemodynamics

<table>
<thead>
<tr>
<th>References</th>
<th>N</th>
<th>Population</th>
<th>Categorized by increasing WHR</th>
<th>GFR assessment</th>
<th>ERPF assessment</th>
<th>Renal haemodynamics in central obese subjects versus peripheral obese controls</th>
<th>Indexing measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>[31]</td>
<td>315</td>
<td>Healthy subjects, 35% overweight and 10% obese</td>
<td>WHR: 0.87</td>
<td>Iothalamate</td>
<td>Hippurate</td>
<td>↑ FF, ↓ ERPF and ↓ GFR associated with higher WHR, independent of BMI</td>
<td>Unindexed, and indexed for BSA and height</td>
</tr>
<tr>
<td>[39]</td>
<td>64</td>
<td>Central body fat distribution versus peripheral body fat distribution (normo- and hypertensive subjects)</td>
<td>WHR: 0.95 versus 0.85</td>
<td>Tc-DTPA</td>
<td>Hippurate</td>
<td>↑ FF (nominally significant) and ↓ ERPF/ERBF in subjects with central body fat distribution (in both normo- and hypertensive subjects)</td>
<td>Unindexed</td>
</tr>
<tr>
<td>[38]</td>
<td>81</td>
<td>Black hypertensive subjects</td>
<td>WHR 0.96</td>
<td>—</td>
<td>Hippurate</td>
<td>↓ RBF with increasing WHR</td>
<td>Indexed for BSA</td>
</tr>
</tbody>
</table>

N, number of subjects; BMI, body mass index; BSA, body surface area; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; RBF, renal blood flow; FF, filtration fraction.
relative to ERPF, i.e. a higher Kf, due to a larger glomerular capillary surface area, such as for instance can occur by glomerulomegaly [25], or redistribution of renal blood flow (RBF) to juxtamedullary nephrons that have a higher FF. These data on FF in humans should always be interpreted with caution.

Usually, GFR and ERPF are indexed for body dimensions, and expressed per 1.73 m² body surface area (BSA). However, for assessing renal function in relation to weight excess, this indexing practice can induce a bias as weight excess leads to a higher BSA. Thus, when an individual gains weight, BSA-normalized kidney function would ‘decrease’ in the absence of a true change in renal function. The validity of this approach is therefore questionable and several authors recommended indexing for height [26–28]. Several other authors proposed to normalize GFR to the extracellular volume (ECV) [29, 30]. Visser et al. [29] showed that this alternative way of indexing annihilates the difference in GFR between men and women, as well as the difference in GFR between low and high sodium intake, as found for GFR/1.73 m² BSA and GFR/height and with the MDRD equation. Overall, no consensus exists about the best way to index GFR and ERPF for between-individual differences in body dimensions. Therefore, FF is highly useful to analyse renal haemodynamics in relation to weight excess, since it is not dependent on assumptions on the best way of indexing.

Associations between BMI and body fat distribution with renal haemodynamics in humans

Studies on the association between renal haemodynamics with BMI and body fat distribution are summarized in Table 1. Generally, FF was increased in proportion to BMI. Of note, no lower threshold of BMI was found for this association that extends across the normal, overweight and obese range as illustrated in Figure 1 (upper panels) [31]. This association was independent of sex, age, blood pressure and BSA. In addition, several, albeit not all, studies report that the higher FF occurs along with a higher GFR as well as ERPF (or RBF), indicating hyperperfusion with a more than proportional rise in GFR, consistent with glomerular hypertension [2, 27, 28, 31–37]. Ribstein et al. [27], in a relatively small study, found that obesity was associated with altered renal haemodynamics in hypertensive, but not

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![Figure 1](image1.png)

**Figure 1:** Scatter plots showing the univariate associations between BMI (upper panel) and WHR (lower panel), respectively, with BSA-indexed GFR and ERPF, and FF. WHR, waist-to-hip ratio; BMI, body mass index; BSA, body surface area; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fraction. Adapted from Kwakernaak et al. [31].

![Figure 2](image2.png)

**Figure 2:** Three-dimensional bar graph showing the combined effects of WHR and BMI on FF, showing mean FF (y-axis) by a break-up of the sex-stratified median of WHR (x-axis) and break-up of the median of BMI (z-axis). Median WHR was 0.86 and median BMI was 24.6 kg/m². WHR, waist-to-hip ratio; BMI, body mass index; FF, filtration fraction. Copied from Kwakernaak et al. [31].
in normotensive subjects, indicating the relevance of co-morbidity. Body fat distribution is associated with renal haemodynamics as well [31, 38, 39]. A more central body fat distribution was associated with a higher FF (Figure 1, lower panel) [31]. This was independent of sex, age, blood pressure, BSA, as well as BMI. As a result, FF is determined by both BMI and body fat distribution, as illustrated in Figure 2 [31]. Interestingly, in this study, a waist-to-hip ratio (WHR) was inversely associated with BSA-indexed GFR, whereas no association with BMI was present. One interpretation might be that the increase in GFR is physiological as the association with BMI disappeared after adjustment for BSA—which, in this setting, might be considered to be reflective of the overall increased metabolic need of the obese body. In contrast, the WHR was inversely associated with GFR, even after adjustment of BSA, possibly reflecting a true detrimental effect. Several studies demonstrated the reversibility of the BMI-associated changes in renal haemodynamics. Chagnac et al. [37] reported that even pronounced hyperfiltration and hyperperfusion are reversible with weight loss after bariatric surgery. Krikken et al. [32], in a different setting, showed that dietary salt restriction reversed the increased GFR and FF in overweight but otherwise healthy subjects. Furthermore, renin-angiotensin-aldosterone system (RAAS) blockade reversed the renal haemodynamic changes in obesity as well [40].

