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

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.

**TNF-α**

TNF-α is derived from adipose tissue, and correlates with the pathophysiologic state of insulin resistance and obesity. TNF-α promotes serine phosphorylation of insulin receptor substrate-1 (IRS-1) in adipocyte. This procedure competes serine phosphorylation of insulin, and accelerates breakdown of IRS-1 resulting in the induction of insulin resistance. TNF-α plays a pivotal role in the disruption of macrovascular and microvascular circulation. The increase in TNF-α expression induces the production of ROS, resulting in endothelial dysfunction in many pathophysiological conditions. The direct effect of TNF-α on vascular endothelium has been recognized. TNF-α and ROS would injure vascular endothelium and would increase urinary albumin excretion. Macrophage infiltrates under the endothelium of peripheral micro-vessels, and excretes TNF-α which increases production of monocyte chemoattractant protein-1 (MCP-1). It is reported that plasma IL-6 level would correlate with that of CRP, and leptin would promote inflammation process. Moreover, leptin is also reported to worse cachexia on uremic patients. On the direct effect to peripheral micro-vascular wall, leptin is reported as a regulator against ischemia/reperfusion injury. Leptin is also reported to correlate with arterial stiffness. 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. Leptin is known to induce the growth of cultured glomerular endothelial cells and to increase the production of transforming-growth-factor-beta 1 (TGF-β1). Wolf G. et al. reported that infusion of recombinant leptin was able to induce TGF-β1 expression and to increase proliferating cells with an amplified glomerular expression of type IV collagen. 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. It has been suggested that leptin induces oxidative stress responses, and increases TNF-α, IL-6, and potentiates proliferation, resulting in impaired endothelium-dependent vasodilation promoting hypertension and atherosclerosis.

**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. 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. Pradhan et al. reported that plasma IL-6 level increased in case of obesity and/or insulin resistance. IL-6 promotes endothelial activation by expressing MCP-1 and adhesion molecules that recruits immune cells into sub-intimal space. Moreover, IL-6 activates macrophages to migrate and differentiate, which potentially accelerates atherogenesis. IL-6 would directly contribute to the process of tissue injury in glomerulus as a inflammatory cytokine.
Previously authors reported that interleukin 18 (IL-18) of interleukin family contributed to the expression of glomerular injury in T2DM patients[37]. IL-18 is produced by vascular endothelial cells or activated macrophages, and induces interferon-γ production[38]. IL-18 is therefore a marker of inflammation, and is a prognostic marker for forthcoming cardiovascular events[39]. In nephropathy, the activated macrophage infiltrates the glomerulus and produces IL-18 in the course of kidney injury[40]. 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-β and IL-6 injure glomerular mesangial cells during the inflammation reaction[41, 42]. IL-18 has been reported to play a role in the formation of inflammation and endothelial dysfunction[43]. Tucci et al. reported that IL-18 induced the accumulation of dendritic cells in the glomerulus, resulting in kidney injury[44]. Araki et al. reported predictive impact of IL-18 on diabetic renal dysfunction in a follow-up study[45]. 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[46]. Circulating C3 is slowly activated and broken down to C3b and C3a under the existence of chylomicron[47]. On binding to C3a receptor (C3ar), C3a promotes insulin resistance at adipocyte, and accelerates inflammatory process at macrophage[48]. C3a is immediately inactivated to acylation stimulating protein on binding to C3a receptor at adipocyte[49]. C3b also activates C5 and serial late complement pathway, and membrane attack complex infiltrates to vessel wall to form atherosclerosis[50]. C5a also binds to C5a receptor to promote inflammation process in tissue and insulin resistance[51]. 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[52, 53]. The plasma C3 level is associated with the development of T2DM and several risk factors such as obesity, dyslipidemia, and insulin resistance[54, 55]. 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[56, 57]. During the course of T2DM, the following pathophysiological states are often recognized in association with complement activation and renal involvement. van Greevenbroek et al.[58], 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).

**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 (PPARα) and S’ adenosine monophosphate- activated protein kinase (AMPK) activity[59], and regulates de novo glucose synthesis in liver[60]. 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[61]. The plasma C3 level is associated with the pathophysiological state of obesity and insulin resistance[62]. The expression of adiponectin is specific in adipocyte, and its circulating levels correlate to the risk of ischemic heart disease and diabetic nephropathy[63, 64]. The plasma C3 level is associated with the development of T2DM and several risk factors such as obesity, dyslipidemia, and insulin resistance[65, 66]. 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[67, 68]. During the course of T2DM, the following pathophysiological states are often recognized in association with complement activation and renal involvement. van Greevenbroek et al.[69], 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).
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[87]. Plasma adiponectin levels are inversely correlated with albumin in overweight individuals[87], but the relevance of CTRP9 levels in patients with type 2 diabetes is not yet well understood (Figure 3).

### CONCLUSION

Diabetic vasculopathy complicates 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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