Adiponectin and Its Receptors in Diabetic Kidney Disease: Molecular Mechanisms and Clinical Potential

Dongqing Zha,[1]* Xiaoyan Wu,[1]* and Ping Gao[1]

[1]Division of Nephrology, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430071, China

Diabetic kidney disease (DKD) is a major complication for diabetic patients. Adiponectin is an insulin sensitizer and anti-inflammatory adipokine and is mainly secreted by adipocytes. Two types of adiponectin receptors, AdipoR1 and AdipoR2, have been identified. In both type 1 and type 2 diabetes (T2D) patients with DKD, elevated adiponectin serum levels have been observed, and adiponectin serum level is a prognostic factor of end-stage renal disease. Renal insufficiency and tubular injury possibly play a contributory role in increases in serum and urinary adiponectin levels in diabetic nephropathy by either increasing biodegradation or elimination of adiponectin in the kidneys, or enhancing production of adiponectin in adipose tissue. Increases in adiponectin levels resulted in amelioration of albuminuria, glomerular hypertrophy, and reduction of inflammatory response in kidney tissue. The renoprotection of adiponectin is associated with improvement of the endothelial dysfunction, reduction of oxidative stress, and upregulation of endothelial nitric oxide synthase expression through activation of adenosine 5′-monophosphate–activated protein kinase by AdipoR1 and activation of peroxisome proliferator-activated receptor (PPAR)-α signaling pathway by AdipoR2. Several single nucleotide polymorphisms in the *AdipoQ* gene, including the promoter, are associated with increased risk of the development of T2D and DKD. Renin-angiotensin-aldosterone system blockers, adiponectin receptor agonists, and PPAR agonists (*e.g.*, tesaglitazar, thiazolidinediones, fenofibrate), which increase plasma adiponectin levels and adiponectin receptors expression, may be potential therapeutic drugs for the treatment of DKD. **(*Endocrinology* 158: 2022–2034, 2017)**

Diabetic kidney disease (DKD), including diabetic nephropathy (DN), is a major long-term complication for diabetic patients and is also the primary cause of end-stage renal disease (1, 2). DKD has been defined as diabetes with the presence of microalbuminuria (≥30 mg/g in ratio of urine albumin to creatinine) and/or impaired glomerular filtration rate (GFR) (GFR <60 mL/min/1.73 m^2) (3, 4). Etiologies of podocyte dysfunction, mesangial cell abnormality, thickened glomerular basement membrane, renal tubular injury, and vascular damage have attracted substantial attention in DKD studies (5–7). However, the specific pathophysiology of DKD is complicated (2), and new pathologic mechanisms for DKDs are continuing to be identified. Many studies have found that a large number of factors contribute to the development of DKD, including the renin-angiotensin-aldosterone system (RAAS), reactive oxygen species, inflammatory cytokines, and advanced glycation end products (8–12).

Adiponectin, secreted by adipose tissue, serves as an insulin-sensitizing, anti-inflammatory, vasculoprotective cytokine (13). The dysfunction regulation of adiponectin and its receptors has been observed in the development of

ISSN Print 0013-7227 ISSN Online 1945-7170
Printed in USA

Received 16 October 2016. Accepted 4 April 2017.
First Published Online 11 April 2017

*These authors contributed equally to this study.

Abbreviations: ACC, acetyl coenzyme A carboxylase; AdipoR1, adiponectin receptor 1; AdipoR2, adiponectin receptor 2; AdipoQ, adiponectin; AMPK, adenosine 5′-monophosphate–activated protein kinase; cAMP, cyclic adenosine monophosphate; CKD, chronic kidney disease; db/db, non-insulin-dependent diabetic; DKD, diabetic kidney disease; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; Epac, exchange protein activated by cyclic adenosine monophosphate; FOXO1, forkhead box O1; GFR, glomerular filtration rate; IGF-1, insulinlike growth factor-1; LKB1, liver kinase B1; MKR, muscle insulinlike growth factor-1 receptor-lysine-arginine; NADPH, reduced form of NAD phosphate; PODATTAC, podocyte-apoptosis through targeted activation of caspase-8; PPAR, peroxisome proliferator-activated receptor; RAAS, renin-angiotensin-aldosterone system; SNP, single nucleotide polymorphism; T1D, type 1 diabetes; T2D, type 2 diabetes; TZD, thiazolidinedione.

various diseases, including obesity, insulin resistance, chronic kidney disease (CKD), and type 1 (T1D) and type 2 diabetes (T2D) (14–16). The adiponectin gene is expressed exclusively in both white and brown adipose tissue. The protein exists in a wide range of multimeric complexes in plasma (17). Adiponectin combines via its collagen domain to create three major oligomeric forms: a low-molecular-weight trimer, a mid-molecular-weight hexamer, and a high-molecular-weight 12- to 18-mer adiponectin (17).

Two types of adiponectin receptors have been identified: AdipoR1 and AdipoR2. Both receptors contain seven transmembrane domains (18). AdipoR1 and AdipoR2 serve as the major receptors for adiponectin *in vivo*, with AdipoR1 activating the adenosine 5′-monophosphate–activated protein kinase (AMPK) pathways and AdipoR2 activating the peroxisome proliferator-activated receptor (PPAR)-α pathways (19). The adiponectin receptor AdipoR1 can be expressed by four cell types which constitute the glomerulus, namely endothelial cells, podocytes, mesangial cells, and Bowman capsule epithelial cells. It is also present in proximal tubular cells in kidneys. The location of the receptor suggests that both adiponectin and its receptors may influence renal physiology and pathologic change relating to obesity and diabetes (20).

Plasma adiponectin levels have been reported to be reduced in obese humans, particularly those with visceral obesity, and to correlate inversely with insulin resistance. Prospective and longitudinal studies have shown that lower adiponectin levels are associated with a higher incidence of diabetes and correlate with insulin resistance and the development of T2D (17). Obesity decreases not only plasma adiponectin levels but also AdipoR1/R2 expression, thereby reducing adiponectin signaling and leading to insulin resistance (17). Previous studies reported a direct correlation between low serum adiponectin levels and increased urinary albumin excretion in diabetic patients (21).

However, compared with nondiabetics, adults with T1D had significantly higher adiponectin, and the difference remained substantial after adjusting for albumin excretion rate and/or estimated GFR (eGFR). Adiponectin at baseline in T1D patients was positively associated with rapid GFR decline, incidence of CKD, and persistent macroalbuminuria over 6 years in adjusted models (22). In T1D patients with DN, elevated adiponectin was found to be an independent predictor of the progression to end-stage renal disease (15).

Therefore, the essential questions to be answered are as follows: (1) what is the role of adiponectin in pathologic change in diabetic patients with DKD? and (2) how do adiponectin and its receptors affect the renal functions in diabetic patients with DKD? In this review, we focus on recent advances in understanding the roles and molecular mechanisms of adiponectin and its receptors in the development of DKD. Their clinical value as therapeutic targets for DKD is also evaluated.

Expression of Adiponectin and Its Receptors in DKD

Adiponectin expression in DKD

The serum levels of adiponectin vary in different diseases (Table 1) (15, 16, 23–39). Adverse metabolic states, such as metabolic syndrome, lipodystrophy, atherosclerotic cardiovascular disease, and obesity, have low serum adiponectin levels (23–26). Circulating adiponectin levels are also low in patients with insulin resistant and T2D (27). However, the serum adiponectin level is increased in patients with T1D, and the serum adiponectin level is elevated in both T1D and T2D patients with DN (15, 16, 29, 30). Serum adiponectin is significantly elevated in different stages of DN, particularly during macroalbuminuria stages IV and V (15, 16, 20, 30). The elevation of total plasma adiponectin in T1D and DN could be mainly attributed to the increase of high-molecular-weight adiponectin (40, 41); high-molecular-weight adiponectin levels are positively correlated with insulin sensitivity in T1D and severity of DN (41, 42). Serum and urinary adiponectin levels are also increased in T2D patients with overt nephropathy, characterized by microvascular damage (43). In fact, the serum level of both total adiponectin and high-molecular-weight adiponectin were independent risk factors for nephropathy stage in T2D patients. This correlation remained substantial when serum creatinine (or eGFR) was added as an independent variable (42). Another study also demonstrated that high circulating levels of adiponectin might predict an increase in mortality in CKD patients whose adiponectin levels may be three times higher than that of healthy subjects (21).

Adiponectin levels appear to closely associate with renal function. Serum adiponectin levels are inversely associated with eGFR in T1D patients (22, 44). A strong association between increased adiponectin levels and low eGFR was also observed among T2D patients with micro-/macro-albuminuria, as compared with those with normoalbuminuria. Hence, the inverse association between adiponectin and renal functions in different clinical sets is also observed in diabetic patients (44).

