Review Article
Adiponectin and glomerular diseases

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Abstract: Glomerular diseases are caused by an immune-mediated inflammation of the glomeruli. Often presenting as nephrotic syndrome, glomerular diseases are the most common causes of chronic kidney disease and end-stage renal disease. Among several mechanisms, oxidative stress and inflammation in response to renal injury may play crucial role. Accordingly, antioxidants and anti-inflammatory medications are generally used to slow the disease progression. Adiponectin is an anti-inflammatory cytokine that is produced by adipose tissue and may offer a renoprotective effect. The specific association between adiponectin and glomerular diseases, however, appears to vary in different types of diseases. As such, the interplay between the level of adiponectin and proteinuria, which is a marker of the progression of glomerular diseases, has not been adequately characterized. Therefore, the purpose of our review was to summarize and evaluate current evidence regarding the role of adiponectin in the development of glomerular diseases, including experimental and clinical studies. On the basis of accumulated data, targeting adiponectin may be a novel therapeutic strategy for the treatment of glomerular diseases.

Keywords: Adiponectin, glomerular diseases, proteinuria

Introduction

Glomerular diseases belong to an immune-mediated inflammatory disease that carries a risk for progressive loss of kidney function. Glomerular diseases can present as a primary disease of the glomeruli, as well as a secondary symptom of a systemic disease, such as diabetes. The incidence rate of glomerular diseases has increased in recent years and, consequently, kidney diseases have become a public health concern worldwide.

Adiponectin was originally identified as an anti-inflammatory protein produced by adipose tissue. This protein exerts multiple biological functions, including insulin sensitization and lowering of glomerular fibrosis and atherosclerosis [1]. More recently, the renoprotective role of adiponectin has attracted attention. However, accumulated data show that the adiponectin response varies among different forms of glomerular diseases and, consequently, the role that adiponectin plays in glomerulonephritis has not yet been adequately characterized. As there is evidence of an association between adiponectin and the development of proteinuria, which is a marker of disease progression [2, 3], understanding the role of adiponectin in glomerular diseases could provide new insight into the clinical indicators and therapeutic strategies.

Adiponectin—an overview

Adiponectin is an anti-inflammatory cytokine that is secreted by adipose tissue and is involved in glucose and lipid metabolism. Of note, adiponectin is eliminated through the kidneys, crossing the glomerular filtration barrier. Adiponectin is classified into two types, namely, high-molecular-weight (HMW) adiponectin and low-molecular-weight (LMW) adiponectin [4]. The biological activity of circulating HMW adiponectin appears to be higher than that of LMW adiponectin [5].

Adiponectin receptors (AdipoR1 and AdipoR2) are mainly expressed in skeletal muscle and in liver [6]. AdipoR1 is also present in renal endothelial cells, podocytes, mesangial cells, and the epithelial cells of renal tubules [7-9]. HMW
Adiponectin and glomerular diseases

Adiponectin has a strong affinity with AdipoR1 and, thus, can cross the glomerular filtration barrier to act on the AdipoR1-mediated activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway. The AMPK pathway can inhibit reactive oxygen species (ROS), which are involved in oxidative stress injury, as well as act directly on podocytes to reduce their permeability to albumin and reduce their dysfunction [10, 11]. By reducing oxidative stress, the adiponectin-AMPK pathway can control local inflammation and restore podocyte function to protect against albuminuria (Figure 1). By contrast, AdipoR2 activates the peroxisome proliferator-activated receptor alpha (PPAR-α) pathway, which regulates lipid metabolism and fatty acid oxidation. The binding of adiponectin to AdipoR2 might protect against renal ischemia-reperfusion injury via the PPAR-α-HO-1 signaling pathway [12].

Adiponectin and primary glomerular diseases

Primary glomerular diseases are characterized by inflammation in glomeruli with unknown etiology. The common clinical manifestation of different primary glomerular diseases is proteinuria. Proteinuria is the most important risk factor for renal failure. However, accurate determination of the 24 h proteinuria value is difficult because of the natural fluctuation of urine protein levels over 24 h. Moreover, proteinuria is influenced by multiple factors, other than renal function, including protein intake, exercise, blood pressure, and infection. However, the level of circulating adiponectin may provide a surrogate measure of proteinuria that is more reliable.

Circulating levels of adiponectin have been reported to be higher in individuals with nephrotic syndrome than in healthy controls [13, 14]. In the study on serum levels of adiponectin among patients with chronic glomerulonephritis, Hayakawa et al. noted that adiponectin levels were higher among patients with macroproteinuria than among those with microproteinuria [15]. In patients with focal segmental glomerulosclerosis, both serum and urine adiponectin levels were found to be closely related to proteinuria [16]. Therefore, adiponectin can be used to monitor changes in proteinuria in chronic glomerulonephritis.

