

## Role of Adipokines in the Development of Diabetic Renal Vascular Complication

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### ABSTRACT

Adipokine, the adipocyte-derived cytokine, plays a role in the establishment of vascular complications in patients with type 2 diabetes mellitus (T2DM). Adipokine, excreted from active adipocyte, continuously accelerates insulin resistance and chronic inflammation process in the pathophysiology of T2DM, resulting in the development of systemic macro-vascular injury, and may also promote atherosclerosis and endothelial dysfunction of the micro-vascular wall. Leptin, tumor necrosis factor-alpha, interleukin-6, complement proteins, and adiponectin are known as adipokines in capable of several actions to both systemic macro-vessels and local micro-vessels in organ. In this review, these adipokines are high-lighted and discussed in the development of diabetic renal complication.

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**Key words:** Leptin; Tumor necrosis factor-alpha; Interleukin-6; Complement; Adiponectin

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### INTRODUCTION

Recently, adipose tissue has been recognized as an endocrine organ which excretes fluid factors affecting glucose and lipid metabolism, blood pressure, and coagulation in addition with a preservation organ of the excessive energy<sup>[1]</sup>. Cytokines excreted from active adipocytes are called "adipokine," which concentrates macrophage to activate, and induces insulin resistance, chronic inflammation, atherosclerosis, and endothelial dysfunction<sup>[2]</sup>. Insulin resistance, not to speak of oxidative stress and chronic inflammation, plays a central role in the diabetic pathophysiology, and may induce atherosclerosis and micro-vascular endothelial dysfunction<sup>[3,4]</sup>. In this review, authors would discuss about the etiological effect of adipokines in the development of macro-vascular complications, and would examine the role of adipokines in the development of diabetic micro-angiopathy. Insulin resistance in the peripheral artery is induced from the imbalance between nitric oxide (NO) production via the phosphatidylinositol 3-kinase (PI3K) pathway by over-stimulation of hyperinsulinemia and endothelin-1 excretion via the mitogen activated protein kinase (MAPK) pathway. PI3K-NO pathway is decreased and MAPK-endothelin-1 pathway is accelerated in obese patients<sup>[5]</sup>. Oxidative stress is also known to be accelerated in patients with type 2 diabetes mellitus. Persistent hyperinsulinemia and/or hyperglycemia would increase the production of reactive oxygen species (ROS) in mitochondria, resulting in the acceleration of oxidative stress<sup>[6]</sup>. Atherosclerosis and vascular endothelial dysfunction are known as promotive factors for diabetic microangiopathy. Previous evidences and perspectives on the direct effect of adipokines to the micro-vascular wall and organs are provided in addition with the systemic macro-vascular injuries such as insulin resistance and chronic inflammation. Leptin, tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), complement proteins, and adiponectin are taken up and discussed here (Figure 1).

### LEPTIN

Leptin was identified as an etiological gene of obesity, and would

accelerate energy consumption and appetite regulation via its receptor at hypothalamus<sup>[7]</sup>. In obesity, excess eating with insulin resistance is recognized in spite of increased leptin excretion from adipocyte. This phenomenon is called as “leptin resistance,” and is induced by phosphorylation disturbance of signal transducer and activator of transcription 3 (STAT3), and is also induced by passage disturbance of leptin through blood brain barrier<sup>[8]</sup>. It is reported that continuous hyperleptinemia itself would induce leptin resistance<sup>[9]</sup>. Leptin possesses high similarity with inflammatory cytokines and their receptors<sup>[10]</sup>. It is reported that plasma leptin level would correlate with that of CRP, and leptin would promote inflammation process<sup>[11]</sup>. Moreover, leptin is also reported to worsen cachexia on uremic patients<sup>[12]</sup>. On the direct effect to peripheral micro-vascular wall, leptin is reported as a regulator against ischemia/reperfusion injury<sup>[13]</sup>. Leptin is also reported to correlate with arterial stiffness<sup>[14]</sup>. Leptin accelerates sympathetic nerve activity, induces hypertension, and promotes imbalance between endothelial NOS expression and intra-cellular L-arginine expression, resulting in endothelial dysfunction and the breakdown of micro-vascular tonus<sup>[15,16]</sup>. Leptin is known to induce the growth of cultured glomerular endothelial cells and to increase the production of transforming-growth-factor-beta 1 (TGF- $\beta$ 1). Wolf G. et al. reported that infusion of recombinant leptin was able to induce TGF- $\beta$ 1 expression and to increase proliferating cells with an amplified glomerular expression of type IV collagen<sup>[17]</sup>. Leptin has been shown to induce the synthesis of type I collagen in mesangial cells, as well as type IV collagen in glomerular endothelial cells contributing to extracellular matrix deposition, glomerulosclerosis, and proteinuria<sup>[18]</sup>. It has been suggested that leptin induces oxidative stress responses, and increases TNF- $\alpha$ , IL-6, and potentiates proliferation, resulting in impaired endothelium-dependent vasodilation promoting hypertension and atherosclerosis<sup>[19]</sup>.