These data support the functional nature of the haemodynamic changes, although glomerulomegaly may contribute in obese subjects [41]. Implantation biopsies in 49 obese kidney donors, with a higher iothalamate clearance than non-obese controls, showed a larger glomerular planar surface area (Kf) than in non-obese controls, which correlates with body weight and urinary albumin excretion [42]. The dynamics of the kidney response to body dimensions is also illustrated by data from renal transplant recipients. After transplantation, the kidney adapts to the body dimensions of the recipients [43]. Interestingly, recipient BMI is independently associated with FF in the transplanted kidney, notwithstanding the single kidney state, the denervation and multiple medications that can affect renal haemodynamics, illustrating the robustness of the association [2].

**Figure 3:** Effect of BMI on GFR, FF and ECV during low (white bars) and high (black bars) sodium intake in healthy male subjects. GFR, FF and ECV during, respectively, low and high dietary sodium intake are shown for a break-up of BMI. White and black bars represent low and high dietary sodium intake, respectively. Results are expressed as mean ± SD. *P < 0.01 LS versus HS intake. #P < 0.01 low BMI versus high BMI. BMI, body mass index; GFR, glomerular filtration rate; FF, filtration fraction; ECV, extracellular volume. Adapted from Krikken et al. [32] and Visser et al. [47].

**Pathophysiological consequences of altered renal haemodynamics in overweight and obesity**

The renal haemodynamic profile in overweight and obesity, and in subjects with a central body fat distribution, can affect sodium and volume homeostasis, as well as long-term susceptibility to renal damage. Sodium homeostasis is closely interlinked with renal haemodynamics. A high FF, indicating a relatively high efferent vascular tone, is associated with blunted sodium excretion by reducing peritubular hydrostatic pressure and hence facilitating tubular sodium reabsorption. Thus, a higher FF predisposes to ECV expansion, in particular during high sodium intake, and consequently to salt-sensitive hypertension. This is in line with older data on renal haemodynamics in salt-sensitive hypertension [44, 45], and with the clinical association between weight excess and salt-sensitive hypertension, that is reversible by weight loss [46]. Interestingly, in young normotensive subjects, overweight is associated with a rise in FF in response to high salt intake, whereas in lean subjects GFR increases without a rise in FF. In overweight subjects, moreover, high salt intake is associated with a larger increase in the ECV than in lean subjects, supporting the impact of subtle changes in renal haemodynamics on volume homeostasis (Figure 3) [32, 47]. The long-term consequences of this unfavourable renal haemodynamic profile, elicited by the combination of overweight and excess sodium intake, have not been documented, but it may well contribute to the development of salt-sensitive hypertension and renal damage later in life. Whereas the adverse effect of a high FF on renal damage has been well documented in the rat remnant kidney model, human data on the association between an unfavourable renal haemodynamic pattern and long-term renal outcome are particularly sparse. To the best of our knowledge, there is only the report by Bosma et al., showing that high BMI was associated with both and increased FF and worse death-censored graft loss in renal transplant recipients, and where higher FF was a predictor of worse graft outcome, indepen-
association is probably not straightforward, as higher FF was also associated with patient mortality.

**MECHANISMS AND IMPLICATIONS**

Increased activity of the RAAS has been implicated in the renal haemodynamic profile in overweight and obesity [48]. The reversibility by RAAS blockade is in line with this assumption [40]. Interestingly, a higher BMI is also associated with a better long-term renal outcome of RAAS blockade, suggesting that inappropriately elevated RAAS activity is particularly involved in renal damage in overweight and obese subjects [49]. The interaction between BMI, renal haemodynamics and sodium status suggests that overweight hampers the suppression of RAAS activity by high sodium intake and/or volume expansion. Whereas this could not be substantiated for circulating components of the RAAS, tissue RAAS activity has been shown to be increased in obesity, and not suppressed by high sodium intake. Taken together, these data indicate that RAAS blockade would be a rational pharmacotherapy for overweight or obese subjects with hypertension and or renal damage—preferably combined with dietary sodium restriction. It would be logical to assume corresponding mechanisms for subjects with a central body fat distribution, but so far, no data are available. Yet, additional intrarenal factors may be involved, in particular increased glomerular and tubular dimensions [41].

**CONCLUSIONS**

Weight excess and/or central body fat distribution have been extensively linked to renal damage in CKD and in the general population. The effects of weight excess on the kidney are not limited to overt obesity, but extend to the much more prevalent overweight range, both for the short-term effects on renal haemodynamics and the long-term effects on renal outcome. Weight excess therefore may become the main renal risk factor for the near future, especially in subjects with a central body fat distribution. Renal haemodynamic factors may contribute to the propensity of salt-sensitivity and salt-sensitive hypertension in overweight and obesity, and to the development and progression of renal damage. Whereas weight excess and a central body fat distribution are independent renal risk factors, the overall renal risk is also determined by the added risks of their comorbid conditions, i.e., hypertension, dyslipidaemia, insulin resistance and diabetes mellitus, which should receive proper treatment. For preventive purposes, it is relevant that the renal haemodynamic changes are reversible, by weight loss, RAAS blockade and by dietary sodium restriction, and moreover, that they are already present in young adults, in the absence of hypertension or diabetes, suggesting that early intervention is feasible. Therefore, the effect of lifestyle improvement, i.e., weight loss, physical activity and sodium restriction on renal risk, should be a target for further research.

**REFERENCES**


**CONFLICT OF INTEREST STATEMENT**

None declared.