

Synergy of low nephron number and obesity: a new focus on hyperfiltration nephropathy

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The 'hyperfiltration theory', originally postulated by Brenner's group more than 20 years ago, represented a revolutionary advance in defining the mechanisms responsible for the seemingly inexorable progression of renal insufficiency [1]. Brenner's group and others demonstrated that rats submitted to renal ablation (more than five-sixths nephrectomy) developed proteinuria, glomerulosclerosis and progressive renal failure during the months following nephrectomy. They found that the functional and structural changes appearing in the remnant glomeruli correlated with the haemodynamic adaptations observed closely after renal ablation: increments in single nephron glomerular filtration rate (GFR) mediated by preferential vasodilation of afferent glomerular arterioles, together with increments in glomerular transcapillary hydraulic pressure and filtration fraction [1–3]. Attenuation of these haemodynamic adaptations by low protein diets or ACE inhibitors (that induce preferential vasodilation of efferent glomerular arteriole) largely prevents the appearance of glomerulosclerosis and renal failure. Brenner and collaborators postulated that 'maladaptive' haemodynamic changes in the remaining glomeruli after the reduction of renal mass below some critical level (by surgical ablation or any other type of renal disease) would represent a final common path for the progression of renal diseases independently of their original cause [1–3].

The hyperfiltration theory encouraged a tremendous amount of investigations in the field of unspecific renal failure progression, and extensive renal ablation has remained as a definite model with which to investigate the mechanisms of progression and therapeutic interventions in many different types of nephropathies.

However, the general applicability of hyperfiltration theory to humans has remained largely controversial. Some studies published in the 1990s showed that a significant number of patients submitted to extensive surgical removal of renal parenchyma developed proteinuria and progressive renal insufficiency, resembling the hyperfiltration nephropathy observed in experimental animals [4–6]. Furthermore, renal biopsies performed in a minority of these cases showed the typical findings of hyperfiltration nephropathy: glomerulomegaly with lesions of focal and segmental glomerulosclerosis [4]. However, other patients with similar severe reductions in renal mass did not develop proteinuria or renal function decline over prolonged follow-up. Reasons for these discrepant evolutions were not apparent. Some authors emphasize the fact that many patients with remnant kidneys and mild renal insufficiency after surgery did not show progression of renal insufficiency, casting serious doubts about the validity of simplistic translation of studies performed in rats to humans [7].

Unilateral renal agenesis is another pathological condition in which a high risk of developing proteinuria and glomerulosclerosis has been reported [8–10]. The common co-existence of other congenital urological malformations, such as vesicoureteral reflux and ureteropelvic obstruction would induce further nephron damage in these solitary kidneys with a congenital reduced number of nephrons [11]. However, the same discrepancy pointed out in the case of remnant kidneys has also been noted in renal agenesis: a significant proportion of cases with this congenital abnormality maintain a normal renal function without proteinuria throughout their entire life. The discrepancy even persists when considering patients submitted to unilateral nephrectomy: there is general agreement that the incidence of proteinuria and hypertension among living kidney donors is low and very similar to the general population in several series [12]. In contrast, other studies have shown a worrying incidence of proteinuria and even progressive renal insufficiency among patients submitted to unilateral nephrectomy for reasons other than donation of kidneys [13,14].

Why some patients tolerate extreme reductions in renal mass without any sign of renal damage whereas others develop end-stage renal failure is unknown. Our group has recently published a study analysing those factors influencing the progression of renal damage in patients with unilateral renal agenesis and remnant kidney [15]. Fifty-four patients (33 with unilateral renal agenesis and 21 with remnant kidneys) were studied. Patients with remnant kidneys had a reduction of more than 75% in functioning renal mass. Twenty patients had a normal renal function with negative proteinuria at presentation, whereas the remaining 34 patients showed different degrees of proteinuria and renal insufficiency. The most remarkable difference between both groups was a body mass index (BMI) significantly higher in patients with renal dysfunction ($29 \pm 7.4 \text{ kg/m}^2$, ranging from 17.7 to 45) than in patients with normal renal function ($24 \pm 4.1 \text{ kg/m}^2$, 19 to 30.5). Furthermore, the long-term follow-up of the patients (100 ± 72 months, ranging from 24 to 288 months) revealed the appearance of proteinuria and renal insufficiency in almost one half (45%) of patients showing no renal abnormalities at presentation. Again, BMI was the most significant difference between these patients and those who remained normal throughout the entire follow-up: $27 \pm 3.6 \text{ kg/m}^2$ in the former and $21.6 \pm 2.6 \text{ kg/m}^2$ in the latter. Only one patient among those who maintained negative proteinuria was overweight (BMI between 25 and 29.9 kg/m^2) and none of them was obese. By contrast, only one case of those who developed proteinuria and renal insufficiency had a normal BMI (lower than 25 kg/m^2), the remaining showing overweight or obesity (BMI higher than 30 kg/m^2). By univariate and multivariate analysis, BMI was the only clinical variable statistically associated with the risk of developing proteinuria and progression of renal failure.

