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PAPER

Obesity and target organ damage: the kidney

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Obesity is a risk marker for progressive renal function loss in patients with known renal disease. There is, however, increasing evidence that obesity may also damage the kidney in otherwise healthy subjects. There appears to be an intriguing parallel between the renal effects of obesity and those of diabetes. First, an increased renal blood flow and glomerular filtration rate has been described in obesity and, second, microalbuminuria is found to be related to obesity. These two events are known to predict future loss of renal function in diabetes. The mechanism responsible for the renal damage in obesity has not been established but there is evidence suggesting that this might be related to both hormonal changes as well as low-grade inflammation.
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Introduction

The prevalence of obesity is increasing worldwide and the impact of obesity on metabolic and cardiovascular diseases has been well documented. So far, less attention has been paid to the impact of obesity on the kidney. In this overview we will discuss the evidence that obesity may enhance the progression of renal function deterioration to end stage renal failure in subjects with known pre-existing renal disease, the renal effects of obesity in otherwise healthy subjects, and the potential mechanisms of obesity-induced renal damage.

The impact of obesity on renal function loss in pre-existing renal disease

Praga *et al* showed the long-term effects of obesity on the kidney in a follow-up study of 73 patients who had undergone unilateral nephrectomy.[1] Fourteen of the 73 patients were obese at the time of nephrectomy. At the 20y follow-up, most of the non-obese subjects but only 30 – 40% of the obese subjects still had normal renal function (Figure 1). Bonnet *et al* showed a similar phenomenon in another recent study in 162 patients with IgA nephropathy.[2] The presence of an elevated body mass index (BMI $\geq$ 25kg/m^2) at the time of renal biopsy correlated with the severity of the pathological abnormalities and with the clinical progression to end stage renal failure (Figure 2).

The type of renal abnormalities seen in obese patients has been investigated by Kasiske *et al*,[3] who compared the clinical and histological patterns in 17 patients with massive obesity (mean weight 126kg) and marked proteinuria with an age- and sex-matched control group of 34 patients with similar clinical presentation but normal body weight (mean weight 68kg). Although urinary protein excretion was similar in the two groups, serum albumin was higher in the obese subjects, probably because proteinuria develops more gradually in subjects with obesity and the liver is still able to

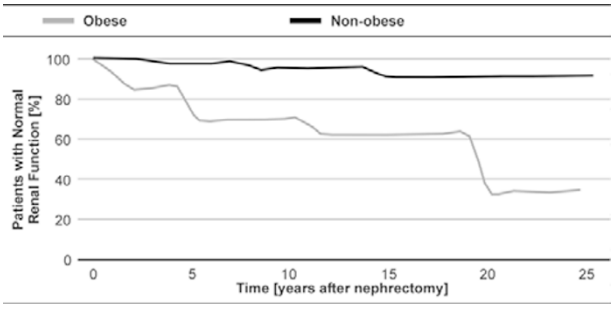

Figure 1 The percentage of patients remaining with normal renal function after unilateral nephrectomy in those with or without obesity at the time of nephrectomy. Source: Praga *et al*.[1]

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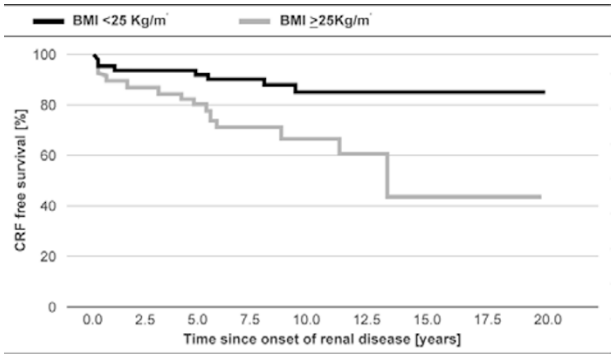

Figure 2 The percentage of subjects remaining free of chronic renal failure after the diagnosis of IgA nephropathy according to the presence of an elevated body mass index. Source: Bonnet *et al.*[2]

compensate for the increased protein loss. With respect to the histological data, most of the obese patients had a focal glomerulosclerosis while most of the control subjects had a minimal change nephrotic syndrome or membranous nephropathy.

It has recently been reported that the incidence of obesity-related glomerulopathy, defined by the authors of a biopsy-based study as focal segmental glomerulosclerosis and glomerulomegaly, has increased ten-fold over the last 15y.[4] Therefore, if obesity results in glomerulosclerosis in some specified patient groups, what is the impact of obesity for the kidney in the general population?