Several animal studies have investigated the role of adiponectin in kidney function to clarify the mechanism of adiponectin regulation. Ohashi et al. [17] reported that after partial nephrectomy urine protein, cell apoptosis, glomerular hypertrophy, renal tubule and renal interstitial fibrosis were more severe in adiponectin gene knockout mice than in normal mice. Therefore, adiponectin may minimize adverse reactions to nephrectomy, with a specific positive effect on reducing urine protein. Rutkowski et al. reported that mice lacking adiponectin experienced irreversible proteinuria with reduced podocytes, leading to kidney failure after nephrectomy, whereas mice with excessive adiponectin expression developed less renal interstitial fibrosis and podocyte damage, with significant recovery from proteinuria [17]. An in vitro study demonstrated that the addition of adiponectin to podocytes reduced levels of urine protein and increased the activity of the AMPK pathway, resulting in a decrease in the oxidative stress level [18]. As such, adiponectin could prevent the development of proteinuria by podocyte repair.

Tsuruoka et al. reported an improvement in the concentration of serum adiponectin after Irbesartan treatment in patients with chronic glomerulonephritis [19]. In this case, adiponec-
Adiponectin and glomerular diseases

Adiponectin and secondary glomerular diseases

Adiponectin and diabetic nephropathy

Diabetic nephropathy (DN) is the most common type of secondary glomerular diseases and presents as changes in the renal microvascular with different levels of proteinuria. The most common pathological feature of DN is kidney hypertrophy, due to an increase in the glomerular basement membrane and mesangial cells, which gradually progresses to glomerular sclerosis and, finally, kidney failure.

Using a murine model, Fang et al. identified a protective role of adiponectin in DN [22]. Specifically, in an akita/adiponectin (/-) mouse model of DN, they observed that deletion of the adiponectin gene exacerbated inflammation, kidney hypertrophy and fibrosis in the tubulointerstitial and glomerular compartments. In another study, adiponectin effectively enhanced antioxidative products, promoted insulin secretion and reduced the accumulation of glycosylated products in the kidneys of mice with type 2 diabetes [23]. However, the relationship between serum adiponectin level and proteinuria might be different between type 1 and type 2 diabetes. Specifically, higher levels of adiponectin are predictive of lower proteinuria (negative relationship) in type 1 diabetes, while being predictive of higher proteinuria (positive relationship) in type 2 diabetes [24-26]. Based on the increase in total serum adiponectin as a function of increasing stage of type 2 DN [27], adiponectin appears to offer a weak renoprotective effect in type 2 diabetes, which might account for the frequent presence and rapid development of albuminuria in these patients. In fact, Kacso et al. demonstrated that a lower level of serum adiponectin was associated with a higher urine albumin/creatinine ratio in patients with type 2 diabetes [28], whereas increasing levels of serum adiponectin were associated with a decline in renal function [29]. In contrast, Saraheimo et al. [30] reported higher levels of adiponectin were associated with higher macroalbuminuria in patients with type 1 diabetes, whose finding was confirmed by Bjornstad et al. [31]. Therefore, adiponectin can be used to estimate the degree of albuminuria in DN. An important issue to consider, however, is that the adiponectin level can be influenced by the use of oral glucose-lowering drugs and obesity, making it difficult to establish the relationship between proteinuria and serum adiponectin level in patients with diabetes.

Taking advantage of the fact that adiponectin passes through the normal glomerular filtration barrier and thus can be detected in urine, recent studies have focused on evaluating the clinical significance of urine adiponectin. The urine level of adiponectin was found to be an independent predictor of end-stage renal disease in type 1 DN, and its predictive value of renal disease progression is superior to that of urine albumin excretion [32]. In their evaluation of urine albumin excretion, glomerular filtration rate and urine HMW adiponectin levels in 141 patients with type 2 diabetes, Kopf et al. confirmed that the urine HMW adiponectin level could predict the decline in renal function in this clinical population [33]. Therefore, the urine adiponectin level could contribute to more accurate detection of DN progression.

With regard to the role of adiponectin in protecting podocytes, Rutkowski et al. reported a positive association between the plasma level of adiponectin and podocyte function, with higher adiponectin levels promoting a recovery of podocyte function after PPAR-γ agonist treatment in a murine model [18]. Therefore, adiponectin-promoting activity is closely associated with activation of PPAR-γ [34]. Of note, the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers dramatically increases the serum adiponectin level, leading to significant improvement in most clinical
parameters of renal function [35, 36]. These findings suggested that the treatment effects of PPAR-γ agonists and blockers of the renin-angiotensin-aldosterone system (RAAS) may be mediated by adiponectin. Thus, adiponectin level can be considered a biomarker of the therapeutic efficacy of these drugs. Support for this therapeutic role of adiponectin was provided in a murine model, in which exogenous adiponectin treatment in mice with type 2 diabetes was effective in reducing albuminuria and improving renal fibrosis [37]. However, further studies are required to confirm this result, especially in humans. Taken together, current evidence indicates that adiponectin may exert a therapeutic role in the prevention of DN progression.

