After all those fat years: renal consequences of obesity

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Bigger is not better

Our genetic background and physiological homeostasis, orchestrated through endocrine and neuronal networks, are optimized for a world with intermittent food supply and permit us to survive periods of starvation [1]. However, these systems are counterproductive in our current industrial society with fast-food restaurants, an abundance of high-energy food and an increasingly sedentary lifestyle. The consequence is an alarming increase in obese adults and, even more disturbing, of overweight children [1]. The consequences of obesity such as the metabolic syndrome with its ultimate development of type 2 diabetes mellitus, cardiovascular diseases, an increased incidence of certain types of cancer, musculoskeletal disorders and pulmonary diseases are well known.

What about renal diseases? Almost 30 years ago, Weisinger et al. [2] described focal-segmental glomerulosclerosis with nephrotic syndrome in four extremely obese patients. Only two of them exhibited hypertension by office blood pressure measurements [2]. In the following years, several case reports describing glomerulosclerosis in very obese patients have been published, but this entity was considered as rare and rather bizarre. However, a recent study showed a dramatic increase of histologically proven renal disease in obese patients in the absence of diabetes [3]. The patients had rapidly progressive renal disease [4]. Furthermore, obesity is an important risk factor for the progression of renal disease in IgA nephropathy [5], and is also associated with an enhanced risk of chronic graft dysfunction after renal transplantation [6]. On the other hand, overweight patients with a body mass index (BMI) $\geq 27$ kg/m$^2$ with various chronic renal diseases experienced a significant reduction in proteinuria after only moderate weight loss [7]. A problem with all these studies is the fact that confounding factors such as hypertension were not totally ruled out.

Adipose tissue as a source of hormones and cytokines

Fat cells are much more than a passive store of excess energy. Adipose tissue is a source of various hormones that may very well influence renal function [8,9]. An incomplete list of these factors is shown in Table 1. Some of these hormones and growth factors could reach the kidney and exert their pathophysiological effects [8]. For example, transgenic mice with angiotensinogen expression restricted to adipose tissue have increased circulating angiotensinogen, and the angiotensin II thus generated has renal effects [10]. Overexpression of angiotensinogen in adipocytes leads to hypertension [10]. Thus, the adipose tissue renin–angiotensinogen system could exert direct effects on the kidney. The detrimental effects of continuously enhanced angiotensin II concentrations on renal function and structure are well appreciated [11]. Although not the subject of this review, an increase in local formation of angiotensin II in adipose tissue probably contributes to the development of insulin resistance and promotes the metabolic syndrome [12]. Renal effects of tumour necrosis factor-$\alpha$ (TNF-$\alpha$) through the induction of proinflammatory cytokines and the profibrogenic role of plasminogen activator inhibitor-1 (PAI-1) have been studied in detail. Other factors such as adiponectin may inhibit some of TNF-$\alpha$’s

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<th>Table 1. Some hormones, cytokines and growth factors produced in adipose tissue</th>
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proinflammatory effects, but circulating adiponectin levels are paradoxically lower in obese individuals and patients with type 2 diabetes [9].

**What about leptin?**

Leptin, the product of the *ob* gene, is a satiety factor produced in adipocytes. It acts on specific receptors localized in the hypothalamus and influences other neurohormones [13]. Leptin suppresses food intake by inhibiting neuropeptide Y and by increasing melanocyte-stimulating hormone (MSH), and decreasing agouti-related peptide, an antagonist of MSH at the MC4 receptor [14]. Interestingly, an experimentally induced disruption of the MSH system induces salt-sensitive hypertension, indicating a central role for these peptides in blood pressure regulation [15]. Leptin centrally stimulates sympathetic nerve action; transgenic mice overexpressing leptin are hypertensive and have elevated urinary catecholamine excretion [16]. However, despite high circulating leptin concentrations, obese individuals are characterized by a relative leptin resistance [17]. The molecular mechanisms of this leptin resistance are subject to active current research and may be heterogeneous. As a small peptide hormone, leptin is cleared by the kidney [14,18]. Consequently, patients with impaired renal function have high circulating leptin concentrations.

Mice with a deficient leptin gene (*ob/ob*) as well as animals with a defect for the long leptin receptor (*db/db*) are both obese and develop type 2 diabetes. However, only *db/db* mice with high circulating leptin concentrations show histological changes reminiscent of diabetic nephropathy, whereas the kidneys of *ob/ob* mice appear relatively normal [18]. This provided the impetus for us to study whether leptin could have direct renal effects [18]. Leptin stimulates the proliferation of cultured rat glomerular endothelial cells [19]. Angiotensin II and leptin have additive proliferative effects on glomerular endothelial cells [19]. This proliferation is cell type specific because mesangial cells failed to replicate in the presence of leptin [19]. Glomerular endothelial cells express the short leptin receptor previously thought to act solely as a clearance receptor without signal transduction. However, leptin induces STAT1 phosphorylation, suggesting active signal transduction, but further studies are necessary to define whether the signals are indeed mediated through the short leptin receptor [19]. Moreover, leptin induces mRNA expression and protein secretion of transforming growth factor-β (TGF-β) in glomerular endothelial cells [19]. Leptin increases the expression of TGF-β type II receptors on mesangial cells from the rat and from *db/db* mice, suggesting that the long leptin receptor is not necessary for this effect [20]. In addition, exogenous leptin increases cellular glucose uptake and enhanced type I collagen synthesis [20]. The addition of both TGF-β and leptin increases mesangial cell type I collagen secretion more than either stimulus alone [20]. These findings suggest a paracrine TGF-β pathway between glomerular endothelial and mesangial cells that is mediated by leptin. Leptin-induced TGF-β from endothelial cells could easily reach mesangial cells where it binds to the leptin-induced upregulated TGF-β type II receptors [18]. The consequence is an increase in extracellular matrix deposition. To test a potential role for leptin in *vivo*, recombinant leptin was infused with osmotic minipumps into normal rats. Short-term infusion for 72 h stimulated glomerular TGF-β expression and increased in parallel the number of cells expression proliferating cell nuclear antigen (PCNA). After 3 weeks of leptin infusion into rats, glomerular expression of type IV collagen was significantly enhanced compared with pair-fed controls [19]. Leptin did not influence blood pressure, but proteinuria was significantly enhanced in leptin-infused animals [19]. These studies provide for the first time evidence that leptin exerts pathophysiological effects in the kidney. However, retrospective measurements of serum leptin at a single time point did not correlate with the decline in renal function in non-diabetic patients from the Modification of Diet in Renal Disease Study (MDRD [21]).