The association of adiponectin with different diseases suggests that its expression and levels may be regulated by different pathologic conditions. Among many factors identified that regulate adiponectin (*AdipoQ*) gene transcription, PPAR-γ, CCAAT–enhancer binding protein α, sterol regulatory element binding protein-1 c, forkhead box

Table 1. Expression of Adiponectin and AdipoR1/2 in Patients or Animal Models With Different Diseases

	Location	Diseases	Expression	Reference
Adiponectin	Serum/plasma	Lipodystrophy patients	↓	Haque *et al.* (23)
		ASCVD patients	↓	Iwashima *et al.* (24)
		Metabolic syndrome	↓	Ntzouvani *et al.* (25)
		Obese mice	↓	Ohashi *et al.* (26)
		T2D patients	↓	Lindberg *et al.* (27)
		T2D patients with CAD	↓	Hotta *et al.* (28)
		T1D patients	↑	Jorsal *et al.* (15)
		T1D patients with DN	↑	Saraheimo *et al.* (16)
		T1D mice	↑	Combs *et al.* (29)
		T2D patients with DN	NS	Tavridou *et al.* (30)
AdipoR1	Skeletal muscle	STZ-induced T1D mice	↑	Inukai *et al.* (31)
		T2D mice	↓	Bonnard *et al.* (32)
	Heart	T1D mice	↓↑	Ma *et al.* (33)
		T2D rats	↓	Guo *et al.* (34)
	Renal tissues	T1D rats	↓	Guo *et al.* (35)
		T2D mice	↓	Tamura *et al.* (36)
		Diabetic rat with DN	↓	Ji *et al.* (37)
		T2D mice with DN	↓	Park *et al.* (38)
AdipoR2	Skeletal muscle	T2D patients	↓	Jang *et al.* (39)
	Liver	STZ-induced T1D mice	No change	Inukai *et al.* (31)
	Renal tissues	T1D rats	No change	Guo *et al.* (35)
		T2D mice with DN	NS	Tamura *et al.* (36)
		T2D mice with DN	↓	Park *et al.* (38)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; NS, no significant association with diabetes; STZ, streptozotocin; ↑, increased; ↓, decreased; ↓↑, dynamic change (*i.e.*, levels increased and decreased at different times).

O1 (FOXO1), and specificity protein 1 are prominent. Their specific response elements and binding consensus sequences have been identified in the *AdipoQ* gene (45) (Fig. 1). It is intriguing that insulin suppresses the activity of FOXO1, which may negatively regulate the expression of adiponectin (45).

Adiponectin may have a protective effect on renal functions by reducing albuminuria (20). Both adiponectin levels and albuminuria are associated with kidney dysfunction. Increased albuminuria is associated with obesity and diabetes and is a risk factor for renal disease (46). Adiponectin may attenuate the adverse effects of partial nephrectomy on renal structure and function by reducing the albuminuria associated with this procedure (20). Albuminuria had a negative correlation with plasma adiponectin in obese patients, and adiponectin gene knock-out Ad($^{-/-}$) mice exhibited increased albuminuria (46). Adiponectin may reduce albuminuria through the

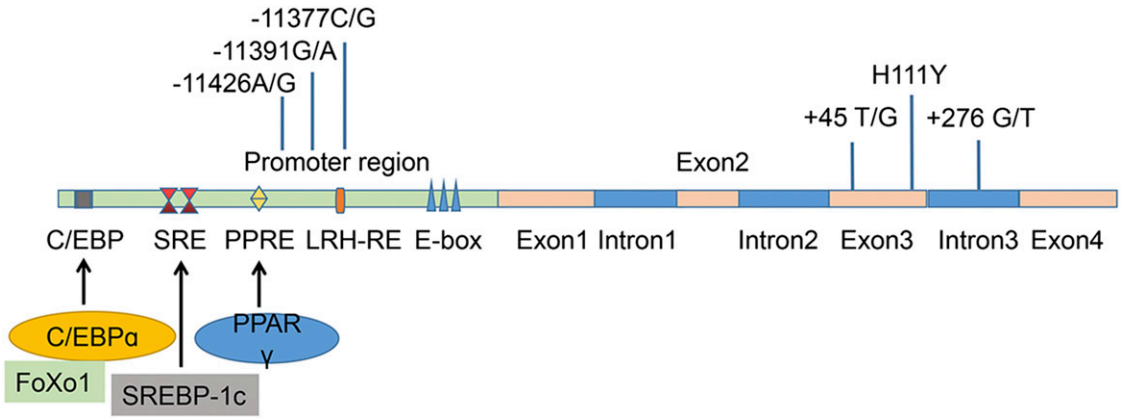

Figure 1. Structure of adiponectin gene and genetic association between adiponectin and T2D. The promoter region of Adipo*Q* gene includes one putative PPAR response element (PPRE), one liver receptor homolog 1–response element (LRH-RE), two serum response elements (SREs) several C/EBP elements, and a number of E boxes. PPAR-γ, C/EBPα, and sterol regulatory element binding protein-1 c (SREBP-1c), respectively, recognize and bind to PPRE site, CCAAT box motif (C/EBP response element), and SRE DNA sequence, TCACNCCAC, which stimulate adiponectin gene expression. FOXO1 results in adiponectin promoter activation mainly through binding to C/EBPα and forming a complex. SNPs +45G15G(T/G) in exon 3, SNPs+276G/T in intron 3, SNPs-11426A/G, SNPs-11377C/G, and SNPs-11391G/A in the promoter region, and H111Y in exon 3 are associated with T2D.

AdipoR1 pathway by stimulating AMPK and inhibiting reactive oxygen species (47). Adiponectin gene knock-out Ad($^{-/-}$) mice also exhibited increased fusion of podocyte foot processes (46). In cultured podocytes, adiponectin administration was associated with increased activity of AMPK, and both adiponectin and AMPK activation reduced podocyte permeability to albumin and podocyte dysfunction (46). These effects may act by reducing oxidative stress because adiponectin and AMPK activation both reduced protein levels of the reduced form of NAD phosphate (NADPH) oxidase Nox4 in podocytes (46). In a podocyte ablation animal model, podocyte-apoptosis through targeted activation of caspase-8 (POD-ATTAC) mice exhibited substantial kidney damage, such as foot process effacement, mesangial expansion, and glomerulosclerosis. The POD-ATTAC mice were subsequently crossed with mice lacking or overexpressing adiponectin. POD-ATTAC mice lacking adiponectin developed irreversible albuminuria and renal failure. Conversely, POD-ATTAC mice overexpressing adiponectin recovered more rapidly and exhibited less interstitial fibrosis (48), suggesting that adiponectin also protects other renal tissue and functions. The renoprotective role of adiponectin was further confirmed by the patients receiving renal transplantation. Patients with lower pretransplant adiponectin concentrations was a strong risk factor of developing new-onset diabetes mellitus after transplantation (49).

If it is true that adiponectin has a protective role in renal tissue and function, then the elevation of the adiponectin level in diabetic patients may be the result of, rather than the cause of, DN. The enhanced adiponectin production might be related to renal tubular injury and tubulointerstitial inflammation. Renal insufficiency and tubular injury may play a contributory role in increases in serum and urinary adiponectin levels in overt DN. The increase in adiponectin might be a physiologic response in overt DN that acts to mitigate renal tubular injury and to prevent the further progression of DN through its anti-inflammatory and antiatherogenic effects (50). Hence, the upregulation of the adiponectin production in DKD/DN may be a compensatory mechanism to alleviate further renal injury (20).

How renal dysfunction results in increased adiponectin levels is not well understood. Two possible mechanisms are as follows: (1) renal insufficiency may affect adiponectin clearance, and (2) renal insufficiency may stimulate adiponectin production. Clearance of adiponectin from the circulation is mainly renal dependent. Thus, the kidneys may play an important role in the biodegradation and/or elimination of adiponectin. However, altered clearance rates are not likely to fully account for the increase in circulating adiponectin in DKD. In DKD patients, enhanced production of adiponectin in the adipose tissue rather than a reduced clearance in kidneys may be a major mechanism that triggers an increase in adiponectin concentrations (15, 16).

Adiponectin receptors expression in DKD

The expression of AdipoRs varies in different organs and is affected by type of diabetes (Table 1). The expression levels of AdipoR1 in skeletal muscle are increased in T1D and decreased in T2D patients. In normal glucose-tolerant individuals with strong family history of diabetes, a high level of AdipoR1 expression was also observed (31, 32, 51, 52). Cardiac AdipoR1 expression is decreased in T2D and at early T1D, but is increased in late-stage T1D (33, 34). AdipoR2 in skeletal muscle is decreased in T2D patients and in normal glucose-tolerant individuals with a strong family history of diabetes (38, 52). Interestingly, hepatic AdipoR2 expression was not significantly changed in either streptozotocin-induced T1D mice or obese non-insulin-dependent diabetic (db/db) mice (31).

AdipoR1 and AdipoR2 are also expressed in rat, mice, and human renal tissues. Western blots of isolated rat distal tubules revealed the presence of adiponectin receptor AdipoR1 and both unphosphorylated and phosphorylated catalytic AMPK subunits α-1 and α-2. The glycogen-binding AMPK subunit β-2 was also present. AdipoR2 was not detected in distal tubules (53). Expression levels of AdipoR1, AMPK α-1, AMPK α-2, and AMPK β-2 in distal tubules were increased in streptozotocin-induced T1D rats, whereas phosphorylated active AMPK levels were strongly decreased, suggesting that the function of AdipoR1 was reduced in this tissue (53). However, the expression of AdipoR1 messenger RNA was found to be decreased in renal tissues of T1D and T2D rats and mice with DKD, suggesting that high glucose and renal insufficiency significantly decreases messenger RNA and protein expression levels of AdipoR1 (35–38) (Table 1).