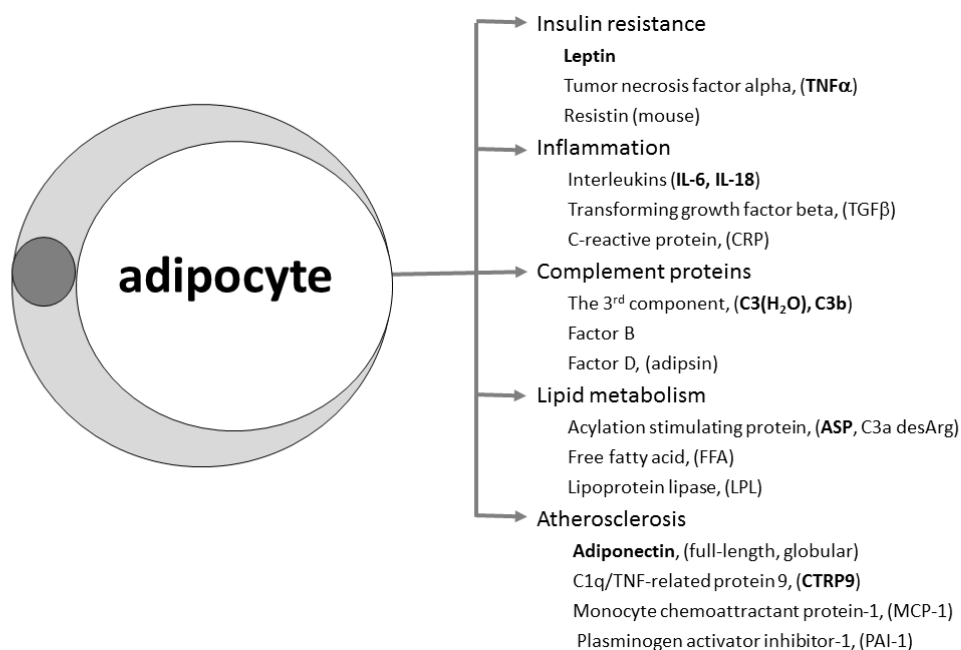
## TUMOR NECROSIS FACTOR- $\alpha$

TNF- $\alpha$  is derived from adipose tissue, and correlates with the

pathophysiological state of insulin resistance and obesity<sup>[20]</sup>. TNF- $\alpha$  promotes serine phosphorylation of insulin receptor substrate-1 (IRS-1) in adipocyte<sup>[21]</sup>. This procedure competes serine phosphorylation of insulin, and accelerates breakdown of IRS-1 resulting in the induction of insulin resistance<sup>[22]</sup>. TNF- $\alpha$  plays a pivotal role in the disruption of macrovascular and microvascular circulation. The increase in TNF- $\alpha$  expression induces the production of ROS, resulting in endothelial dysfunction in many pathophysiological conditions<sup>[23]</sup>. The direct effect of TNF- $\alpha$  on vascular endothelium has been recognized<sup>[24,25]</sup>. TNF- $\alpha$  and ROS would injure vascular endothelium and would increase urinary albumin excretion<sup>[26,27]</sup>. Macrophage infiltrates under the endothelium of peripheral micro-vessels, and excretes TNF- $\alpha$  which increases production of monocyte chemoattractant protein-1 (MCP-1). Awad AS. et al reported that blockade of TNF- $\alpha$  reduced albuminuria, serum creatinine histopathologic changes, kidney macrophage recruitment, and plasma inflammatory cytokine levels<sup>[28]</sup>. Adiponectin predominantly inhibits TNF- $\alpha$  excretion through nuclear factor-kappa B<sup>[29]</sup>.

