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Role of renal haemodynamics in the renal risks of overweight

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The complications of weight excess will heavily burden the health care system in the near future, considering the increasing prevalence of overweight and obesity [body mass index (BMI) > 25 and BMI > 30 kg/m^2, respectively]. Renal damage is an emerging complication of weight excess. Fuelled by recent data, this paper will review the role of renal haemodynamics in the renal complications of weight excess.

The increasing impact of morbid obesity as a primary cause of renal damage is supported by a large series of renal biopsies, showing an increase in the prevalence of glomerulosclerosis associated with morbid obesity from 0.2 to 2% over a period of 15 years [1]. Recent studies, moreover, highlight the impact of less extreme weight excess as a risk factor for renal damage in patients with a pre-existing renal disorder [2], after uninephrectomy [3], in renal transplant recipients [4,5] and in the general population [6,7]. Whereas a BMI over 40 kg/m^2 is associated with a 7-fold increased long-term risk for end-stage renal disease (ESRD) as compared to lean subjects, a BMI over 25 kg/m^2 in young adults still carries a 3-fold elevated long-term risk of ESRD [6,7]. Together with the endemic prevalence of obesity and particularly overweight, these data suggest that weight excess will become the main risk factor for renal damage in the next decades, providing a major contribution to the increasing prevalence of ESRD worldwide [8].

Several factors contribute to the adverse renal effects of weight excess. First, it is frequently associated with hypertension and diabetes that lead to renal damage in themselves. In addition, as shown in recent studies, unfavourable renal effects of weight excess occur independent of comorbidity as well [4,6,7].

As a possible mechanism for obesity-induced renal damage, older studies in morbid obesity reported renal hyperfiltration [9,10], suggesting a sequence of events analogous to diabetes, with hyperfiltration and glomerular hypertension leading to subsequent progressive renal damage [11]. However, the relevance of hyperfiltration in less extreme weight excess remained uncertain as most morbidly obese subjects in the older studies had diabetes and/or hypertension that might be involved in the renal haemodynamic changes. Moreover, the role of glomerular hypertension as a pathogenetic factor for renal damage, demonstrated by animal experiments in the 1980s [12], was still unproven in man. Of note, we recently showed first that milder weight excess is associated with an unfavourable renal haemodynamic profile independent of blood pressure and glycaemia [13], and second, that an unfavourable renal haemodynamic profile independently predicts a worse long-term renal outcome [4], together supporting the pathogenetic relevance of renal haemodynamic changes in the long-term renal risks of weight excess.

Impact of weight excess on renal haemodynamics

Weight excess has a fairly consistent effect on renal haemodynamics, suggestive of glomerular hypertension [14]. As a common denominator, weight excess is associated with an elevated glomerular filtration rate (GFR) with a less pronounced increase, or even a decrease in renal perfusion and effective renal plasma flow (ERPF), resulting in an increased filtration fraction (FF, calculated as GFR/ERPF) in most studies. This points towards an altered afferent–efferent glomerular vasomotor balance, resulting in increased glomerular pressure. FF can be considered a non-invasive approximation of glomerular pressure in man, albeit depending on assumptions on tracer extraction and distribution of renal blood flow. However, it is not dependent on assumptions on the best way to normalize renal function, which is an advantage when studying renal haemodynamics in relation to BMI. The changes in renal haemodynamics are reversible by weight loss, showing their functional nature. In morbidly obese subjects in whom the BMI fell from 48 to 32 kg/m^2 after bariatric surgery, GFR decreased from 145 to 110 ml/min and RPF from 803 to 698 ml/min [15]. Increased activity of the renin–angiotensin–aldosterone system (RAAS) is likely to be involved in the renal haemodynamic profile of weight excess with its predominance of efferent vascular tone, as suggested by intervention data in healthy subjects as well as type 2 diabetes in whom the renal vasodilator response to RAAS blockade was closely associated with BMI [16,17].