The AdipoR2 expression in renal tissue of T2D patients with DKD remains controversial (Table1). Guo and Zhao (35) found that AdipoR2 was not changed in renal tissue (*e.g.*, renal cortex) of T1D rats with DN compared with non-DN rates (Table 1). Similarly, Tamura *et al.* (36) found that AdipoR2 expression in renal tissue was similar between T2D mice with DN (*db/db* mice) and their lean control mice. However, a recent study found that the expression of AdipoR2 levels in the renal cortex was markedly decreased in T2D mice with DN (38). Because the reduction of AdipoRs in either number or function in DKD kidneys may result in reduced adiponectin sensitivity, downregulation of AdipoR1/2 in the kidney of DKD may affect the protective function of

adiponectin in renal tissue and function. Further studies are necessary to better understand how renal function influences AdipoR1/2 activity and the adiponectin-induced pathway.

Polymorphism of AdipoQ and AdipoRs Gene

Adiponectin gene (*apM1* gene or *AdipoQ* gene) and its promoter are highly polymorphic and carry several single nucleotide polymorphisms (SNPs) (Fig. 1). The AdipoQ gene is a promising candidate susceptibility gene for T2D. Among the SNPs in the *AdipoQ* gene, H111Y in exon 3 is a unique nonsynonymous SNP and is significantly associated with low plasma adiponectin levels and T2D (54). SNP +45T/G (rs2241766) in exon 3 and +276G/T (rs1501299) in intron 3, located 45 and 276 bp downstream of the translational start site (Fig. 1), respectively, are significantly associated with decreased plasma adiponectin levels and an increased risk of T2D (17, 55, 56). Given that adiponectin is a crucial protective factor of renal tissue and functions, adiponectin gene polymorphism may closely associate with development of diabetes and related kidney disease. In support of this, SNPs +45T/G and +276G/T of *AdipoQ* gene confer increased risk for the development of T2D, obesity, and DKD (57). The promoter SNPs interfere with the promoter activity and subsequently affect the gene expression. The SNPs −11426A/G (rs16861194), −11377C/G (rs266729), and −11391G/A (rs17200539) in the promoter region of the *AdipoQ* gene are also associated with T2D and DKD (17, 58) (Fig. 1).

Hypoadiponectinemia can result from genetic factors (*e.g.*, promoter region of SNP in the *AdipoQ* gene, adiponectin gene knockout mice) or obesity-related environmental factors (*e.g.*, carbohydrate-rich diet, sex hormone) and is closely associated with insulin-resistant, T2D, metabolic syndrome, and obesity in humans and rodents (51, 58). However, not all adiponectin-deficient mice showed insulin resistance. For example, Ohashi *et al.* (26) found no substantial difference in a homeostasis model in insulin resistance between adiponectin gene knockout and wild-type mice.

The evidence for association between SNPs in *AdipoR1/AdipoR2* genes and T2D has been inconsistent. Hara *et al.* (59) and Wang *et al.* (60) found that none of the SNPs in *AdipoR1* or *AdipoR2* were significantly associated with T2D. Namvaran *et al.* (61) also found that the SNP 795G/A (rs16928751) in *AdipoR2* was not association with T2D. However, some studies have reported a correlation between SNP in the *AdipoR1/2* genes and insulin resistance. Stefan *et al.* (62) found that the SNP −8503G/A (rs6666089) of *AdipoR1* located in the promoter region and −1927T/C (novel SNP) in the intron 1 were related to insulin resistance and fat liver, respectively. Damcott *et al.* (63) also found that SNP −102T/G (rs2275737) and SNP +5843 A/G (rs1342387) in *AdipoR1* and SNP +219 A/T (rs11061971) and SNP +33447C/T (rs1044471) in *AdipoR2* were associated with T2D. For the link between gene polymorphism and DKD, a strongest interaction was found between *AdipoR2* +219A/T and the pathogenesis of nephropathy in diabetic patients (64).

Mechanism of Adiponectin and Its Receptors in Renoprotection

Several model organism experiments have demonstrated the renoprotective functions of adiponectin and its receptors. *AdipoQ*$^{-/-}$ (APN$^{-/-}$; APN-knockout) mice displayed albuminuria, glomerular hypertrophy, effacement of podocyte foot processes, and tubulointerstitial fibrosis (46, 65–68). Treatment of APN-knockout mice or diabetic adiponectin knockout mice with adiponectin resulted in amelioration of albuminuria, glomerular hypertrophy, improvement of podocyte foot process effacement, and tubulointerstitial fibrosis (46, 65, 66) (Table 2). Adiponectin also attenuated glomerulosclerosis after podocyte ablation in POD-ATTAC mice, which protects against the development of albuminuria and promotes reconstitution of kidney function (48).

The mechanism of adiponectin-associated renoprotection is likely complex. Adiponectin alleviates the clinical feature of CKD, such as foot process effacement, kidney hypertrophy, increased albuminuria, and fibrosis, through inhibiting the oxidative stress, mammalian target of rapamycin signaling, and inflammatory response (Fig. 2). Adiponectin may attenuate the adverse renal effects of angiotensin II. Specifically, adiponectin was found to reduce angiotensin II–induced oxidative stress (NADPH oxidase activation), inflammation (nuclear factor κB activity), and fibrosis (fibronectin expression) in renal tubular cells (70) (Fig. 2). Adiponectin was shown to inhibit angiotensin II–induced activation of NADPH oxidase via the AdipoR1-mediated activation of both AMPK- and cyclic adenosine monophosphate (cAMP)–exchange protein directly activated by cAMP (Epac) pathways (70). Similarly, in mesangial cells, adiponectin reduced high-glucose-induced increase of reactive oxygen species levels, NADPH oxidase, and nuclear factor κB activation (65) (Fig. 2). Adiponectin also attenuated high-glucose-induced phosphorylation of mammalian target of rapamycin and ribosomal protein S6 kinase, and inhibited transforming growth factor-β–induced phosphorylation of Smad2 and Smad3 proteins in mesangial cells (65) (Fig. 2). The renoprotection of adiponectin is

Table 2. Functions of Adiponectin and AdipoRs Studied in Diabetic Animal Models

	Change in Levels	Models	Biologic Activities	Reference
Adiponectin	Deficiency	Adiponectin-deficient *AdipoQ* ($^{-/-}$) mice	Insulin resistance with glucose intolerance	Yamauchi *et al.* (19)
		Akita mice (diabetic mice); Akita/APN($^{-/-}$) mice (*AdipoQ* gene knockout)	Exaggerated inflammatory response; renal hypertrophy and fibrosis	Fang *et al.* (65)
		AdipoQ gene knockout ($^{-/-}$) mice	Increased albuminuria and fusion of podocyte foot processes; reduced oxidative stress	Sharma *et al.* (46)
		Subtotal (5/6) nephrectomy in *AdipoQ* gene knockout ($^{-/-}$) mice	Urinary albumin excretion; glomerular hypertrophy; tubulointerstitial fibrosis No effect on insulin resistance	Ohashi *et al.* (66)
		Podocyte-ablation mice crossed with *AdipoQ* gene knockout ($^{-/-}$) mice	Irreversible albuminuria and renal failure	Rutkowski *et al.* (48)
	Overexpression	Transgenic mice with overexpression of ApN (ApN-Overex)	Downregulation of proinflammatory factors; less inflammatory phenotype	Ge *et al.* (67)
		Injected adenovirus APN (Ad-APN) in db/db mice	Improved endothelial-dependent vasodilation; decreasing superoxide production; inhibiting inflammation	Lee *et al.* (68)
		Podocyte-ablation mice crossed with ApN-Overex mice	Recovery from kidney damage, foot process effacement, mesangial expansion, and glomerulosclerosis	Rutkowski *et al.* (48)
AdipoRs	Deficiency	*AdipoR1/2* double knockout mice in *Lepr*$^{-/-}$ mice	Increased tissue triglyceride content; increased inflammation and oxidative stress; insulin resistance and marked glucose intolerance	Yamauchi *et al.* (19)
	Functional activated	*db/db* mice stimulated by AdipoR agonist	Ameliorated reduction of insulin sensitivity and glucose tolerance; decreased inflammation; reduced oxidative stress	Okada-Iwabu *et al.* (69)

also associated with enhanced nephrin expression, improvement of the endothelial dysfunction, activation of the AMPK signaling pathway, and upregulation of endothelial nitric oxide synthase expression in the renal tissue of diabetic rats (70, 71). The renoprotection of adiponectin is independent of reducing high blood sugar (65). These data from animal models indicate that adiponectin has beneficial effects on preventing the progression of CKD, including DN.

Loss of AdipoR1/2 activity resulted in similar affects as loss of adiponectin (Table 2). AdipoR1 and AdipoR2 double knockout mice abolished adiponectin binding, resulting in insulin resistance and impaired glucose tolerance, increased inflammation, and oxidative stress (19, 69). These changes result in increased gluconeogenesis and decreased glucose uptake in key metabolic organs, such as liver, skeletal muscle, and adipose tissue (19, 69). The importance of the two receptors in regulating normal glucose metabolism, insulin sensitivity, and oxidative stress is indicated by the findings of an experiment in which a small molecule AdipoR agonist (AdipoRon) was administered to obese *db/db* mice (T2D model). Addition of the agonist stimulated AdipoR, resulted in amelioration of insulin sensitivity and glucose tolerance reduction, suppression of inflammation and oxidative stress, and improvement in the survival rate of obese diabetic mice (72).

