The Link Between Obesity and Albuminuria: Adiponectin and Podocyte Dysfunction

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Abstract

With the recent rise in world wide obesity, obesity-related albuminuria is now being recognized as a critical risk factor for cardiovascular disease. However, there is an urgent need to better understand this association. Recent clinical studies suggest that the adipocyte hormone adiponectin may play a key role in the development of obesity-related albuminuria. Moreover, studies with the adiponectin knockout mouse indicate that adiponectin can regulate podocyte function and thus contribute to the initial development of albuminuria. Future studies to examine adipocyte-renal cell biology are needed to develop preventive and therapeutic strategies for combatting the complications of obesity.
Introduction

It is well known that obesity is a risk factor for many medical illnesses. Specifically, obesity has been associated with subtle effects in the decline of kidney function and low grade albuminuria \(^1\text{-}^4\). Indeed, albuminuria is now considered as one of the strongest risk factors for cardiovascular disease in patients with obesity \(^5\text{-}^6\). However, it remains unclear how obesity-related albuminuria develops and why a relationship exists between albuminuria and cardiovascular morbidity and mortality.

Several explanations may address these questions: 1. There are common unmeasured factor (s) produced outside the kidney that provide the link between albuminuria and the risk for cardiovascular morbidity and mortality. 2. Factors produced by the kidney in association or due to albuminuria contribute to overall cardiovascular risk. 3) The relationship between albuminuria and cardiovascular risk is a fortuitous relationship that belies an unknown factor responsible for the risk and is independent of albuminuria. The consensus widely quoted in the medical literature is that low grade albuminuria is due to “endothelial dysfunction” and thus reflects a widespread systemic vascular disturbance. However, the data to support endothelial dysfunction as the causative mechanism of albuminuria with obesity is largely circumstantial.

Identifying the cell types involved in the association between obesity and albuminuria may lead to understanding the relationship between albuminuria cardiovascular risk. Several key early studies that have established a potential important
relationship between obesity and albuminuria may provide clues about which are the potential cell types involved. It is well recognized that patients with obesity may develop heavy proteinuria and an FSGS syndrome. The characteristic renal findings seen with obesity include glomerular enlargement and focal segmental sclerosis pattern. From a nephrologist’s perspective, such a pattern of anatomic abnormalities clearly suggests a role for podocytes. In a recent study, weight reduction with bariatric surgery led to a decrease in proteinuria, suggesting that a circulating factor from adipocytes may play a role. Several animal models of obesity have examined the effects on the glomerulus. Although variable results on the kidney have been noted, a recent study in the C57Bl6 mouse demonstrated that feeding a high fat diet led to development of obesity, large glomeruli, and albuminuria. Interestingly the mice fed a high fat diet exhibited hypoadiponectinemia and podocyte foot process effacement. However, the mice also developed insulin resistance and exhibited stimulation of a variety of growth factors and inflammatory mediators, making it difficult to identify the mechanisms involved in the genesis of albuminuria.

**Adipocytes as an Endocrine Organ**

The second major conceptual breakthrough arose with the recognition that adipocytes are an active endocrine cell type. Adipocytes have now been demonstrated to have an intact renin-angiotensin system (RAS), secrete TNF-α, IL-6, PAI-1, and TGF-β. These factors are clearly involved in a paracrine or autocrine role to enhance the inflammatory phenotype of visceral adipocytes, likely in concert with
infiltrating macrophages. All of these factors may also act in an endocrine manner and lead to podocyte and endothelial dysfunction. In addition, adipocytes secrete hormones that are specifically produced by adipocytes including leptin, adiponectin, and resistin. Leptin production is associated with increased size of adipocytes and is positively correlated with the body mass index. Leptin has effects on appetite suppression, although hyperleptinemia is commonly seen with obesity and exogenous leptin does not lead to consistent and profound weight loss. Leptin may have direct effects on the kidney although the specific leptin receptors that mediate the effects of leptin have not been clearly identified in renal cells. Resistin is a relatively recently described adipokine that is linked to insulin resistance in mice and in humans. Resistin is increased with obesity and may contribute to the kidney disease and albuminuria associate with obesity. However, a mechanistic role for resistin to mediate kidney disease has not been established. Of the numerous factors that are regulated with increased visceral obesity, only a few adipokines are reduced with obesity. The best characterized of these is adiponectin.

**Adiponectin**

Adiponectin is a 30 kDa protein secreted by adipocytes and exists as oligomers in the circulation. Adiponectin production has been demonstrated in other cell types such as cardiomyocytes, but the predominant cell type responsible for circulating adiponectin is the adipocyte. The human and mouse adiponectin promoter contains binding sites for sterol regulatory element-binding protein 1-c (SREBP-1c), peroxisome proliferator-activated receptor gamma PPARg, CCAAT/enhancer binding protein C-EBP as well as
E-boxes (CANNTG). SREBP1c is increased with adipocyte differentiation and is a
positive upregulator of adiponectin gene. Id3 is a member of the family of inhibitor of
differentiation transcription factors and has been recently found to inhibit adiponectin
promoter activity by binding to E47 (an E-box binding protein) and preventing E47
augmentation of SREBP-induced adiponectin promoter activation\textsuperscript{17}. The precise
mechanism of reduced adiponectin levels with obesity is unclear, although both inhibition
of gene expression as well as decreased secretion\textsuperscript{18} are contributory.