Importantly, the association between BMI and renal haemodynamics is not limited to morbid obesity. In healthy subjects, a higher BMI was associated with a higher FF and GFR within the range from 18 to 30 kg/m^2, without an apparent lower threshold [13,18]. In transplant recipients, we found a similar association, which allows several inferences on possible mechanisms. First, apparently, the donor kidney 'knows' the recipients' BMI, suggesting a role for circulating factors as triggers for BMI-associated hyperfiltration. Second, the effect is apparently robust as it persists despite effects of ischaemia reperfusion, cyclosporin and allo-factors. Finally, the effect apparently persists in the single-kidney state that is assumed to be associated with hyperfiltration itself [4].

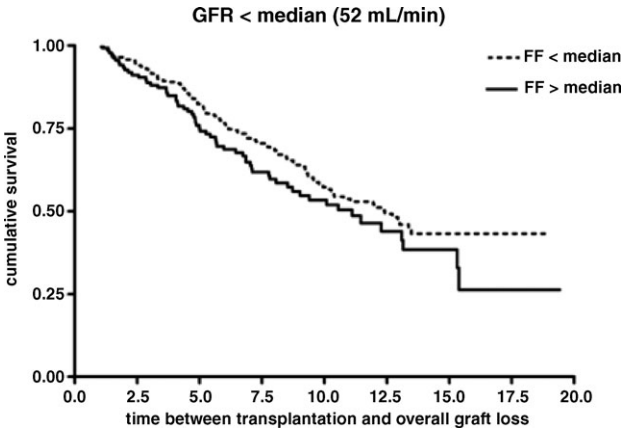

Fig. 1. Kaplan–Meier curve showing overall graft loss in 838 renal transplant recipients stratified for GFR (higher and lower than median, respectively). Only the stratum with GFR < median is shown. All recipients were transplanted between 1984 and 2002 with a mean overall graft survival of 8.2 ± 4 years. Data are shown by a break-up by median of FF. Figure redrawn from the data as published in [4].

Of note, these results were obtained by gold standard renal function measurements. Currently, creatinine-based renal function equations are increasingly used for renal function assessment for reasons of simplicity and costs. However, both the MDRD equation and the Cockroft–Gault equation are subject to a BMI-dependent systematic error which impairs their validity for studies on the association of BMI with renal function [19,20]. Not surprisingly, therefore, the recent insights into the renal effects of weight excess were obtained by gold standard renal function measurements [13,15,18], hard renal end points (ESRD) [6,7] or both [4].

Filtration fraction predicts renal function loss independent of blood pressure and proteinuria

We recently established the prognostic impact of FF for progression to ESRD in line with Brenner's hyperfiltration hypothesis [12]. In a cohort of over 800 renal transplant recipients, a higher FF at 1 year after transplantation predicted an increased risk for death-censored graft loss [4], independent of age, sex and GFR, and moreover, independent of blood pressure and proteinuria (Figure 1). This is in line with older data showing that a decrease in FF at onset of antihypertensive treatment [21,22] predicts a favourable course of renal function in native kidney disease, but for the latter no data on prognostic impact for progression to

ESRD were available. Together with the current data, this warrants renewed emphasis on renal haemodynamics as a target for intervention.

Weight excess impairs post-donation renal reserve capacity in kidney donors

Data from kidney donors support the assumption that a higher BMI is associated with hyperfiltration. For a given pre-donation GFR, the early post-donation decrease in GFR is slight, but significantly larger in donors with a higher BMI [23]. This suggests that pre-donation GFR in overweight subjects is partly determined by BMI-related hyperfiltration that is unmasked when the renal haemodynamic reserve is addressed to account for the decrease in renal mass by donor nephrectomy. This assumption is supported by a BMI-dependent reduction in renal vasodilator capacity early after donation, whereas the BMI was not associated with renal vasodilator capacity before donation [24]. These data support the conceptual validity of the hyperfiltration hypothesis to understand the renal effects of weight excess. However, for clinical purposes it should be emphasized that the prognostic impact of a decrease in renal reserve after kidney donation is unknown and a subject of ongoing long-term studies.

The early renal phenotype of weight excess: target for intervention?