The effects of the agonist are dependent on activation of AMPK by AdipoR1 (69, 72) (Fig. 3). Both the liver kinase B1 (LKB1)/AMPK signaling and Ca^{2+}/CaMKK-β are necessary for adiponectin-induced full activation of AMPK (73–76). Adiponectin also promotes activation of PPAR-α via AdipoR2, leading to increased insulin sensitivity (72) (Fig. 3). Therefore, adiponectin activates AMPK and PPAR-α, via the AdipoR1/2 receptors, to regulate glucose and lipid metabolism, fatty acid oxidation, and insulin sensitivity (19, 76). Adiponectin also suppresses inflammatory response and mitigates the oxidative stress in popocytes via activation of AMPK pathway (19, 76), which may protect the kidney structure and function in patients with DN.

Adiponectin Resistance and Diabetes

Patients with insulin receptor mutations have severe insulin resistance and elevated plasma adiponectin levels (77). In animal models, adiponectin levels are also increased in insulin-resistant L1 mice (*i.e.*, insulin receptor

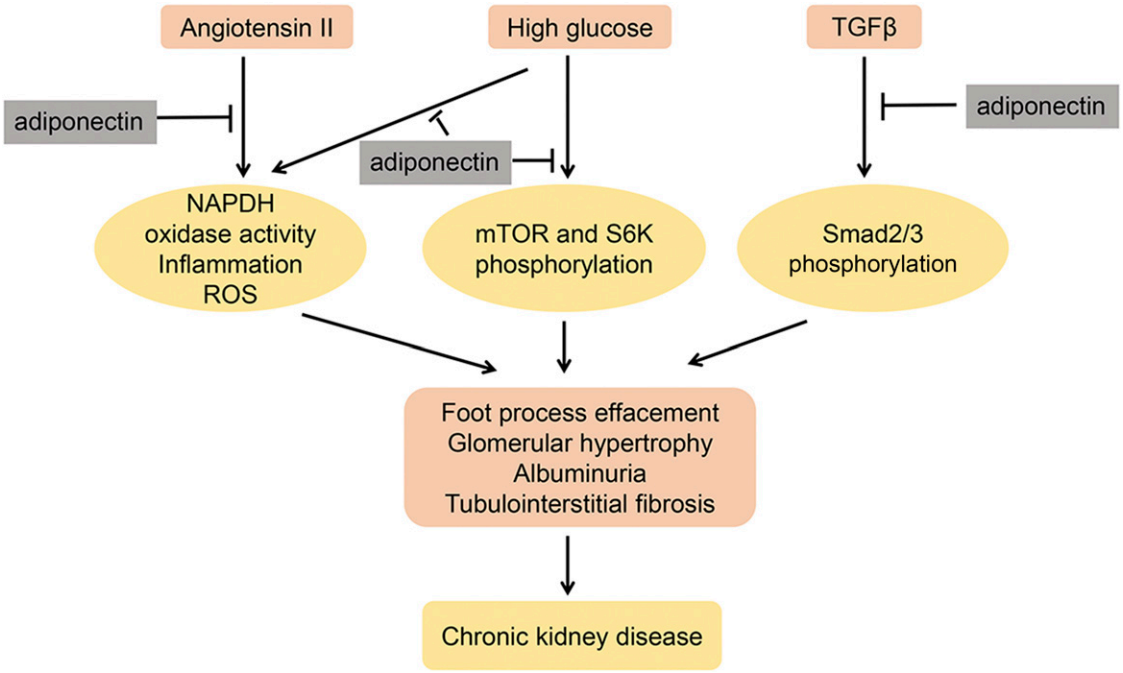

Figure 2. Role of adiponectin and AdipoRs in CKD. Adiponectin was found to reduce Ang II-induced oxidative stress (NADPH oxidase activation), inflammation (nuclear factor κB activity), and fibrosis (fibronectin expression). Adiponectin also reduced high-glucose–induced increased reactive oxygen species (ROS) levels, NADPH oxidase, nuclear factor κB activation, mammalian target of rapamycin (mTOR) and S6K phosphorylation, and inhibited transforming growth factor-β (TGFβ)–induced Smad2 and Smad3 phosphorylation. Adiponectin alleviates the clinical feature of CKD, such as foot process effacement, kidney hypertrophy, albuminuria, and fibrosis.

transgenic knockout mice) (17, 78). In insulin-resistant L1 mice, adiponectin administration is unable to lower glucose levels or induce activation of AMPK, suggesting a condition of adiponectin resistance (17). The author proposed that AMPK resistance and decreases in PPAR activation in L1 mice may be involved in adiponectin resistance (17). Adiponectin levels were also increased in muscle insulinlike growth factor-1 (IGF-1) receptor-lysine-arginine (MKR) mice (mice express dominant-negative mutant IGF-1 receptors in skeletal muscle) (78). The phenotype of MKR mice showed diabetes with insulin resistance. Chronic adiponectin treatment significantly improved both insulin sensitivity and glucose tolerance in obese *db/db* mice but not in MKR mice, suggesting that MKR mice were adiponectin resistant (79). However, the expression of adiponectin receptors and AMPK phosphorylation appeared normal in MKR mice, suggesting that the adiponectin resistance may lie further downstream in the signaling pathways, such as Akt and mitogen-activated protein kinase pathway (79). Therefore, adiponectin resistance may occur via multiple mechanisms (78).

The link between expression of AdipoRs and adiponectin resistance may not be ruled out in patients with diabetes and obesity (Fig. 4). It has been proposed that obesity results in reduced expression of AdipoRs in the skeletal muscle and adipose tissue (51, 80). For example, in insulin resistant *db/db* mice, expressions of both AdipoR1 and AdipoR2 were significantly decreased in muscle and adipose tissue, thereby reducing adiponectin sensitivity (*i.e.*, adiponectin resistance) and leading to insulin resistance, the so-called vicious cycle (51, 81) (Fig. 4). Posttranslational modifications of AdipoR1/2 may affect receptor affinity and may also result in adiponectin resistance (44). Given that hyperadiponectinemia does occur in certain diseases and disorders, such as T1D, we speculate that adiponectin resistance may also exist independently or in combination with insulin resistance and/or leptin resistance. Recent data suggest that adiponectin levels increase acutely in situations of adiponectin resistance in T1D (22).

In patients with DKD, increased adiponectin production and increased AdipoR1/2 expression can be found, despite high levels of serum adiponectin and adiponectin resistance status, suggesting the presence of a positive feedback system on adiponectin levels in patients with uremia and nephropathy (81). In muscle of humans with end-stage renal disease, phosphorylation of AMPK is higher than expected because of both higher circulating adiponectin and higher AdipoR1 levels in target tissues. Activation of AMPK pathway causes inactivation of acetyl coenzyme A carboxylase (ACC) via phosphorylation. The inactivation of ACC results in decreased production of malonyl coenzyme A, which increases the production of carnitine palmitoyl transferase-1, a crucial step for fatty acid oxidation. However, in the study of

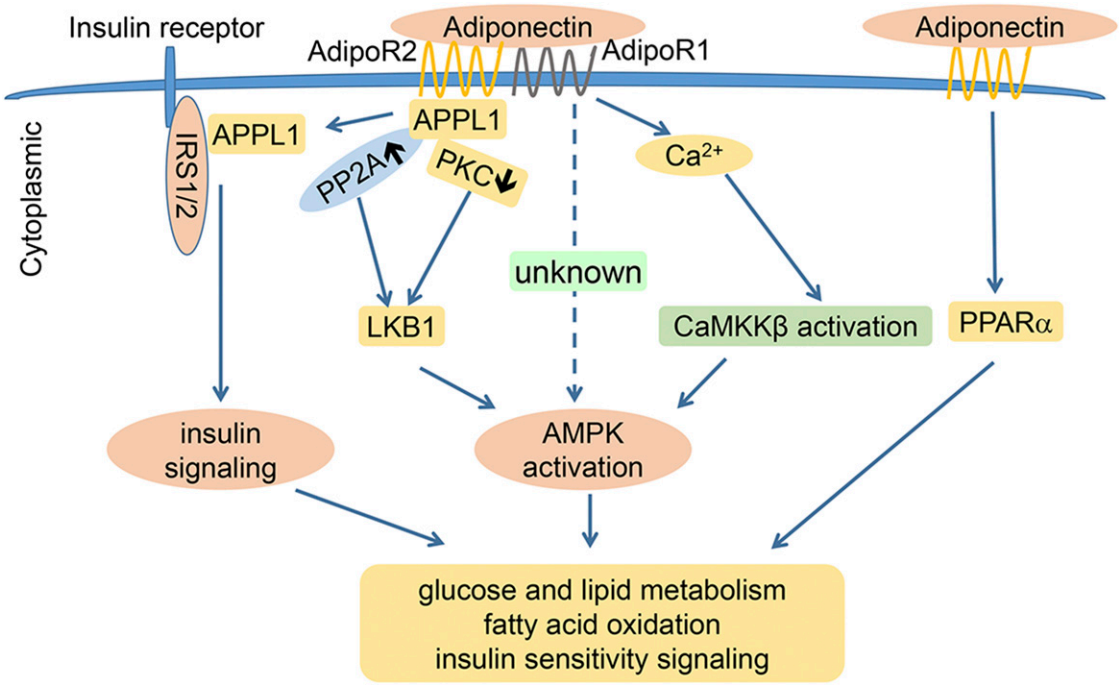

Figure 3. Adiponectin and adiponectin receptor signaling. Adiponectin can directly activate AMPK via AdipoR1. Adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1 (APPL1) binds to the intracellular domains of AdipoR1 or AdipoR2. On adiponectin stimulation, APPL1 binds to protein phosphatase 2A (PP2A) and protein kinase C (PKC), thereby activating PP2A and inactivating PKC. The inactivation of PKC results in the dephosphorylation of LKB1, allowing LKB1 to translocate from nucleus to cytoplasm and activate AMPK. Adiponectin induces extracellular Ca^{2+} influx necessary for activation of Ca2+/calmodulin-dependent protein kinase kinase β (CaMKKβ) via AdipoR1, thereby activating AMPK. Adiponectin also promotes activation of PPAR-α via AdipoR2, leading to increased insulin sensitivity.