Adiponectin and obesity related nephropathy

Obesity is a worldwide health problem that has greatly increased in prevalence over the past few decades, and it is directly associated with insulin resistance and oxidative stress. Obesity itself decreases the level of adiponectin, owing to reduced expression of AdipoR, oxidative stress, and impaired mitochondrial function [38, 39]. The resulting hypoadiponectinemia contributes to a low-grade systemic chronic inflammatory state, which can result in obesity-related renal injury. Furthermore, the excessive adipose burden increases the vulnerability of the glomerular filtration barrier to injury, resulting in glomerular hypertrophy, mesangial cell proliferation and focal and segmental glomerulosclerosis, causing obesity-related nephropathy. Increased body weight is directly associated with an increased risk of developing chronic kidney disease, with slowly progressing proteinuria.

An experimental study demonstrated that adiponectin deficiency in obese mice was associated with podocyte effacement and fusion, accompanied by albuminuria [40]. These changes did not occur in normal mice. Thus, adiponectin could possibly reverse podocyte damage and reduce albuminuria. Yano et al. [41] demonstrated that urine albumin excretion in obese individuals with low levels of adiponectin was higher than that in mice with high levels of adiponectin. This negative correlation between urine protein and the level of adiponectin in obese individuals was confirmed by Meyvis et al. [42]. These studies indicated that adiponectin may play a key role in the development of obesity-related albuminuria, although the specific mechanism remains to be fully characterized. Numao et al. found that vigorous aerobic exercise in obese patients can improve the proportion of HMW adiponectin [43], which was confirmed by Kelly et al. [44]. Taken together, these studies demonstrate that the protective role of adiponectin is likely to be significant in obesity-related nephropathy.

**Adiponectin and lupus nephritis**

Lupus nephritis (LN) is the most common complication of systemic lupus erythematosus (SLE), resulting from the chronic immune-mediated inflammation. LN easily progresses to end-stage renal disease and becomes the leading cause of death in patients with SLE. Adiponectin may play a role in the pathogenic process of LN.

Adiponectin deficiency in a lupus model in wild-type mice resulted in more severe renal injury, with a striking presence of glomerular crescents and renal fibrosis in adiponectin-deficient mice [45]. In a human study, the serum adiponectin level was found to be lower in patients with SLE-associated kidney damage compared to patients with SLE without kidney damage [46]. In a multivariate analysis, Diaz-Rizo et al. reported comparable results and further reported that the serum adiponectin level was significantly correlated to the severity of 24-h proteinuria after adjusting for confounders [47]. The increase in serum adiponectin levels in patients with LN might reflect a compensatory response to systemic inflammation. The possibility of “adiponectin resistance” in autoimmune disease has also been proposed, which would lead to an upregulation of adiponectin. Loghman et al. reported a significant elevation in the urine adiponectin level in patients with LN, with this elevation being positively associated with proteinuria, with a threshold value of urine adiponectin of 7.5 ng/mL (sensitivity of 80%, specificity of 52%) being predictive of LN-associated kidney injury [48]. Rovin et al. [46] and Loghman et al. [48] also showed that the level of urine adiponectin was associated with the SLE Disease Activity Index score, confirming the possible role of this cytokine in SLE disease activity and the induction of renal complications. Therefore, the urine adiponectin level could be used in combination
Adiponectin and glomerular diseases

with traditional diagnostic markers of LN (anti-dsDNA, C3, and C4) to better identify SLE-associated kidney damage. Thus, treatment strategies targeting adiponectin may have positive therapeutic effects in patients with SLE, including those with LN. A recent meta analysis indicated that there was insufficient evidence to support a correlation between the serum adiponectin level and the SLE disease activity index score [49]. However, future studies are required as some studies have not identified a correlation between circulating adiponectin and SLE activity [50, 51].

Conclusion

Adiponectin plays a renoprotective role by attenuating albuminuria or proteinuria and maintaining renal function. As such, adiponectin could serve as a potential biomarker to monitor the development of glomerular diseases and provide a prognosis of the disease outcome. As well, targeting adiponectin might provide novel therapeutic strategies for glomerular diseases. However, research on adiponectin within the context of renal disease is still in its preliminary stage, and further studies are needed to clarify the molecular mechanisms of adiponectin in different types of glomerular diseases.

Disclosure of conflict of interest

None.

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Adiponectin and glomerular diseases


Adiponectin and glomerular diseases

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