These data strongly suggest that overweight/obesity is the fundamental factor that precipitates the appearance of renal dysfunction among patients with severe reductions in renal mass. Indeed, these data entirely agree with a previous study of our group, showing that obese patients are at risk for developing proteinuria and chronic renal failure after unilateral nephrectomy [16]. Although the appearance of renal abnormalities (slowly progressive proteinuria and renal insufficiency) is relatively uncommon after unilateral nephrectomy, we found that BMI at the time of nephrectomy and throughout follow-up was significantly higher among patients who developed these abnormalities in comparison with patients who did not. About 92% of obese patients at the time of nephrectomy developed proteinuria/renal insufficiency, whereas these complications appeared in only 12% of patients with a BMI lower than 30 kg/m^2 at nephrectomy. It should be considered that both studies [15,16] were a retrospective analyses of cohorts of patients with renal mass reduction and that potential confounding factors are inherent in such retrospective analyses. However, the characteristic slowness of hyperfiltration

nephropathy makes it very difficult to plan prospective studies in this entity.

The role of overweight/obesity as a key factor that precipitates the appearance of hyperfiltration nephropathy has a coherent physiological basis. Recent experimental and clinical studies have demonstrated that obesity induces important haemodynamic changes consistent with glomerular hyperperfusion and hyperfiltration. An increase of GFR, RPF, glomerular pressure and filtration fraction through a dilated glomerular afferent arteriole, has been found in obese subjects and in obese experimental animals [17,18]. These changes are identical to the haemodynamic consequences of extensive renal ablation in experimental studies, as outlined above [1,2]. In addition, it has been recently demonstrated that obesity-related hyperfiltration improves substantially after weight loss [19]. Although the mechanisms through which overweight induces these renal haemodynamic changes are partially unknown, several studies have demonstrated increased renal sodium reabsorption in obesity; this impaired natriuresis is likely to play a role in the vasodilation of afferent glomerular arterioles and the consequent transmission of increased arterial pressure to the glomerular capillary [17–19]. Other experimental studies point out increased renal sympathetic activity and activation of the renin–angiotensin system as the most important stimulus for obesity-related increased renal sodium reabsorption [18,19]. In summary, the synergy between the renal haemodynamic changes induced by nephron loss and those induced by obesity explain the impact of the latter as an unmasking factor in hyperfiltration-related renal disorders. Recent studies have emphasized that a central pattern of fat distribution (abdominal adiposity) rather than overweight or obesity by itself is crucial for the development of renal disease [20].

The clinical importance of the above summarized findings is evident, taking into account the epidemic of obesity all over the world and that unilateral renal agenesis and other congenital urologic abnormalities that lead to a reduction in nephron mass are not uncommon disorders. Among the causes of remnant kidney after extensive surgical nephrectomy, bilateral renal cancer or cancer appearing in solitary kidneys is one of the most frequent [4,6]. This fact is worthy of mention, because obesity has been pointed out as a risk factor for the appearance of renal cancer [21]. Unfortunately, the importance of obesity in the appearance of hyperfiltration nephropathy has not been considered so far. In fact, body weight or BMI were not recorded in the previous clinical studies concerning patients with remnant kidneys or other causes of reduced renal mass. It is likely that the presence or absence of overweight/obesity may be the neglected clinical factor that explains the discrepancies so far observed in the outcome of these patients. From a practical point of view, overweight should be prevented or treated in every patient with reduced renal mass, including unilateral nephrectomy. It should

be stressed that the rate of progression of these hyperfiltration-related disorders is remarkably slow. Therefore, long-term follow-up is mandatory in every patient with a significant reduction in renal mass, particularly if the patient is overweight. Early introduction of drugs that block the renin-angiotensin system (ACE inhibitors or angiotensin receptor antagonists) in patients developing microalbuminuria/proteinuria or in those patients in whom low calorie diet fails to suppress overweight is warranted: we found that these drugs significantly reduced the risk for renal failure progression among patients with unilateral renal agenesis and remnant kidney [15].