Reduction of adiponectin levels is a consistent feature among obese patients that
have evidence of insulin resistance and often go on to develop diabetes\textsuperscript{19}. Several studies
have shown that low adiponectin levels are associated with increased long term risk of
CVD\textsuperscript{20,21}. However, high adiponectin levels may also be associated with increased CVD
and mortality\textsuperscript{22,23}. Adiponectin levels that decrease with obesity in mouse models and
measures of insulin resistance are improved with exogenous adiponectin administration.
Importantly, adiponectin has been considered to have a vascular protective effect as it
suppresses reactive oxygen species (ROS) production in a variety of cell types, including
endothelial and cardiomyocytes\textsuperscript{24-26}. The best characterized receptors for adiponectin are
the AdipoR1 and Adipo R2 receptors\textsuperscript{27}. T-cadherin has also been identified as a plasma
membrane binding protein that binds adipoenctin and may function as a co-receptor. The
AdipoR1 and R2 receptors are 7 transmembrane spanning proteins but are distinct from
the G-protein coupled receptors (GPCRs) and do not activate heterotrimeric G-proteins.
In contrast to GPCRs the N-terminus of the adiponectin receptors is cytoplasmic and the
C-terminus is extracellular. AdipoR1 is present ubiquitously whereas AdipoR2 is
primarily expressed in the liver. Based on studies with the AdipoR1 and AdipoR2 knockout mice, AdipoR1 is primarily responsible for activating adiponectin-induced AMPK whereas AdipoR2 mediates PPAR-α activation. Both receptors are required for adiponectin mediated insulin sensitivity. APPL1 (adaptor protein containing pleckstrin homology domain, phosphotyrosine binding (PTB) domain and leucine zipper motif) is the first protein identified to bind directly to the adiponectin receptors and appears to be involved in the cross talk between adiponectin and insulin signaling.

**Adiponectin and Albuminuria**

The potential link between adiponectin levels and low grade albuminuria was first identified in a clinical study wherein men with essential hypertension had a significant negative correlation of adiponectin levels and low grade albuminuria. This clinical observation has now been replicated in obese Japanese patients (males and females) and in our recent study with obese male and female African Americans. However, similar to the bi-directional relationship of adiponectin with cardiovascular disease (see above) there are also reports demonstrating a positive correlation between adiponectin with high grade albuminuria and declining renal function. Nevertheless, the clinical data suggests that there could be a potential causative role for adiponectin in the initial development of albuminuria in the obese population.

To demonstrate a causative relationship for adiponectin with albuminuria, we recently studied the adiponectin knockout (KO) mouse and demonstrated that the mice
had baseline increased albuminuria (twice normal) with podocyte foot process effacement. The endothelium appeared normal by electron microscopy. Furthermore, podocytes expressed the AdipoR1 receptor and adiponectin regulated an isoform of NAPDH oxidase (Nox4), via the AMPK pathway. Treatment of the adiponectin KO mice with adiponectin was able to normalize albuminuria and restore podocyte foot processes. Adiponectin deficiency was also demonstrated to be a susceptibility factor for early diabetic kidney disease \(^{32}\) and progressive non-diabetic renal disease, in an independent study \(^{35}\).

There are several implications of these studies. We can now conclude that the podocyte is a key cell type involved in the initial development of albuminuria and may play the dominant role in the albuminuria associated with obesity. The role of endothelial dysfunction may well be important for albuminuria, however definitive studies to document the presence of glomerular endothelial dysfunction with low grade albuminuria have not been published. Furthermore, the mechanisms of endothelial dysfunction that lead to podocyte dysfunction have not been established.

That podocyte dysfunction can lead to endothelial dysfunction has been well established; recent studies by Quaggin’s group has shown that podocyte regulation of VEGF can regulate endothelial function \(^{36,37}\). Another implication is that the adiponectin KO mouse model may serve to demonstrate that the initial development of albuminuria involves podocytes and may be independent of tubular uptake of albumin. Further examination of tubular uptake of albuminuria in this model may help to resolve the ongoing controversy \(^{38}\) as to whether the genesis of increased albuminuria with obesity is primarily a podocyte phenotype or a tubular cell phenotype. The regulation of podocyte
function by adiponectin also further establishes the ongoing communication between adipocytes and renal cells \(^{13,14}\). It would be of interest to examine the potential interactive roles of adiponectin, leptin, and resistin in the development of albuminuria and podocyte dysfunction.

A further implication of our studies is that there could be a potential role for the podocyte in the progression of systemic vascular disease associated with albuminuria. Low adiponectin levels could lead to a consequent increase in Nox4 production by the podocytes (Figure 1) and potentially other renal cell types. Increased Nox activity in the kidney may contribute to release of ROS from the kidney and potentially lead to a systemic increase in ROS and vascular injury. Thus the kidney could play an important contributory role in the systemic vascular inflammation noted with obesity and albuminuria \(^5\).

**Concluding remarks**

With the rapidly growth of the obesity epidemic, a better understanding of the risk factors for the complications of obesity is critical. Now that albuminuria is now recognized as perhaps the most important risk factor for the increased morbidity and mortality in the obese population \(^5\), a mechanistic understanding of the development of albuminuria in the early stages of obesity is necessary. It is likely that adiponectin plays an important role. Hopefully, further research in adipocyte-renal cell biology will lead to novel therapeutic approaches that combat the increased morbidity and mortality associated with obesity.
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References


Figure 1. With increasing fat mass, visceral adipocytes decrease production of circulating adiponectin and increase production of adipokines that enhance insulin resistance. The lower adiponectin levels would lead to impaired podocyte function possibly due to increased podocyte NADPH oxidase. Podocyte dysfunction will lead to albuminuria and urine levels of hydrogen peroxide. Potentially the increased production of hydrogen peroxide from renal NADPH oxidase may enter the circulation and contribute to the systemic inflammation accompanying observed with low grade albuminuria.