Translational Nephrology

Obesity, diabetes, adiponectin and the kidney: a podocyte affair*

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Introduction

Elegant studies by Sharma et al. [26] implicate low adiponectin (ADPN) in the pathogenesis of renal disease in obesity. ADPN-knockout mice exhibited effacement and fusion of podocyte foot processes as well as albuminuria and high oxidative stress in the kidney. ADPN abated albumin permeability in cultured podocytes, and via an AMPK-dependent pathway it induced translocation of zona occludens-1 (ZO-1) to the plasma membrane. Intriguingly, ADPN also reduced NADPH oxidase 4 (Nox4) in podocytes, which is the dominant NADPH oxidase in the kidney. These detailed in vitro studies were corroborated by parallel in vivo studies showing that exogenous ADPN administration to the ADPN null mice reduces albuminuria and oxidative stress and attenuates podocyte damage. Thus, podocytes are a physically distant but quite relevant target of a peculiar product of fat cells such as ADPN. These results provide a novel interpretative framework for obesity-related glomerulopathy and diabetic nephropathy. Drugs that stimulate ADPN synthesis and ADPN derivatives are investigated with increasing interest by the industry. This flurry of interest may soon bring ADPN into the translational research arena, i.e. the area of phase 1 and phase 2 clinical trials.

Background

Obesity is now recognized as the most concerning epidemic of the third millennium. From 1999 to 2004, the prevalence of obesity in the USA rose from 23% to 30.5% [1]. From an epidemiological point of view, body weight excess has been solidly linked to CKD in two large community studies in Japan [5] and in the USA [6]. However, mechanisms responsible for renal damage in obesity and type 2 diabetes remain largely unknown.

Renal disease in obesity and type 2 diabetes

Even though there may be relevant histology overlapping between obesity-associated CKD and type 2 diabetes, glomerulomegaly and focal sclerosis appear characteristics of the first condition while mesangial expansion, glomerular basement membrane thickening and glomerular sclerosis are typically seen in the second.

In humans, the earliest clinical manifestation of obesity-associated kidney damage and of diabetic nephropathy is microalbuminuria, an alteration associated with insulin resistance independently of diabetes [7]. The reason why abnormalities of insulin secretion and/or action are conducive to albuminuria is still unclear. Insulin-dependent glucose uptake in adipocytes and muscle cells occurs through the glucose transporters GLUT4 and GLUT1. Of note, podocytes take up glucose in response to insulin by a mechanism involving these transporters. These findings suggest that insulin sensitivity may influence protein filtration via podocytes, a key component of the glomerular filtration barrier [8]. The Zucker, obese (ZDF-fa/fa), diabetic rat is an attractive model for obesity and type 2 diabetes. Glomerulosclerosis starts at an early stage in the ZDF-fa/fa rat. This phenomenon is associated with glomerular hypertrophy and mesangial expansion and with...
Adiponectin in CKD

ADPN is a 30-kDa protein secreted by adipocytes that circulates in multimeric forms. This protein is an insulin-sensitizing, anti-inflammatory and vasculo-protective cytokine. Both the C-terminal globular head domain and the full-length oligomeric form of this compound act upon specific receptors [13] and signal via stimulation of 5′-AMP-activated protein kinase (AMPK) and other pathways. Like insulin, AMPK stimulates glucose transport, an effect that may be additive to that of insulin. This phenomenon suggests that a cross-talk between the two systems may be of critical importance in insulin resistance states. AMPK activation enhances insulin signalling downstream of protein kinase B in rat hearts in vivo by increasing insulin-mediated phosphorylation of glycogen synthase kinase 3 (GSK3) beta, p70 S6 kinase (p70S6K)(Thr389) and IRS1(Ser636/639) levels. This is a complex phenomenon because AMPK activation also inhibits insulin stimulation of IRS1-associated phosphatidylinositol 3-kinase activity indicating differential effects of AMPK on components of the insulin-signalling pathway [14]. Protective effects of ADPN may also involve reduction of oxidant stress via inhibition of NADPH oxidases [13].

Plasma ADPN concentration is inversely associated with body weight, triglycerides and LDL cholesterol levels and with various inflammation biomarkers and predicts incident type 2 diabetes [15]. The dependence of ADPN from fat mass is epitomized by the observation that this adipokine undergoes a substantial increase after weight loss [16,17] and vice versa. Atherogenic changes characterize the ADPN-deficient knockout mice [18]. Of note, in the ADPN-knockout model subtotal nephrectomy accentuates albuminuria, tubulo-interstitial infiltration by inflammatory cells and renal fibrosis as compared to the wild-type mice and these alterations are ameliorated by ADPN transfection [19]. Hypoadiponectinaemia is associated with endothelial dysfunction and with coronary events in patients with cardiac disease [16] or with ESRD [20]. The relationship of this adipokine with clinical outcomes in patients with CKD is much dependent on the particular clinical context where it is being tested [21]. ADPN is considerably increased both in adults [22] and in children [23] with full blown nephrotic syndrome, and such a direct ADPN–proteinuria association extends to patients with various nephropathies [24]. The strong association between high ADPN and hypoalbuminaemia/proteinuria and dyslipidaemia in nephrotic syndrome suggests that ADPN may serve to mitigate cardio-renal damage triggered by dyslipidaemia and by other risk factors incited by urinary protein loss. In keeping with findings in patients with active nephrotic syndrome or proteinuric nephropathies in general, this adipokine was directly associated with renal disease progression in male patients in a cohort study of middle-aged Caucasians [25]. Therefore, high ADPN may be part of a renal- and cardio-protective mechanism set in motion to counter critical organ damage. However, establishing whether or not ADPN is causally involved in cardiovascular and renal protection is complex and epidemiologic associations per se rarely if ever allow definitive conclusions on causality. Biological experiments and randomized experimental studies in animal models and in man are needed to frame a reliable interpretation of such associations.