Martinez Cantarin *et al.* (81), higher activity of AMPK did not increase phosphorylation of ACC and expression of carnitine palmitoyl transferase-1 in end-stage renal disease tissue. A block in adiponectin receptor signaling after phosphorylation of AMPK suggests that uremia results in upregulation of adiponectin, AdipoR1, and AMPK, consistent with uremia acting at the postreceptor level to cause adiponectin resistance (81).

Clinical Values of Adiponectin and Its Receptors for DKD

Because adiponectin and its receptors have a renoprotective role in DKD patients and animal models, a therapeutic strategy for the treatment of DKD may include the upregulation of plasma adiponectin levels, the upregulation of adiponectin receptors, or the development of adiponectin receptor agonists. It is well-known that blocking RAAS with angiotensin-converting-enzyme inhibitor or angiotensin II receptor blockers improves insulin sensitivity in T2D. The underlying mechanisms may involve increased serum adiponectin induced by RAAS blockades. Some studies found that RAAS blockades by either physiologic (change in sodium status) and pharmacologic modulation of RAAS activity (angiotensin II infusion and enalapril treatment) increased adiponectin production and upregulated circulating adiponectin (82, 83), which might alleviate insulin resistance and reduce the onset of new diabetes (84). These findings provide theoretical basis for clinical application of RAAS blockers as a tool to correct hypoadiponectinemia in T2D patients (82, 84). In addition, increasing level of adiponectin by RAAS blockers may improve anti-inflammatory response in the kidneys of DKD patients by activating the AMPK and cyclooxygenase-2 pathways, and decreasing tumor necrosis factor-α activity (73, 84). Adiponectin was shown to inhibit angiotensin II–induced activation of NADPH oxidase via the AdipoR1-mediated activation of both AMPK and cAMP-Epac pathways (84).

Another potential therapeutic molecule is the adiponectin receptor agonist AdipoRon. AdipoRon has been shown to ameliorate diabetes associated with obesity, increase exercise endurance, and prolong the shortened life span of obese mice fed on a high-fat diet (70, 85).

The PPAR-α/-γ dual agonist (tesaglitazar) has shown promise in clinical trials and basic studies for inhibiting T2D through increasing the plasma adiponectin levels (86). Tesaglitazar treatment not only improved insulin resistance, glycemic control, and lipid profile but also markedly attenuated albuminuria and renal glomerular fibrosis in db/db mice (87). In addition, increasing adiponectin by PPAR-γ agonists in DKD may be a protective and compensatory responses to renal injury. It needs to

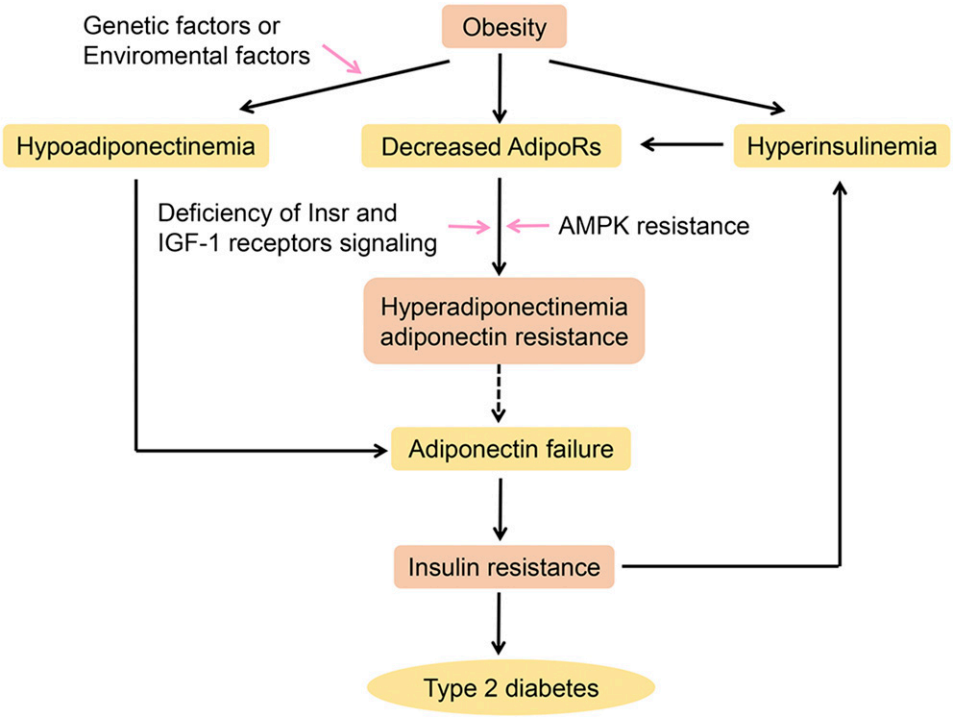

Figure 4. Adiponectin resistance and diabetes. Obesity-linked hyperinsulinemia results in reduction of AdipoRs in the skeletal muscle and adipose tissue of diabetes and obesity, thereby promoting hyperadiponectinemia and adiponectin resistance. Both hypoadiponectinemia resulted from genetic factors or environmental factors and hyperinsulinemia in adiponectin resistance result in adiponectin failure, which further promote the progression from insulin resistance to overt diabetes. Insulin resistance aggravates hyperadiponectinemia and adiponectin resistance. Adiponectin resistance and insulin resistance interact each other, which leads to a vicious cycle. Hyperadiponectinemia and adiponectin resistance may be associated with the lack or inhibition of the insulin receptor (Insr) precursor and insulinlike growth factor-1 (IGF-1) receptors signaling and AMPK resistance.

be emphasized that the serious side effects of tesaglitazar may greatly restrict the use of the drug in patients. However, strategies based on minimizing adverse effects and increasing the efficacy of PPAR-γ agonists are potentially possible (88).

Plasma adiponectin levels can also be upregulated by thiazolidinediones (TZDs) (*e.g.*, pioglitazone, rosiglitazone), a class of PPAR-γ agonists and medications used in the treatment of T2D (89). TZDs play an important role in delaying and preventing the progression of CKD in T2D. Although PPAR-γ activation by TZDs is, in general, considered beneficial for the amelioration of diabetic renal complications in T2D, the underlying mechanism(s) remains to be fully elucidated (88).

Utilization of medicines that induce adiponectin activity may also become a breakthrough in prevention of the progression of albuminuria in DKD (84). For example, fenofibrate, a PPAR-α agonist, has been reported to increase adiponectin expression in adipose tissue and serum adiponectin levels through PPAR-α activation and elevation of high-density lipoprotein (90, 91). Fenofibrate reduces systemic inflammation without improvements in lipoprotein metabolism and without changing insulin sensitivity (92), and potentially provide a new therapeutic choice for DKD patients. Rosiglitazone, a PPAR-γ agonist, has similar therapeutic effects on DKD as fenofibrate (93). Rosiglitazone treatment in albuminuria patients showed a decrease in fasting plasma glucose and tumor necrosis factor-α, and an increase in plasma adiponectin and glucose metabolic clearance rate, suggesting that TZD may also prevent nephropathy in T2D patients (93).

Summary

Evidence from both clinical studies and diabetes/obese animal models demonstrate that lower adiponectin levels and AdipoR1/R2 expression are associated with a higher incidence of T2D. However, in contrast, adults with T1D had significantly higher plasma adiponectin levels. Elevated adiponectin levels are present in both T1D and T2D patients with nephropathy, and the plasma level of adiponectin is an independent predictor of the progression of DKD. Renal insufficiency and tubular injury possibly play a contributory role in the increases in serum and urinary adiponectin levels seen in DN by either increasing biodegradation and/or eliminating adiponectin in the kidney or enhancing production of adiponectin in the adipose tissue. Several SNPs of the *AdipoQ* gene are associated with increased risk of developing T2D,

obesity, and DKD. Very few SNPs of *AdipoR1* and *AdipoR2* significantly associate with DKD. Only one SNP on *AdipoR2* showed a strong interaction with the pathogenesis of nephropathy in diabetic patients.

Increased adiponectin levels reduce albuminuria, glomerular hypertrophy, and inflammatory response in kidney tissue. The renoprotection of adiponectin is associated with improvement of the endothelial dysfunction, reduction of oxidative stress, and upregulation of endothelial nitric oxide synthase expression. These effects are dependent on activation of AMPK by AdipoR1 and activation of PPAR-α signaling pathway by AdipoR2. Patients with T1D and patients or animal models with severe insulin resistance can develop adiponectin resistance. A positive feedback system resulting from the adiponectin resistance may explain the elevation of plasma adiponectin levels in uremia and nephropathy.