The impact of obesity on the kidney in the general population

To gain more insight, we first consider the mechanism for diabetic nephropathy, since there are now data indicating that diabetes and obesity may have similar effects on the kidney. In the initial stages of type I diabetes, glomerular filtration rate tends to increase due to increased glomerular capillary pressure, a process called glomerular hyperfiltration.[5] This may be followed by an increased urinary albumin excretion. This albumin loss may then reach the magnitude of being defined as microalbuminuria, that is 30–300mg/24h. This phase of microalbuminuria is followed by a progressive fall in glomerular filtration rate, in parallel with a further rise in urinary albumin excretion, leading to the development of overt proteinuria and, eventually, end-stage renal failure.[5]

Microalbuminuria is not only the predominant predictor of progressive renal failure, but also of progressive cardiovascular disease in diabetes. From this perspective, it has been speculated that microalbuminuria represents the renal expression of a generalized disorder characterized by an increased endothelial permeability and that endothelial damage may underlie the link between an increased urinary albumin excretion and the increased risk of cardiovascular disease. The question that has been addressed in recent research is whether these predictors (that is glomerular hyperfiltration and microalbuminuria) apply only to patients with diabetes or are also relevant to the general population.

It has previously been shown that an increased BMI is associated with microalbuminuria, especially in hypertensive subjects.[6] We studied the impact of obesity on renal function in the general population in a sub-analysis of the PREVEND (Prevention of Renal and Vascular End stage Disease) study, which was initiated to study the impact of microalbuminuria on renal and cardiovascular risk in the general population.[7,8] To that purpose we determined the prevalence of microalbuminuria in the general population aged 28–75y and found microalbuminuria (urinary albumin concentration> 20mg/l) to be present in 16.4% of subjects with diabetes, in 11.5% of those with hypertension and in 6.6% of 'healthy' subjects who were not known to have either diabetes or hypertension.[7] Presented differently, 75% of all cases of microalbuminuria occurred in non-diabetic, non-hypertensive individuals.

If so many subjects have microalbuminuria, the question arises of what causes microalbuminuria in these non-diabetic and non-hypertensive subjects? In this sub-analysis of the PREVEND study, we questioned to what extent microalbuminuria is mediated by obesity. To that purpose, we used the data of the 8592 subjects in which more detailed physical and laboratory examinations were done, including two 24h urine collections to measure 24h urinary albumin excretion. Microalbuminuria was defined according to the classical criterion of 30–300mg per 24h.[8] Data from 542 subjects were excluded from this analysis because urinary albumin excretion was not reliable due to the presence of erythrocyturia and/or leucocyturia and/or missing data. Table 1 shows the data on the 8050 subjects according to body mass index (BMI) and gender. It shows the number of subjects with a normal body mass index ($<25 kg/m^2$), overweight ($25–29.9 kg/m^2$) and obesity ($>30 kg/m^2$). In men about 47% were overweight and 14% were obese, while among women 34% were overweight and 16% were obese. In both genders a higher BMI was associated with higher levels of cardiovascular risk factors, such as a higher age, blood pressure, glucose and cholesterol level. Furthermore, it was also associated with a higher C-reactive protein level and a greater 24h urinary albumin excretion. In men the prevalence of microalbuminuria increased from 9.5% in those with a normal body weight to 18.3% in those who were overweight and to 29.3% in those with frank obesity. In women these percentages were 6.6, 9.2 and 16.0%, respectively (Figure 3). Multivariate analysis showed that BMI was independently associated with urinary albumin excretion and that there was an interaction between gender and BMI, men having a steeper rise in urinary albumin excretion at increasing BMI compared with women.[9]

In diabetes, glomerular hyperfiltration is present as microalbuminuria develops.[5] Thereafter glomerular filtration rate starts to decrease and urinary albumin excretion rises further

Table 1 Data on the microalbuminuria-enriched population sample studied in PREVEND

	Male			*Female*		
BMI (kg/m^2)	< 25	25 – 29.9	> 30	< 25	25 – 29.9	> 30
n	1597	1969	597	1946	1302	639
Age (y)	46.4 ± 12.6	52.4 ± 12.8	53.2 ± 11.5	43.8 ± 10.7	51.0 ± 12.3	53.4 ± 12.1
Systolic BP (mmHg)	126.3 ± 15.8	136.8 ± 18.4	142.8 ± 18.3	116.9 ± 17.5	129.1 ± 21.0	135.9 ± 21.1
Diastolic BP (mmHg)	73.3 ± 8.7	78.5 ± 9.3	81.2 ± 9.3	68.5 ± 8.6	73.0 ± 8.9	74.3 ± 8.9
Plasma glucose (mmol/l)	4.7 ± 1.0	5.1 ± 1.3	5.5 ± 1.6	4.4 ± 0.6	4.9 ± 1.2	5.3 ± 1.6
Plasma cholesterol (mmol/l)	5.4 ± 1.1	5.8 ± 1.1	6.0 ± 1.0	5.3 ± 1.1	5.9 ± 1.2	5.9 ± 1.1
CRP (mg/l)	0.7(0.3 – 1.8)	1.4(0.7 – 2.8)	2.2(1.2 – 4.2)	0.8(0.3 – 1.9)	1.7(0.8 – 3.5)	3.4(1.6 – 6.5)
UAE (mg/24 h)	8.5(6.3 – 14.5)	11.3(7.2 – 24.0)	17.5(9.7 – 40.5)	7.7(5.6 – 12.2)	8.0(5.8 – 14.1)	10.1(6.6 – 20.4)

BMI, body mass index; BP, blood pressure; P, plasma; CRP, C-reactive protein; UAE, urinary albumin excretion.