Elegant studies by Sharma et al. [26] strongly implicate low ADPN in the pathogenesis of renal disease in obesity. These authors found that albuminuria correlates inversely with plasma ADPN in obese African American patients. Such an association only apparently contrasts with the previously reported direct association between ADPN and proteinuria in nephrotic syndrome. In fact, the glomerular barrier is relatively much less affected in obesity in comparison to nephrotic syndrome, and systemic protein depletion rarely occurs in the obese. Furthermore, as already discussed, obesity per se represents a situation of ADPN deficiency. The most revealing observations in the Sharma study were made in the ADPN-knockout mice. This transgenic model of ADPN deficiency exhibited effacement and fusion of podocyte foot processes and increased urinary levels of albumin and hydrogen peroxide. ADPN abated albumin permeability in cultured podocytes, and via an AMPK-dependent pathway it induced translocation of zona occludens-1 (ZO-1) to the plasma membrane. Intriguingly, ADPN also reduced NADPH oxidase 4 (Nox4) in podocytes, which is the dominant NADPH oxidase in the kidney [13]. These detailed in vitro studies were corroborated by parallel in vivo studies showing that exogenous ADPN administration to the ADPN null mice reduces albuminuria and urinary hydrogen peroxide excretion and attenuates podocyte damage along with increased glomerular AMPK activity and reduced glomerular Nox4 (Figure 1). These data convincingly show that podocytes are a physically distant but quite relevant target of a peculiar product of fat cells such as ADPN and provide a novel interpretative framework for obesity-related glomerulopathy and diabetic nephropathy.
**Can we exploit ADPN to diagnose and treat obesity-related nephropathy and diabetic nephropathy?**

It was suggested that hypoadiponectinaemia might be taken as a biomarker of the renal risk associated with obesity and predisposition to or frank diabetes mellitus [27]. However, this possibility seems very unlikely. In reality, the relationship between ADPN and proteinuria is not so compelling as it appeared to be in the Sharma study. As a matter of fact, the ADPN–proteinuria link is direct rather than inverse in the vast majority of patients with progressive nephropathies [22,24] as well as in Pima Indians, a population at high risk for obesity and type 2 diabetes [28]. Undoubtedly, the most intriguing perspective alimented by Sharma’s observations is that of exploiting the potential of this protein as a reno-protective cytokine. Weight loss apart, ADPN synthesis and/or secretion can be stimulated by a variety of drugs [29]. ACE inhibitors, sartans (telmisartan in particular), oral hypoglycaemic agents like metformin and glimepiride, a beta blocker which functions also as a stimulant to NO synthase like nebivolol, PPAR-gamma agonists like fenofibrate and particularly PPAR-gamma agonists like rosiglitazone [30] all augment plasma ADPN. Rosiglitazone, a compound that activates NO synthase via an AMPK pathway [31], appears of particular interest. In a small series of 10 patients with microalbuminuria randomized to this PPAR-gamma agonist or placebo for 12 weeks, the drug corrected hyperfiltration (GFR, from 133.4 ± 9.8 to 119.6 ± 8.7 ml/min) and reduced microalbuminuria as well (from 116.5 ± 31 to 40.4 ± 12 mg/day), and these effects were associated with improved NO bioavailability [32]. Likewise, rosiglitazone added to background therapy with metformin provided greater reductions in microalbuminuria and blood pressure as compared to glyburide [33]. Rosiglitazone prevented the renal end-point in the DREAM study [34], a large trial in 5269 adults with fasting hyperglycaemia and/or impaired glucose tolerance without known cardiovascular disease or renal insufficiency. However, such a favourable renal effect was counterbalanced by an increased risk of heart failure. PPAR-gamma agonists influence a variety of biological pathways, and the increase in plasma ADPN represents just an important but in no way exclusive pathway mediating the effects of this class of drugs. Compounds that stimulate ADPN synthesis in a selective manner are not available at present.

In conclusion, the paper by Sharma further highlights the relevance of the adipose tissue–kidney connection. Leptin was the first adipose tissue cytokine to be directly implicated in renal damage in obesity. Fresh results in the ADPN null mice show that the lack of ADPN may be conducive to renal damage and that this damage can be reversed by supplementing ADPN. Drugs that stimulate ADPN synthesis and ADPN derivatives are investigated with increasing interest by the industry [35]. This flurry of interest may soon bring ADPN into the translational research arena, i.e. the area of phase 1 and phase 2 clinical trials.

**Conflict of interest statement.** None declared.

**References**

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