## INTERLEUKINS

IL-6 is known as an inflammatory cytokine, which is ordinarily produced at T cell and macrophage. However, up to 30% of circulating IL-6 is thought to be derived from adipocyte. IL-6 enfeebles tyrosine phosphorylation of IRS-1 on adipocyte, and induce insulin resistance<sup>[30]</sup>. STAT-3, which is activated by IL-6, accelerates expression of suppressor of cytokine signaling-3 (SOCS-3). SOCS-3 suppresses phosphorylation of IRS-1 by binding to ubiquitin, resulting in the induction of insulin resistance<sup>[31]</sup>. Pradhan et al. reported that plasma IL-6 level increased in case of obesity and/or insulin resistance<sup>[32]</sup>. IL-6 promotes endothelial activation by expressing MCP-1 and adhesion molecules that recruits immune cells into sub-intimal space<sup>[33, 34]</sup>. Moreover, IL-6 activates macrophages to migrate and differentiate, which potentially accelerates atherogenesis<sup>[35]</sup>. IL-6 would directly contribute to the process of tissue injury in glomerulus as a inflammatory cytokine<sup>[36]</sup>.

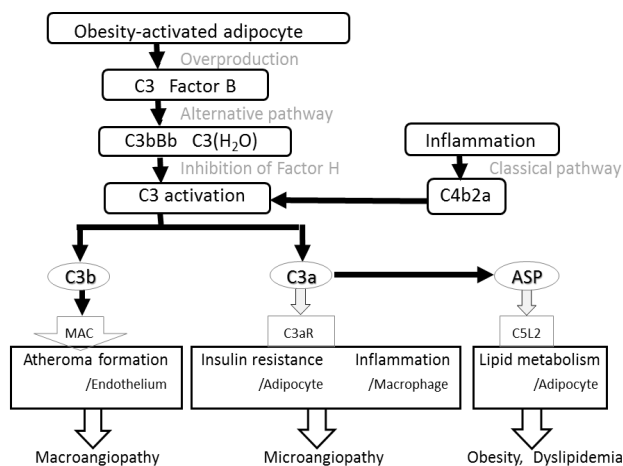


**Figure 1** Cytokines derived from adipocyte. Obesity-activated adipocyte excretes several cytokines and chemokines called “adipokine.” They provide various functions in the pathophysiological condition, and play roles on endothelial dysfunction, resulting in the expression of diabetic vascular complications.

Previously authors reported that interleukin 18 (IL-18) of interleukin family contributed to the expression of glomerular injury in T2DM patients<sup>[37]</sup>. IL-18 is produced by vascular endothelial cells or activated macrophages, and induces interferon- $\gamma$  production<sup>[38]</sup>. IL-18 is therefore a marker of inflammation, and is a prognostic marker for forthcoming cardiovascular events<sup>[39]</sup>. In nephropathy, the activated macrophage infiltrates the glomerulus and produces IL-18 in the course of kidney injury<sup>[40]</sup>. The increase of IL-18 suggests another mechanism of glomerular injury by the infiltrated and activated macrophage in addition to usual endothelial injury. IL-18 from atheroma plaque plays a role on general vascular endothelial injury through the mild and continuous inflammation reaction. While macrophage infiltrated in the kidney excretes IL-18 and induces the glomerular injury in lupus nephritis and other primary glomerular diseases. So, IL-18 may also concern in the development of nephropathy in diabetes mellitus through the effect of macrophage-induced IL-18. The inflammation reaction in glomerulus may occur more strongly than in arteriole. Previous reports indicate that TGF- $\beta$  and IL-6 injure glomerular mesangial cells during the inflammation reaction<sup>[41, 42]</sup>. IL-18 has been reported to play a role in the formation of inflammation and endothelial dysfunction<sup>[43]</sup>. Tucci et al. reported that IL-18 induced the accumulation of dendritic cells in the glomerulus, resulting in kidney injury<sup>[44]</sup>. Araki et al. reported predictive impact of IL-18 on diabetic renal dysfunction in a follow-up study<sup>[40]</sup>. Authors also indicated that IL-18 has a direct role in the acceleration of glomerular injury in addition to its proinflammatory effect.