**Obesity and kidney function and structure**

Obese patients without diabetes mellitus type 2 exhibit a significant increase in glomerular filtration rate (GFR), compared with controls with normal BMI [22]. This hyperfiltration is caused by dilation of the afferent arteriole [22]. One explanation for these haemodynamic changes could be an activated glomerulo-tubular feedback caused by enhanced sodium reabsorption in the proximal tubule. Leptin, through activation of the sympathetic nervous system as well as direct effects on angiotensin II and insulin, could contribute to the increase in sodium reabsorption. It is intriguing to speculate that fat tissue may contribute to the increase in angiotensin II that enhances sodium transport. Glomerular hyperfiltration is a well known pathophysiological link to glomerulosclerosis and proteinuria [11]. In addition, many animal studies demonstrated that chronic intravenous or intracerebroventricular infusion of leptin increases sympathetic activity in the kidneys and induces hypertension [23]. Fat tissue completely encapsulates the kidney of obese animals and increases intrarenal pressure [23]. This mechanism may increase blood pressure further in obese individuals [24]. In addition, this observation may also explain why abdominal obesity correlates better with hypertension than BMI [23].

In an experimental study in dogs, Henegar et al. [25] found that a high calorie diet induces within no more than 7 weeks an increase in mean arterial blood pressure and GFR. Moreover, histological changes including glomerular cell proliferation, thickening of glomerular and tubular basement membranes, increased matrix expansion and glomerular TGF-β expression were...
present [25]. These structural findings are similar to those reported by us in leptin-infused rats [19].

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References

Conclusion
Although the incidence of obesity-related glomerulosclerosis is increasing, which carries a poor renal prognosis, overweight is probably more important as a progression factor in patients with known primary chronic renal diseases. Certainly, more research is needed to understand better how obesity influences renal function. The adipocyte is a source of several hormones, including leptin, that may have detrimental effects on the kidney, indicating that fat tissue itself could be a major culprit. Our genetic hardwiring with neuronal–hormonal loops mainly fostering energy conservation served our ancestors in times of starvation well, but poses a major problem for successful weight reduction. Nevertheless, structured weight reduction and control programmes may help to overcome this difficulty. Good luck!
Senescence of renal cells: molecular basis and clinical implications

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Keywords: allograft nephropathy; cellular senescence; kidney ageing; p16INK4a; renal senescence; telomere

Introduction

Age-associated changes of the kidney are important not only because normal ageing alters renal function but also because of the high frequency of end-stage renal disease in the elderly (ERA–EDTA Registry Report 2000). Old kidneys perform poorly when transplanted, and donor age is a major determinant of graft survival [1]. It has been proposed that interactions between ageing and diseases may contribute to these problems. Understanding the mechanisms of declining organ function with age may be instructive concerning the mechanisms of decline in disease states, since stress might accelerate ageing changes. Kidney ageing is also of interest as a general model for organ ageing, because renal function can be assessed with relative ease in clinical practice and has been quantified in longitudinal studies [2]. The molecular basis of ageing changes in organs is not known, but organ ageing may reflect aspects of cellular senescence which are understood better now than a few years ago.

Here, I will review recent progress in defining the molecular changes and pathways involved in cellular senescence, their relative contribution in cells from different species, in particular human and mouse, and their relevance to renal ageing and disease.

Terms and definitions

‘Cellular senescence’ describes a phenotype of permanent and irreversible growth arrest shown by mammalian cells in culture. Originally described in human fibroblasts by Hayflick and Moorhead [3], this term was used synonymously with ‘replicative senescence’. However, in recent years, the concept of cellular senescence has been expanded to include other forms of permanent, irreversible cell-cycle arrest. The reason for this extension comes partly from the observation that mouse embryonic fibroblasts in culture do not use replicative senescence to cease replication, but share other senescence features with human fibroblasts such as altered morphology, greater heterogeneity, expression of senescence-associated β-galactosidase (SA-β-GAL) and accumulation of lipofuscin granules. This had been referred to as ‘premature senescence’, ‘stress-induced senescence’ and most recently ‘stimulation and stress-induced senescent-like’ arrest (STASIS) [4]. The term ‘renal senescence’ reflects the structural and functional phenotype associated with aged kidneys.

The phenotype of renal senescence

The phenotype of human renal senescence can be described as a phenotype of loss: the loss of mass, particularly in cortex [5,6], and the loss of function, as reflected by increased renal vascular resistance, reduced renal plasma flow and increased filtration fraction [6,7]. The glomerular filtration rate (GFR), as described by multiple equations such as Cockcroft–Gault [8] and MDRD [9], is not an ideal measurement to assess this malfunction. Although studies in selected populations [2,10], excluding all renal diseases, hypertension and