Interestingly, distinct renal abnormalities are already present in young subjects with only mild overweight. In mildly overweight healthy young men, without hypertension or impaired glucose tolerance, a higher BMI was associated with a higher GFR and FF [18] and higher extracellular volume (ECV) [25]. BMI increases gradually with age and displays so-called tracking, and accordingly a higher BMI in young adults predicts overweight and obesity in later life [26]. Subjects at risk for complications of weight excess can thus be identified long before the end-organ damage is established, providing a window of opportunity for prevention in younger overweight subjects. So, weight excess will progress with ageing and the susceptible individuals will develop hypertension and diabetes at middle age. By that time, the kidney has been exposed to BMI-dependent glomerular hypertension for many years, which may (partly) explain the substantial proportion of subjects with renal damage at diagnosis of type 2 diabetes [27]. Thus, in the sequence of events of the complications of weight excess, the renal abnormalities can occur before hypertension and diabetes, as also supported by the predictive effect of micro-albuminuria for subsequent hypertension and diabetes [28,29]. Of note, a higher FF is associated with blunted sodium excretion by its effects on peri-tubular starling forces [30], which may explain the elevated ECV in our overweight subjects, and which has been implicated in the development of (obesity-) hypertension over time.

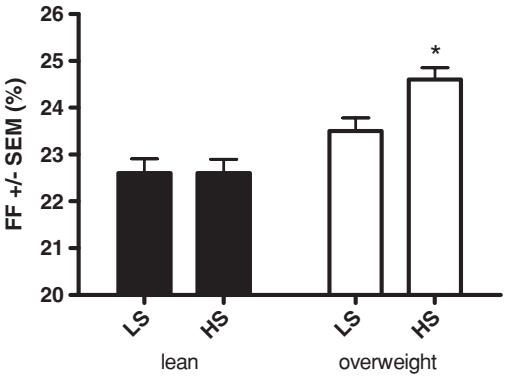

Fig. 2. Filtration Fraction (FF) for lean versus overweight subjects during low sodium (LS) and high sodium (HS) intakes. During LS FF is similar in lean (BMI<25 kg/m^2) and overweight (BMI>25 kg/m^2) subjects. During HS, a rise in FF occurs in overweight subjects only, resulting in a significantly higher FF than in lean subjects. $^*P < 0.05$ versus LS and versus LS and HS in lean subjects. Adapted from the results in [18].

Interestingly, we could abolish the effect of BMI on GFR, FF and ECV by moderate sodium restriction [18,25], providing a tool for intervention (Figure 2). This interaction between sodium intake and BMI in the kidney is in line with cross-sectional data from the general population [31], where high sodium intake is associated with albuminuria only when weight excess is also present. The higher FF during liberal sodium in mildly overweight young men is remarkably similar to prior findings in sodium-sensitive hypertension, where this response to liberal sodium intake was suggested to predispose the kidney to long-term damage, without, however, dissecting cause and consequence [32]. Our data show that a sodium-induced rise in FF can occur without hypertension, sodium sensitivity or established renal damage and thus could potentially be a primary factor in development of (obesity-) hypertension and renal damage. Of note, there are still some controversies with regard to the potential beneficial effects of sodium restriction in preventing renal disease [33]. Especially in obesity and diabetes, sodium-related risk may be modulated by genetic factors [34] or effects of BMI on circulating aldosterone [35]. Therefore, a balanced appraisal is warranted when discussing the complex interrelationships between sodium and overweight on renal damage.

Conclusions

Weight excess is an emerging risk factor for renal damage not only in morbid obesity but also in mild and moderate weight excess. The latter occur in endemic proportions. Programs to prevent complications of weight excess should therefore consider renal prevention. Obviously, general measures should include weight reduction and control of hypertension and glycaemia. However, persistent weight reduction is notoriously difficult to achieve. Specific intervention in renal haemodynamics by dietary sodium restriction and/or RAAS blockade therefore deserves further exploration as measures that could prevent the kidney from the adverse effects of weight excess.

Conflict of interest statement. None declared.

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