Because adiponectin plays an important role in protecting against nephropathy, a therapeutic strategy for the treatment of DKD may include the upregulation of plasma adiponectin levels, the upregulation of adiponectin receptors, or the development of adiponectin receptor agonists. Therefore, RAAS blockers, adiponectin receptor agonists, and PPAR agonists (*e.g.*, tesaglitazar, TZDs, fenofibrate) may be potential therapeutic drugs for the treatment of DKD. Further research on adiponectin and AdipoRs structure and function should facilitate both in understanding the molecular mechanisms of adiponectin actions and in designing novel antidiabetic and DKD therapeutic drugs. Further studies are needed to confirm the elevation of adiponectin expression and production by human adipose tissue in response to various stages of DKD, and to investigate the possible existence of signaling molecules that could transmit these changes.

Acknowledgments

Address all correspondence and requests for reprints to: Xiaoyan Wu, MD, PhD, Division of Nephrology, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuhan, Hubei 430071, China. E-mail: wuxiaoyan2k6@163.com.

This research was supported in part by the National Science Foundation of China (Grant 81170679 to X.W. and Grant 81400694 to D.Z.).

Disclosure Summary: The authors have nothing to disclose.

References

1. Bjornstad P, Cherney D, Maahs DM. Early diabetic nephropathy in type 1 diabetes: new insights. *Curr Opin Endocrinol Diabetes Obes*. 2014;**21**(4):279–286.
2. Nazar CM. Diabetic nephropathy; principles of diagnosis and treatment of diabetic kidney disease. *J Nephropharmacol*. 2014; **3**(1):15–20.
3. KDOQI. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. *Am J Kidney Dis*. 2007; **49**(2 Suppl 2)S12–S154.
4. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA*. 2011;**305**(24):2532–2539.
5. Macisaac RJ, Ekinci EI, Jerums G. Markers of and risk factors for the development and progression of diabetic kidney disease. *Am J Kidney Dis*. 2014; **63**(2 Suppl 2)S39–S62.
6. Merscher-Gomez S, Guzman J, Pedigo CE, Lehto M, Aguillon-Prada R, Mendez A, Lassenius MI, Forsblom C, Yoo T, Villarreal R, Maiguel D, Johnson K, Goldberg R, Nair V, Randolph A, Kretzler M, Nelson RG, Burke GW III, Groop PH, Fornoni A; FinnDiane Study Group. Cyclodextrin protects podocytes in diabetic kidney disease. *Diabetes*. 2013;**62**(11):3817–3827.
7. Weil EJ, Lemley KV, Mason CC, Yee B, Jones LI, Blouch K, Lovato T, Richardson M, Myers BD, Nelson RG. Podocyte detachment and reduced glomerular capillary endothelial fenestration promote kidney disease in type 2 diabetic nephropathy. *Kidney Int*. 2012; **82**(9):1010–1017.
8. Jefferson JA, Shankland SJ, Pichler RH. Proteinuria in diabetic kidney disease: a mechanistic viewpoint. *Kidney Int*. 2008;**74**(1): 22–36.
9. Márquez E, Riera M, Pascual J, Soler MJ. Renin-angiotensin system within the diabetic podocyte. *Am J Physiol Renal Physiol*. 2015; **308**(1):F1–F10.
10. Brezniceanu ML, Lau CJ, Godin N, Chénier I, Duclos A, Ethier J, Filep JG, Ingelfinger JR, Zhang SL, Chan JS. Reactive oxygen species promote caspase-12 expression and tubular apoptosis in diabetic nephropathy. *J Am Soc Nephrol*. 2010;**21**(6):943–954.
11. Wada J, Makino H. Inflammation and the pathogenesis of diabetic nephropathy. *Clin Sci (Lond)*. 2013;**124**(3):139–152.
12. Beisswenger PJ, Howell SK, Russell GB, Miller ME, Rich SS, Mauer M. Early progression of diabetic nephropathy correlates with methylglyoxal-derived advanced glycation end products. *Diabetes Care*. 2013;**36**(10):3234–3239.
13. Herder C, Carstensen M, Ouwens DM. Anti-inflammatory cytokines and risk of type 2 diabetes. *Diabetes Obes Metab*. 2013;**15** (Suppl 3):39–50.
14. Xita N, Tsatsoulis A. Adiponectin in diabetes mellitus. *Curr Med Chem*. 2012;**19**(32):5451–5458.
15. Jorsal A, Tarnow L, Frystyk J, Lajer M, Flyvbjerg A, Parving HH, Vionnet N, Rossing P. Serum adiponectin predicts all-cause mortality and end stage renal disease in patients with type I diabetes and diabetic nephropathy. *Kidney Int*. 2008;**74**(5):649–654.
16. Saraheimo M, Forsblom C, Thorn L, Wadén J, Rosengård-Bärlund M, Heikkilä O, Hietala K, Gordin D, Frystyk J, Flyvbjerg A, Groop PH; FinnDiane Study Group. Serum adiponectin and progression of diabetic nephropathy in patients with type 1 diabetes. *Diabetes Care*. 2008;**31**(6):1165–1169.
17. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest*. 2006;**116**(7): 1784–1792.
18. Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, Murakami K, Ohteki T, Uchida S, Takekawa S, Waki H, Tsuno NH, Shibata Y, Terauchi Y, Froguel P, Tobe K, Koyasu S, Taira K, Kitamura T, Shimizu T, Nagai R, Kadowaki T. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature*. 2003; **423**(6941):762–769.
19. Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, Okada-Iwabu M, Kawamoto S, Kubota N, Kubota T, Ito Y, Kamon J, Tsuchida A, Kumagai K, Kozono H, Hada Y, Ogata H, Tokuyama K, Tsunoda M, Ide T, Murakami K, Awazawa M, Takamoto I, Froguel P, Hara K, Tobe K, Nagai R, Ueki K, Kadowaki T. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nat Med*. 2007;**13**(3):332–339.

