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

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Keywords: adiponectin; diabetic nephropathy; insulin; obesity; risk factors

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]. A recent systematic review of studies published between 1990 and 2008 found that the prevalence of obesity in European countries ranged from 4.0% to 28.3% in men and from 6.2% to 36.5% in women [2]. Overweight and obesity, particularly abdominal obesity, entail the major cluster of cardiovascular risk factors (including fasting hyperglycaemia or frank type 2 diabetes, low HDL cholesterol and high LDL cholesterol, hypertriglyceridaemia and hypertension) responsible for the epidemics of cardiovascular diseases in economically developed countries. Obesity is also directly or indirectly implicated in the emerging epidemic of chronic kidney disease (CKD) and end-stage renal disease (ESRD) [3]. In Europe, several surveys have now been completed and these studies [4] indicate that CKD is a problem of the same order than in the USA. 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

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evidence of accentuated podocyte injury and degeneration of these cells, ultimately leading to glomerulosclerosis [9]. Therefore, podocyte injury appears to be the hallmark of nephropathy in this model, a notion also in keeping with the observation that high concentrations of glucose elicit podocyte hypertrophy and stress *in vitro*. In obesity-related glomerulopathy in humans, glomerular volume is much enlarged, podocyte number and density are decreased, but foot-process width on the peripheral glomerular basement membrane is much increased [10]. Of note, proteinuria in these patients correlates inversely with podocyte density and directly with foot-process width. Furthermore, parallel inverse relationships exist between podocyte number and density with insulin resistance. On the other hand, podocytopaenia and foot-process effacement, glomerular hypertrophy and glomerulosclerosis characterize diabetic nephropathy [11,12]. Overall, coherent evidence exists that podocyte biology is critically altered in the two major drivers of CKD in the general population, namely obesity-associated CKD and diabetic nephropathy. Insulin sensitivity appears to be of major importance for podocyte biology, but intimate mechanisms responsible for podocyte damage in these nephropathies are still poorly understood.

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.

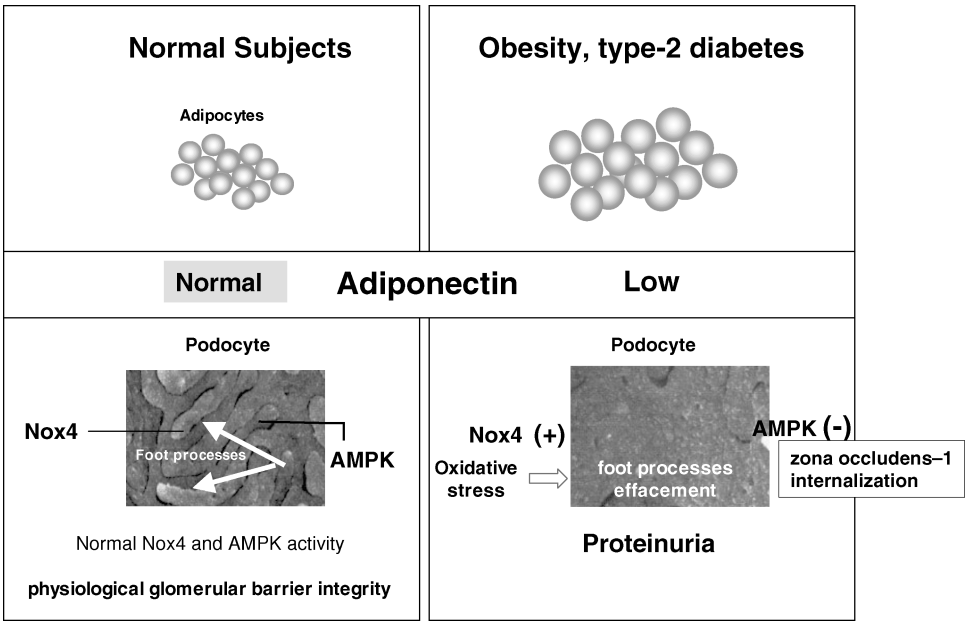

Fig. 1. Low adiponectin in obese and type 2 diabetics triggers oxidative stress [via NADPH oxidase 4 (Nox4) enhancement] and induces podocytes damage (extensive foot-process effacement). On the other hand, reduced 5′AMP-activated protein kinase (AMPK) activation determines zona occludens-1 internalization, a process that together with foot-process effacement contributes to engender proteinuria (see also the text).

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-alpha 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 bioavailibility [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

1. Ogden CL, Carroll MD, Curtin LR *et al*. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* 2006; 295: 1549–1555
2. Berghofer A, Pischon T, Reinhold T *et al*. Obesity prevalence from a European perspective: a systematic review. *BMC Public Health* 2008; 8: 200
3. Ritz E. Metabolic syndrome and kidney disease. *Blood Purif* 2008; 26: 59–62