to macroproteinuric ranges. The same phenomenon might be present in non-diabetic subjects.[10] Creatinine clearance was higher in subjects with a high normal albumin excretion (15 – 30mg/day) than in controls (albumin excretion 0 – 15mg/day) and was still elevated in microalbuminuric (albumin excretion 30 – 300mg/day) persons while it was lower in the macroproteinuric (albumin loss> 300mg/day) subjects. After adjustment for age, gender, BMI, glucose, family history of diabetes, blood pressure and smoking, high-normal albuminuria and microalbuminuria were independently associated with an elevated filtration (RR 1.8 (95% CI 1.30 – 2.51) and 1.7 (1.17 – 2.45)). Macroproteinuria was independently associated with a diminished filtration (4.3(1.97 – 9.36)).[10] This pattern is similar to that described in diabetics, with initial glomerular hyperfiltration, followed by gradual loss of renal function. This suggests that the higher risk for microalbuminuria is associated with a higher risk for glomerular hyperfiltration and ultimately impaired glomerular filtration in non-diabetic subjects. These data are compatible with results of accurate renal function studies, which have shown that obese subjects indeed have an elevated renal blood flow and glomerular filtration rate.[6,11]

The hypothesis that glomerular hyperfiltration and microalbuminuria underlie the pathogenesis of glomerular sclerosis in obesity is substantiated by recent experiments in hyperphagic obese Zucker rats.[12] In this study, glomerular injury correlated with hyperphagia-induced glomerular hyperfiltration. Moreover, food restriction directly prevented the glomerular hyperfiltration and ultimately prevented the development of glomerular sclerosis. Interestingly, the earlier the food restriction was instituted, the better the glomerulosclerosis could be prevented.

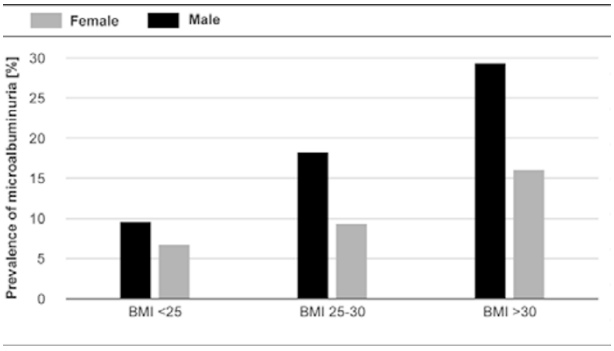

Figure 3 The percentage of men and women with microalbuminuria according to BMI.

The mechanism of obesity-induced renal damage

What then is the mechanism behind the obesity related renal damage? Hormonal factors may be involved. Insulin resistance, which is generally present in obesity, could be one of the mechanisms, as insulin resistance induces systemic[13] and intraglomerular[14] hypertension as well as mesangial hypertrophy and increased mesangial matrix production.[15]

The potential role of leptin is also interesting. Leptin is a small peptide hormone that is mainly, but not exclusively, produced in adipose tissue. Leptin serum concentration is related to body fat.[16] Among other effects, leptin has direct effects on renal pathophysiology. In glomerular endothelial cells, it stimulates cellular proliferation, transforming growth factor-β1 synthesis, and type IV collagen production. Conversely, leptin upregulates synthesis of the TGF-β type II receptor in mesangial cells, but not of TGF-β1, and stimulates glucose transport and type I collagen production.[17] These data suggest that leptin triggers a paracrine interaction in which glomerular endothelial cells secrete TGF-β, to which sensitized mesangial cells may respond. Both cell types increase their expression of extracellular matrix in response to leptin.[18] It is interesting to note that infusion of leptin in normal rats for 3 weeks resulted in glomerulosclerosis and proteinuria.[17]

Finally, the role of an inflammatory process triggered by obesity should be mentioned as a mechanism for the obesity related renal changes. It is known that adipocytes produce cytokines and that C-reactive protein (CRP) levels are elevated in obesity, suggesting a state of low-grade systemic inflammation.[19,20] Table 1 shows that CRP levels increase with BMI, although this increase appears to be more prominent in females than in males, while the BMI-associated rise in urinary albumin excretion seems to be more prominent in males than in females. This rise in CRP levels is thought to

reflect the low grade inflammatory condition associated with atherosclerosis.[21] Indeed an elevated CRP is found to predict future cardiovascular disease. Several studies with long-term follow-up have shown that increased levels of this inflammatory marker are associated with increased risk of coronary heart disease, stroke and peripheral vascular disease.[22] We similarly showed that higher quartiles of CRP levels are associated with a higher relative risk of impaired glomerular filtration, after adjustment for other factors associated with a raised CRP level.[23]

Conclusion

Obesity may lead to glomerular hyperfiltration, increased urinary albumin loss and a progressive loss of renal function, associated with a focal segmental glomerulosclerosis. This may be present not only in subjects with previously manifest renal disease, but also in otherwise healthy subjects. These renal changes may be related to insulin resistance and/or hyperleptinaemia, but may also be mediated by a state of low-grade inflammation induced by obesity. Microalbuminuria may be an easy to measure marker to detect risk of progressive renal failure in obesity.

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