20. Christou GA, Kiortsis DN. The role of adiponectin in renal physiology and development of albuminuria. *J Endocrinol*. 2014; **221**(2):R49–R61.
21. Jia T, Carrero JJ, Lindholm B, Stenvinkel P. The complex role of adiponectin in chronic kidney disease. *Biochimie*. 2012;**94**(10): 2150–2156.
22. Bjornstad P, Pyle L, Kinney GL, Rewers M, Johnson RJ, Maahs DM, Snell-Bergeon JK. Adiponectin is associated with early diabetic kidney disease in adults with type 1 diabetes: A Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study. *J Diabetes Complications*. 2017;**31**(2):369–374.
23. Haque WA, Shimomura I, Matsuzawa Y, Garg A. Serum adiponectin and leptin levels in patients with lipodystrophies. *J Clin Endocrinol Metab*. 2002;**87**(5):2395.
24. Iwashima Y, Horio T, Kumada M, Suzuki Y, Kihara S, Rakugi H, Kawano Y, Funahashi T, Ogihara T. Adiponectin and renal function, and implication as a risk of cardiovascular disease. *Am J Cardiol*. 2006;**98**(12):1603–1608.
25. Ntzouvani A, Fragopoulou E, Panagiotakos D, Pitsavos C, Antonopoulou S. Reduced circulating adiponectin levels are associated with the metabolic syndrome independently of obesity, lipid indices and serum insulin levels: a cross-sectional study. *Lipids Health Dis*. 2016;**15**(1):140.
26. Ohashi K, Kihara S, Ouchi N, Kumada M, Fujita K, Hiuge A, Hibuse T, Ryo M, Nishizawa H, Maeda N, Maeda K, Shibata R, Walsh K, Funahashi T, Shimomura I. Adiponectin replenishment ameliorates obesity-related hypertension [published correction appears in Hypertension. 2007;49(2):e14]. *Hypertension*. 2006; **47**(6):1108–1116.
27. Lindberg S, Jensen JS, Pedersen SH, Galatius S, Frystyk J, Flyvbjerg A, Bjerre M, Mogelvang R. Low adiponectin levels and increased risk of type 2 diabetes in patients with myocardial infarction. *Diabetes Care*. 2014;**37**(11):3003–3008.
28. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol*. 2000;**20**(6):1595–1599.
29. Combs TP, Snell-Bergeon JK, Maahs DM, Bergman BC, Lamarche M, Iberkleid L, AbdelBaky O, Tisch R, Scherer PE, Marliss EB. Adiponectin-SOGA dissociation in type 1 diabetes. *J Clin Endocrinol Metab*. 2015;**100**(8):E1065–E1073.
30. Tavridou A, Georgoulidou A, Roumeliotis A, Roumeliotis S, Giannakopoulou E, Papanas N, Passadakis P, Manolopoulos VG, Vargemezis V. Association of plasma adiponectin and oxidized low-density lipoprotein with carotid intima-media thickness in diabetic nephropathy. *J Diabetes Res*. 2015;**2015**:507265.
31. Inukai K, Nakashima Y, Watanabe M, Takata N, Sawa T, Kurihara S, Awata T, Katayama S. Regulation of adiponectin receptor gene expression in diabetic mice. *Am J Physiol Endocrinol Metab*. 2005; **288**(5):E876–E882.
32. Bonnard C, Durand A, Vidal H, Rieusset J. Changes in adiponectin, its receptors and AMPK activity in tissues of diet-induced diabetic mice. *Diabetes Metab*. 2008;**34**(1):52–61.
33. Ma Y, Liu Y, Liu S, Qu Y, Wang R, Xia C, Pei H, Lian K, Yin T, Lu X, Sun L, Yang L, Cao Y, Lau WB, Gao E, Wang H, Tao L. Dynamic alteration of adiponectin/adiponectin receptor expression and its impact on myocardial ischemia/reperfusion in type 1 diabetic mice. *Am J Physiol Endocrinol Metab*. 2011;**301**(3):E447–E455.
34. Guo Z, Zheng C, Qin Z, Wei P. Effect of telmisartan on the expression of cardiac adiponectin and its receptor 1 in type 2 diabetic rats. *J Pharm Pharmacol*. 2011;**63**(1):87–94.
35. Guo Z, Zhao Z. Effect of N-acetylcysteine on plasma adiponectin and renal adiponectin receptors in streptozotocin-induced diabetic rats. *Eur J Pharmacol*. 2007;**558**(1–3):208–213.
36. Tamura Y, Murayama T, Minami M, Matsubara T, Yokode M, Arai H. Ezetimibe ameliorates early diabetic nephropathy in db/db mice. *J Atheroscler Thromb*. 2012;**19**(7):608–618.
37. Ji H, Wu L, Ma X, Ma X, Qin G. The effect of resveratrol on the expression of AdipoR1 in kidneys of diabetic nephropathy. *Mol Biol Rep*. 2014;**41**(4):2151–2159.
38. Park HS, Lim JH, Kim MY, Kim Y, Hong YA, Choi SR, Chung S, Kim HW, Choi BS, Kim YS, Chang YS, Park CW. Resveratrol increases AdipoR1 and AdipoR2 expression in type 2 diabetic nephropathy [published correction appears in J Transl Med. 2016; 14(1):210]. *J Transl Med*. 2016;**14**(1):176.
39. Jang C, Inder WJ, Obeyesekere VR, Alford FP. Adiponectin, skeletal muscle adiponectin receptor expression and insulin resistance following dexamethasone. *Clin Endocrinol (Oxf)*. 2008;**69**(5):745–750.
40. Leth H, Andersen KK, Frystyk J, Tarnow L, Rossing P, Parving HH, Flyvbjerg A. Elevated levels of high-molecular-weight adiponectin in type 1 diabetes. *J Clin Endocrinol Metab*. 2008;**93**(8): 3186–3191.
41. Pereira RI, Snell-Bergeon JK, Erickson C, Schauer IE, Bergman BC, Rewers M, Maahs DM. Adiponectin dysregulation and insulin resistance in type 1 diabetes. *J Clin Endocrinol Metab*. 2012;**97**(4): E642–E647.
42. Kato K, Osawa H, Ochi M, Kusunoki Y, Ebisui O, Ohno K, Ohashi J, Shimizu I, Fujii Y, Tanimoto M, Makino H. Serum total and high molecular weight adiponectin levels are correlated with the severity of diabetic retinopathy and nephropathy. *Clin Endocrinol (Oxf)*. 2008;**68**(3):442–449.
43. Koshimura J, Fujita H, Narita T, Shimotomai T, Hosoba M, Yoshioka N, Kakei M, Fujishima H, Ito S. Urinary adiponectin excretion is increased in patients with overt diabetic nephropathy. *Biochem Biophys Res Commun*. 2004;**316**(1):165–169.
44. Ortega Moreno L, Lamacchia O, Copetti M, Salvemini L, De Bonis C, De Cosmo S, Cignarelli M, Trischitta V, Menzaghi C. Serum adiponectin and glomerular filtration rate in patients with type 2 diabetes. *PLoS One*. 2015;**10**(10):e0140631.
45. Liu M, Liu F. Transcriptional and post-translational regulation of adiponectin. *Biochem J*. 2009;**425**(1):41–52.
46. Sharma K, Ramachandrarao S, Qiu G, Usui HK, Zhu Y, Dunn SR, Ouedraogo R, Hough K, McCue P, Chan L, Falkner B, Goldstein BJ. Adiponectin regulates albuminuria and podocyte function in mice. *J Clin Invest*. 2008;**118**(5):1645–1656.
47. Nakamaki S, Satoh H, Kudoh A, Hayashi Y, Hirai H, Watanabe T, Adiponectin reduces proteinuria in streptozotocin-induced diabetic Wistar rats. *Exp. Biol. Med. (Maywood)*. 2011;**236**(5):614–620.
48. Rutkowski JM, Wang ZV, Park AS, Zhang J, Zhang D, Hu MC, Moe OW, Susztak K, Scherer PE. Adiponectin promotes functional recovery after podocyte ablation. *J Am Soc Nephrol*. 2013;**24**(2): 268–282.
49. Bayés B, Granada ML, Pastor MC, Lauzurica R, Salinas I, Sanmartí A, Espinal A, Serra A, Navarro M, Bonal J, Romero R. Obesity, adiponectin and inflammation as predictors of new-onset diabetes mellitus after kidney transplantation. *Am J Transplant*. 2007;**7**(2): 416–422.
50. Fujita H, Morii T, Koshimura J, Ishikawa M, Kato M, Miura T, Sasaki H, Narita T, Ito S, Kakei M. Possible relationship between adiponectin and renal tubular injury in diabetic nephropathy. *Endocr J*. 2006;**53**(6):745–752.
51. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev*. 2005;**26**(3):439–451.
52. Civitarese AE, Jenkinson CP, Richardson D, Bajaj M, Cusi K, Kashyap S, Berria R, Belfort R, DeFronzo RA, Mandarino LJ, Ravussin E. Adiponectin receptors gene expression and insulin sensitivity in non-diabetic Mexican Americans with or without a family history of type 2 diabetes. *Diabetologia*. 2004;**47**(5): 816–820.
53. Cammisotto PG, Londono I, Gingras D, Bendayan M. Control of glycogen synthase through ADIPOR1-AMPK pathway in renal distal tubules of normal and diabetic rats. *Am J Physiol Renal Physiol*. 2008;**294**(4):F881–F889.
54. Owecki M, Miczke A, Kaczmarek M, Hoppe-Gołebiewska J, Pupek-Musialik D, Słomski R, Bryll W, Cymerys M, Nikisch E,