## COMPLEMENT PROTEINS

Complement proteins are produced at adipocytes in addition with liver cells. Especially, serum components consisting of the alternative pathway are derived from the active adipocyte in excess<sup>[45]</sup>. Circulating C3 is slowly activated and broken down to C3b and C3a under the existence of chylomicron<sup>[46]</sup>. On binding to C3a receptor (C3aR), C3a promotes insulin resistance at adipocyte, and accelerates inflammatory process at macrophage<sup>[47]</sup>. C3a is immediately inactivated to acylation stimulating protein in circulation, and promotes triglyceride synthesis on binding to C5L2 receptor at adipocyte<sup>[48]</sup>. C3b also activates C5 and serial late complement pathway, and membrane attack complex infiltrates to vessel wall to form atherosclerosis<sup>[49]</sup>. C5a also binds to C5a receptor to promote inflammation process in tissue and insulin resistance<sup>[50]</sup>. Complement components act as the adipokine in addition with ordinary immunological activities, and their circulating levels correlate to the risk of ischemic heart disease and diabetic nephropathy<sup>[51, 52]</sup>. The plasma C3 level is associated with the development of T2DM and several risk factors such as obesity, dyslipidemia, and insulin resistance<sup>[53, 54]</sup>. The link between complement activation and metabolic syndrome is substantiated by the observations that adipose tissue secretes complement components. Several adipocyte-derived cytokines activate proinflammatory cytokines and act on macrophages, resulting in tissue injury in the diabetic kidney<sup>[55, 56]</sup>. During the course of T2DM, the following pathophysiological states are often recognized in association with complement activation and renal involvement. van Greevenbroek et al<sup>[54]</sup>. reported that complement gene expression was up-regulated in patients with obesity and dyslipidemia. Such up-regulation may subsequently influence downstream processes, including macrophage infiltration into adipose tissue and adipocyte insulin resistance (Figure 2).



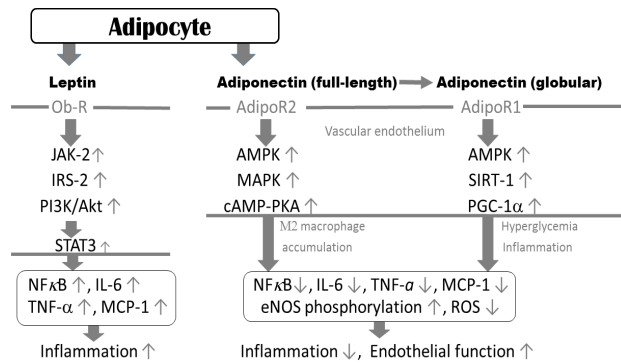
**Figure 2** Differential roles of complement proteins in vascular injury. In patients with T2DM with obesity, activated adipocytes overproduce complement components such as C3 and Factor B. Chylomicron activates the alternative pathway by regulating the effect of Factor H. During this process, C3 is spontaneously and continuously converted to C3a and C3b. C3b excites the terminal complement pathway and forms membrane attack complexes (MACs), which contribute to the formation of atherosclerotic plaque. C3a contributes to the induction of insulin resistance in adipocytes and macrophages, and inflammation in vascular endothelial cells. C3a is immediately converted to acylation stimulating protein (ASP), which leads to the induction of triacylglycerol production and obesity.

## ADIPONECTIN FAMILY

The expression of adiponectin is specific in adipocyte, and its circulating level correlates with the pathophysiological state of obesity and insulin resistance. Adiponectin emphasizes insulin action by activating peroxisome proliferator activated receptor alpha (PPAR $\alpha$ ) and 5' adenosine monophosphate- activated protein kinase (AMPK) activity<sup>[57]</sup>, and regulates de novo glucose synthesis in liver<sup>[58]</sup>. Adiponectin promotes PI3K activity via IRS-1 signal pathway, and accelerates fatty acid consumption by increasing the development of fatty acid transport protein-1 on muscle cell<sup>[59]</sup>. The development of adiponectin is increased in the smaller adipocyte, and regulated in the expanded adipocyte due to obesity<sup>[60]</sup>. Tuchida et al. reported that circulating adiponectin as well as its receptor levels were decreased in obese patients<sup>[61]</sup>. Adiponectin was not recognized in normal intima, but was strongly recognized in the injured subendothelium<sup>[62]</sup>. This indicates that circulating adiponectin would infiltrate to the injured subendothelium. Adiponectin regulates TNF $\alpha$ -dependent increased expression of vascular cell adhesion molecule-1, intercellular adhesion molecule 1, and E-selectin on endothelium, and inhibits adhesion of monocytes to the vessel wall<sup>[63]</sup>. Adiponectin is reported to inhibit proliferation of vascular smooth muscle cell by several cell proliferation factor<sup>[64]</sup>. These evidences indicate the direct protective effect of adiponectin to local atherosclerosis. Ohashi et al. reported that adiponectin would act against the progression of renal injury<sup>[65]</sup>.