4. de Jong PE, van d V Gansevoort RT, Zoccali C. Screening for chronic kidney disease: where does Europe go? *Clin J Am Soc Nephrol* 2008; 3: 616–623
5. Iseki K. Body mass index and the risk of chronic renal failure: the Asian experience. *Contrib Nephrol* 2006; 151: 42–56
6. Hsu CY, McCulloch CE, Iribarren C *et al*. Body mass index and risk for end-stage renal disease. *Ann Intern Med* 2006; 144: 21–28
7. Lane JT. Microalbuminuria as a marker of cardiovascular and renal risk in type 2 diabetes mellitus: a temporal perspective. *Am J Physiol Renal Physiol* 2004; 286: F442–F450
8. Coward RJ, Welsh GI, Yang J *et al*. The human glomerular podocyte is a novel target for insulin action. *Diabetes* 2005; 54: 3095–3102
9. Hoshi S, Shu Y, Yoshida F *et al*. Podocyte injury promotes progressive nephropathy in zucker diabetic fatty rats. *Lab Invest* 2002; 82: 25–35
10. Chen HM, Liu ZH, Zeng CH *et al*. Podocyte lesions in patients with obesity-related glomerulopathy. *Am J Kidney Dis* 2006; 48: 772–779
11. Wolf G, Chen S, Ziyadeh FN. From the periphery of the glomerular capillary wall toward the center of disease: podocyte injury comes of age in diabetic nephropathy. *Diabetes* 2005; 54: 1626–1634
12. Li JJ, Kwak SJ, Jung DS *et al*. Podocyte biology in diabetic nephropathy. *Kidney Int Suppl* 2007; S36–S42
13. Ouedraogo R, Wu X, Xu SQ *et al*. Adiponectin suppression of high-glucose-induced reactive oxygen species in vascular endothelial cells: evidence for involvement of a cAMP signaling pathway. *Diabetes* 2006; 55: 1840–1846
14. Longnus SL, Segalen C, Giudicelli J *et al*. Insulin signalling downstream of protein kinase B is potentiated by 5′AMP-activated protein kinase in rat hearts *in vivo*. *Diabetologia* 2005; 48: 2591–2601
15. Jalovaara K, Santaniemi M, Timonen M *et al*. Low serum adiponectin level as a predictor of impaired glucose regulation and type 2 diabetes mellitus in a middle-aged Finnish population. *Metabolism* 2008; 57: 1130–1134
16. Takemura Y, Walsh K, Ouchi N. Adiponectin and cardiovascular inflammatory responses. *Curr Atheroscler Rep* 2007; 9: 238–243
17. Steffens S, Mach F. Adiponectin and adaptive immunity: linking the bridge from obesity to atherogenesis. *Circ Res* 2008; 102: 140–142
18. Kubota N, Terauchi Y, Yamauchi T *et al*. Disruption of adiponectin causes insulin resistance and neointimal formation. *J Biol Chem* 2002; 277: 25863–25866
19. Ohashi K, Iwatani H, Kihara S *et al*. Exacerbation of albuminuria and renal fibrosis in subtotal renal ablation model of adiponectin-knockout mice. *Arterioscler Thromb Vasc Biol* 2007; 27: 1910–1917
20. Zoccali C, Mallamaci F, Tripepi G *et al*. Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. *J Am Soc Nephrol* 2002; 13: 134–141
21. Zoccali C, Mallamaci F. Adiponectin and renal disease progression: another epidemiologic conundrum? *Kidney Int* 2007; 71: 1195–1197
22. Zoccali C, Mallamaci F, Panuccio V *et al*. Adiponectin is markedly increased in patients with nephrotic syndrome and is related to metabolic risk factors. *Kidney Int Suppl* 2003; S98–S102
23. Bakkaloglu SA, Soylemezoglu O, Buyan N *et al*. High serum adiponectin levels during steroid-responsive nephrotic syndrome relapse. *Pediatr Nephrol* 2005; 20: 474–477
24. Menon V, Li L, Wang X *et al*. Adiponectin and mortality in patients with chronic kidney disease. *J Am Soc Nephrol* 2006; 17: 2599–2606
25. Kollerits B, Fliser D, Heid IM *et al*. Gender-specific association of adiponectin as a predictor of progression of chronic kidney disease: the Mild to Moderate Kidney Disease Study. *Kidney Int* 2007; 71: 1279–1286
26. Sharma K, Ramachandrarao S, Qiu G *et al*. Adiponectin regulates albuminuria and podocyte function in mice. *J Clin Invest* 2008; 118: 1645–1656
27. Ahima RS. Linking adiponectin to proteinuria. *J Clin Invest* 2008; 118: 1619–1622
28. Looker HC, Krakoff J, Funahashi T *et al*. Adiponectin concentrations are influenced by renal function and diabetes duration in Pima Indians with type 2 diabetes. *J Clin Endocrinol Metab* 2004; 89: 4010–4017
29. Han SH, Quon MJ, Kim JA *et al*. Adiponectin and cardiovascular disease: response to therapeutic interventions. *J Am Coll Cardiol* 2007; 49: 531–538
30. Osei K, Gaillard T, Kaplow J *et al*. Effects of rosglitazone on plasma adiponectin, insulin sensitivity, and insulin secretion in high-risk African Americans with impaired glucose tolerance test and type 2 diabetes. *Metabolism* 2004; 53: 1552–1557
31. Boyle JG, Logan PJ, Ewart MA *et al*. Rosiglitazone stimulates nitric oxide synthesis in human aortic endothelial cells via AMP-activated protein kinase. *J Biol Chem* 2008; 283: 11210–11217
32. Pistrosch F, Herbrig K, Kindel B *et al*. Rosiglitazone improves glomerular hyperfiltration, renal endothelial dysfunction, and microalbuminuria of incipient diabetic nephropathy in patients. *Diabetes* 2005; 54: 2206–2211
33. Bakris GL, Ruilope LM, McMorn SO *et al*. Rosiglitazone reduces microalbuminuria and blood pressure independently of glycemia in type 2 diabetes patients with microalbuminuria. *J Hypertens* 2006; 24: 2047–2055
34. Dagenais GR, Gerstein HC, Holman R *et al*. Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. *Diabetes Care* 2008; 31: 1007–1014
35. Mancini MC, Halpern A. Investigational therapies in the treatment of obesity. *Expert Opin Invest Drugs* 2006; 15: 897–915

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