Sowiński J. The Y111 H (T415C) polymorphism in exon 3 of the gene encoding adiponectin is uncommon in Polish obese patients. *Horm Metab Res*. 2007;**39**(11):797–800.
55. Hara K, Boutin P, Mori Y, Tobe K, Dina C, Yasuda K, Yamauchi T, Otabe S, Okada T, Eto K, Kadowaki H, Hagura R, Akanuma Y, Yazaki Y, Nagai R, Taniyama M, Matsubara K, Yoda M, Nakano Y, Tomita M, Kimura S, Ito C, Froguel P, Kadowaki T. Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population [published correction appears in Diabetes. 2002;51(4):1294]. *Diabetes*. 2002;**51**(2):536–540.
56. Momin AA, Bankar MP, Bhoite GM. Association of single nucleotide polymorphisms of adiponectin gene with type 2 diabetes mellitus, and their influence on cardiovascular risk markers. *Indian J Clin Biochem*. 2017;**32**(1):53–60.
57. Gu HF. Biomarkers of adiponectin: plasma protein variation and genomic DNA polymorphisms. *Biomark Insights*. 2009;**4**:123–133.
58. Vasseur F, Helbecque N, Dina C, Lobbens S, Delannoy V, Gaget S, Boutin P, Vaxillaire M, Leprêtre F, Dupont S, Hara K, Clément K, Bihain B, Kadowaki T, Froguel P. Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. *Hum Mol Genet*. 2002;**11**(21):2607–2614.
59. Hara K, Horikoshi M, Kitazato H, Yamauchi T, Ito C, Noda M, Ohashi J, Froguel P, Tokunaga K, Nagai R, Kadowaki T. Absence of an association between the polymorphisms in the genes encoding adiponectin receptors and type 2 diabetes. *Diabetologia*. 2005; **48**(7):1307–1314.
60. Wang H, Zhang H, Jia Y, Zhang Z, Craig R, Wang X, Elbein SC. Adiponectin receptor 1 gene (ADIPOR1) as a candidate for type 2 diabetes and insulin resistance. *Diabetes*. 2004;**53**(8):2132–2136.
61. Namvaran F, Rahimi-Moghaddam P, Azarpira N, Dabbaghmanesh MH. Polymorphism of adiponectin (45T/G) and adiponectin receptor-2 (795G/A) in an Iranian population: relation with insulin resistance and response to treatment with pioglitazone in patients with type 2 diabetes mellitus. *Mol Biol Rep*. 2012;**39**(5): 5511–5518.
62. Stefan N, Machicao F, Staiger H, Machann J, Schick F, Tschritter O, Spieth C, Weigert C, Fritsche A, Stumvoll M, Häring HU. Polymorphisms in the gene encoding adiponectin receptor 1 are associated with insulin resistance and high liver fat. *Diabetologia*. 2005;**48**(11):2282–2291.
63. Damcott CM, Ott SH, Pollin TI, Reinhart LJ, Wang J, O'connell JR, Mitchell BD, Shuldiner AR. Genetic variation in adiponectin receptor 1 and adiponectin receptor 2 is associated with type 2 diabetes in the Old Order Amish. *Diabetes*. 2005;**54**(7):2245–2250.
64. Blech I, Katzenellenbogen M, Katzenellenbogen A, Wainstein J, Rubinstein A, Harman-Boehm I, Cohen J, Pollin TI, Glaser B. Predicting diabetic nephropathy using a multifactorial genetic model. *PLoS One*. 2011;**6**(4):e18743.
65. Fang F, Bae EH, Hu A, Liu GC, Zhou X, Williams V, Maksimowski N, Lu C, Konvalinka A, John R, Scholey JW. Deletion of the gene for adiponectin accelerates diabetic nephropathy in the Ins2 ($^{+/C96Y}$) mouse. *Diabetologia*. 2015;**58**(7):1668–1678.
66. Ohashi K, Iwatani H, Kihara S, Nakagawa Y, Komura N, Fujita K, Maeda N, Nishida M, Katsube F, Shimomura I, Ito T, Funahashi T. Exacerbation of albuminuria and renal fibrosis in subtotal renal ablation model of adiponectin-knockout mice. *Arterioscler Thromb Vasc Biol*. 2007;**27**(9):1910–1917.
67. Ge Q, Ryken L, Noel L, Maury E, Brichard SM. Adipokines identified as new downstream targets for adiponectin: lessons from adiponectin-overexpressing or -deficient mice. *Am J Physiol Endocrinol Metab*. 2011;**301**(2):E326–E335.
68. Lee S, Zhang H, Chen J, Dellsperger KC, Hill MA, Zhang C. Adiponectin abates diabetes-induced endothelial dysfunction by suppressing oxidative stress, adhesion molecules, and inflammation in type 2 diabetic mice. *Am J Physiol Heart Circ Physiol*. 2012; **303**(1):H106–H115.
69. Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami K, Matsuda K, Yamaguchi M, Tanabe H, Kimura-Someya T, Shirouzu M, Ogata H, Tokuyama K, Ueki K, Nagano T, Tanaka A, Yokoyama S, Kadowaki T. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. *Nature*. 2013;**503**(7477): 493–499.
70. Fang F, Liu GC, Kim C, Yassa R, Zhou J, Scholey JW. Adiponectin attenuates angiotensin II-induced oxidative stress in renal tubular cells through AMPK and cAMP-Epac signal transduction pathways. *Am J Physiol Renal Physiol*. 2013;**304**(11):F1366–F1374.
71. Yuan F, Liu YH, Liu FY, Peng YM, Tian JW. Intraperitoneal administration of the globular adiponectin gene ameliorates diabetic nephropathy in Wistar rats. *Mol Med Rep*. 2014;**9**(6): 2293–2300.
72. Yamauchi T, Iwabu M, Okada-Iwabu M, Kadowaki T. Adiponectin receptors: a review of their structure, function and how they work. *Best Pract Res Clin Endocrinol Metab*. 2014;**28**(1):15–23.
73. Mao X, Kikani CK, Riojas RA, Langlais P, Wang L, Ramos FJ, Fang Q, Christ-Roberts CY, Hong JY, Kim RY, Liu F, Dong LQ. APPL1 binds to adiponectin receptors and mediates adiponectin signalling and function. *Nat Cell Biol*. 2006;**8**(5):516–523.
74. Zhou L, Deepa SS, Etzler JC, Ryu J, Mao X, Fang Q, Liu DD, Torres JM, Jia W, Lechleiter JD, Liu F, Dong LQ. Adiponectin activates AMP-activated protein kinase in muscle cells via APPL1/LKB1-dependent and phospholipase C/Ca2+/Ca2+/calmodulin-dependent protein kinase kinase-dependent pathways. *J Biol Chem*. 2009;**284**(33):22426–22435.
75. Deepa SS, Zhou L, Ryu J, Wang C, Mao X, Li C, Zhang N, Musi N, DeFronzo RA, Liu F, Dong LQ. APPL1 mediates adiponectin-induced LKB1 cytosolic localization through the PP2A-PKCzeta signaling pathway. *Mol Endocrinol*. 2011;**25**(10):1773–1785.
76. Ruan H, Dong LQ. Adiponectin signaling and function in insulin target tissues. *J Mol Cell Biol*. 2016;**8**(2):101–109.
77. Semple RK, Soos MA, Luan J, Mitchell CS, Wilson JC, Gurnell M, Cochran EK, Gorden P, Chatterjee VK, Wareham NJ, O'Rahilly S. Elevated plasma adiponectin in humans with genetically defective insulin receptors. *J Clin Endocrinol Metab*. 2006;**91**(8): 3219–3223.
78. Lin HV, Kim JY, Pocai A, Rossetti L, Shapiro L, Scherer PE, Accili D. Adiponectin resistance exacerbates insulin resistance in insulin receptor transgenic/knockout mice. *Diabetes*. 2007;**56**(8): 1969–1976.
79. Kim CH, Pennisi P, Zhao H, Yakar S, Kaufman JB, Iganaki K, Shiloach J, Scherer PE, Quon MJ, LeRoith D. MKR mice are resistant to the metabolic actions of both insulin and adiponectin: discordance between insulin resistance and adiponectin responsiveness. *Am J Physiol Endocrinol Metab*. 2006;**291**(2): E298–E305.
80. Tsuchida A, Yamauchi T, Ito Y, Hada Y, Maki T, Takekawa S, Kamon J, Kobayashi M, Suzuki R, Hara K, Kubota N, Terauchi Y, Froguel P, Nakae J, Kasuga M, Accili D, Tobe K, Ueki K, Nagai R, Kadowaki T. Insulin/Foxo1 pathway regulates expression levels of adiponectin receptors and adiponectin sensitivity. *J Biol Chem*. 2004;**279**(29):30817–30822.
81. Martinez Cantarin MP, Keith SW, Waldman SA, Falkner B. Adiponectin receptor and adiponectin signaling in human tissue among patients with end-stage renal disease. *Nephrol Dial Transplant*. 2014;**29**(12):2268–2277.
82. Lely AT, Krikken JA, Bakker SJ, Boomsma F, Dullaart RP, Wolffenbuttel BH, Navis G. Low dietary sodium and exogenous angiotensin II infusion decrease plasma adiponectin concentrations in healthy men. *J Clin Endocrinol Metab*. 2007;**92**(5):1821–1826.
83. Rojas E, Rodríguez-Molina D, Bolli P, Israili ZH, Faría J, Fidilio E, Bermúdez V, Velasco M. The role of adiponectin in endothelial dysfunction and hypertension. *Curr Hypertens Rep*. 2014;**16**(8): 463.
84. Kintscher U, Unger T. Vascular protection in diabetes: a pharmacological view of angiotensin II type 1 receptor blockers. *Acta Diabetol*. 2005;**42**(Suppl 1):S26–S32.

85. Okada-Iwabu M, Iwabu M, Ueki K, Yamauchi T, Kadowaki T. Perspective of Small-Molecule AdipoR Agonist for Type 2 Diabetes and Short Life in Obesity. *Diabetes Metab J*. 2015;**39**(5):363–372.
86. Wilding JP, Gause-Nilsson I, Persson A; GALLANT 7 Study Group. Tesaglitazar, as add-on therapy to sulphonylurea, dose-dependently improves glucose and lipid abnormalities in patients with type 2 diabetes. *Diab Vasc Dis Res*. 2007;**4**(3):194–203.
87. Cha DR, Zhang X, Zhang Y, Wu J, Su D, Han JY, Fang X, Yu B, Breyer MD, Guan Y. Peroxisome proliferator activated receptor alpha/gamma dual agonist tesaglitazar attenuates diabetic nephropathy in db/db mice. *Diabetes*. 2007;**56**(8):2036–2045.
88. Yang J, Zhang D, Li J, Zhang X, Fan F, Guan Y. Role of PPARgamma in renoprotection in Type 2 diabetes: molecular mechanisms and therapeutic potential. *Clin Sci (Lond)*. 2009;**116**(1):17–26.
89. Oz O, Tuncel E, Eryilmaz S, Fazlioglu M, Gul CB, Ersoy C, Ocak N, Dirican M, Cangur S, Baran I, Imamoglu S. Arterial elasticity and plasma levels of adiponectin and leptin in type 2 diabetic patients treated with thiazolidinediones. *Endocrine*. 2008;**33**(1):101–105.
90. Oki K, Koide J, Nakanishi S, Nakashima R, Yamane K. Fenofibrate increases high molecular weight adiponectin in subjects with hypertriglyceridemia. *Endocr J*. 2007;**54**(3):431–435.
91. Tsunoda F, Asztalos IB, Horvath KV, Steiner G, Schaefer EJ, Asztalos BF. Fenofibrate, HDL, and cardiovascular disease in Type-2 diabetes: The DAIS trial. *Atherosclerosis*. 2016;**247**:35–39.
92. Belfort R, Berria R, Cornell J, Cusi K. Fenofibrate reduces systemic inflammation markers independent of its effects on lipid and glucose metabolism in patients with the metabolic syndrome. *J Clin Endocrinol Metab*. 2010;**95**(2):829–836.
93. Miyazaki Y, Cersosimo E, Triplitt C, DeFronzo RA. Rosiglitazone decreases albuminuria in type 2 diabetic patients. *Kidney Int*. 2007;**72**(11):1367–1373.