C1q/TNF-related protein-9 (CTRP9), a newly identified member of adiponectin family, was reported to act protectively to the ischemic heart<sup>[66]</sup>. CTRP9 activates AMPK, Akt and p42/44MAPK, and stimulation of muscle glucose uptake can contribute to reduce blood glucose<sup>[67]</sup>. CTRP9 induces vasodilation through the AMPK/eNOS pathway via nitric oxide production<sup>[68]</sup>. CTRP9 over-expression reduces neointimal formation by suppressing vascular smooth muscle cell proliferation and migration through the cAMP/PKA/ERK pathway<sup>[69]</sup>. Therefore, obesity and insulin resistance are risk factors for renal vascular damage as well as cardio-vascular damage

in patients with type 2 diabetes. Like adiponectin, CTRP9 reduces myocardial infarct size and hypoxia-induced apoptosis of cardiomyocytes through AMPK signaling similarly to adiponectin<sup>[70]</sup>. Plasma adiponectin levels are inversely correlated with albumin in overweight individuals<sup>[71]</sup>, but the relevance of CTRP9 levels in patients with type 2 diabetes is not yet well understood (Figure 3).



**Figure 3** Pivotal effects of adipokines in vascular endothelium. Full-length adiponectin activates AMPK, cAMP-PKA, MAPK, and PI3K-Akt on binding to AdipoR2. Activation of cAMP-PKA/AMPK causes increased NO production, decreased ROS generation, and NFκB suppression leading to the reduction of IL-6. Ordinarily, globular adiponectin activates NFκB via AdipoR1/AMPK-Akt pathway. However, globular adiponectin oppositely improves endothelial dysfunction via activation of Akt-AMP-eNOS pathway and suppression of endothelial ROS generation via inhibition of NFκB signaling in hyperglycemia and inflammation. Leptin leads to phosphorylate Ob-R/JAK2 complex on binding to OB-Rb. Subsequently, PI3K/Akt-STAT3 cascade is activated, and induces atherogenic and inflammatory effects by the transcription of genes such as MCP-1, TNF-α, and IL-6. (AMPK: adenosine mono phosphate-activated protein kinase, cAMP-PKA: cyclic AMP-protein kinase A, MAPK: mitogen activated protein kinase, PI3K: phosphatidylinositol 3-kinase, Akt: protein kinase B, AdipoR2: adiponectin receptor 2, NO: Nitric oxide, eNOS: endothelial nitric oxide synthase, ROS: reactive oxygen species, NFκB: nuclear factor kappa B, IL-18: interleukin-18, AdipoR1: adiponectin receptor 1, NAD: nicotinamide adenine dinucleotide, SIRT-1: NAD-dependent deacetylase sirtuin-1, PPARγ: peroxisome proliferator activated receptor gamma, PGC-1α: PPARγ coactivator-1 alpha, JAK: Janus kinase, OB-R: leptin receptor, IRS: insulin receptor substrate, STAT3: signal transducer and activator of transcription 3, MCP-1: monocyte chemoattractant protein-1, TNF-α: tumor necrosis factor-α, IL-6: interleukin-6).

## CONCLUSION

Diabetic vascular complication develops in the pathophysiology of insulin resistance which is induced from systemic abnormal glucose/lipid metabolism and in the pathophysiology of atherosclerosis which is induced from local vascular endothelial dysfunction. Adipokine, derived from active adipocyte in obesity, possesses these systemic and local action, and might play a role in the development of vascular injury and organ damage.

## CONFLICT OF INTERESTS

There is no conflict of interest.

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