The notion that excess weight fuels the progression of renal diseases associated with a low nephron number should not be restricted to surgical causes of nephron loss or to obvious congenital malformations such as renal agenesis. In the last few years, several studies have demonstrated that nephron number at birth is a widely distributed function in otherwise healthy human beings, ranging from 250 000 per kidney to as high as 1 800 000 [22]. In this regard, it might be conceivable that individuals endowed at birth with a greater number of nephrons would be more resistant to the deleterious effects of obesity than those with a reduced number. On the other hand, as several epidemiologic studies have shown, kidney size and nephron number per kidney at birth are closely related to birth weight and, in turn, a solid relationship between low birth weight and increased risk for developing adult metabolic syndrome and obesity has been established in other studies [23,24]. In experimental studies, offspring of pregnant rats maintained in low-calorie and low-protein diets during pregnancy exhibit low birth weight and reduced sizes of kidneys, pancreas and liver. However, when exposed to normal diets later in life, these rats show an accelerated growth accompanied by hyperphagia, hyperinsulinism, abdominal obesity and hypertension [25]. Some epidemiologic data suggest that this phenomenon might also be present in humans: children with low birth weight and low birth BMI frequently exhibit an exaggerated growth in weight and BMI greater than height during late childhood and adolescence [26]. This rapid compensatory growth increases the risk for hypertension, obesity, diabetes and cardiovascular events in adult life [24,26]. In summary, these epidemiologic data, of which the pathogenic bases are unknown, suggest that the combination of inborn reduction in renal mass (associated with low birth weight) and obesity during adult life are very common. Very interestingly, the prevalence of both conditions is remarkably high in countries and communities with a poor socioeconomic development. The disproportionate rate of chronic renal failure found in many of these underdeveloped social scenarios could be explained, at least partially, by the harmful synergy between obesity and an inborn reduction in the number of nephrons.

In the last few years, renal diseases induced by obesity have emerged as an important clinical problem

[27,28]. In addition, recent epidemiologic studies single out obesity as a significant risk factor for the appearance of new-onset kidney disease in community-based populations [29,30]. However, very few clinical studies have addressed the possible role of obesity as a contributory factor to the progression of renal diseases whatever their cause. This lack is particularly astonishing taking into account that most patients suffering type 2 diabetic nephropathy are obese, that low birth weight is a risk factor for the appearance of type 2 diabetes in adult life, and that weight loss induces a marked reduction in proteinuria in patients with diabetic and non-diabetic chronic proteinuric diseases [31]. Whereas some studies reported a significant role for obesity in the progression of specific renal diseases (IgA nephropathy) [32], subanalysis of the MDRD study did not find any significant influence of baseline BMI on the progression of chronic renal insufficiency [33]. On the other hand, no studies have clarified the possible pathogenic links between low birth weight, adult obesity and progressive renal disease. Considering that the increasing prevalence of overweight and obesity currently is a worldwide health concern, clinical and experimental studies about these questions are urgently needed.

Conclusion

Although proteinuria and progressive renal insufficiency develop in a significant number of patients with unilateral renal agenesis and in patients submitted to extensive surgical removal of renal parenchyma, other cases with similar reductions in renal mass did not develop these complications. Recent studies strongly suggest that obesity is the fundamental factor that precipitates the appearance of renal dysfunction in these patients. Experimental and clinical studies have demonstrated that obesity induces renal haemodynamic changes (glomerular hyperperfusion and hyperfiltration), identical to the haemodynamic consequences of extensive renal ablation. Thus, the synergy between the functional changes induced by nephron loss and those induced by obesity would explain the impact of the latter as an unmasking factor in hyperfiltration-related renal disorders.

Conflict of interest statement. None declared.

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