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The Role of Adipose Tissue in Diabetic Kidney Disease

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1. Introduction

Chronic kidney disease has become an important global public health threat. There are currently approximately 387,000 patients with end-stage kidney disease in the United States and 1.8 million patients worldwide who require dialysis therapy or a transplant for survival (DuBose, 2007). Over 23 million children and adults have diabetes mellitus in the United States, representing nearly 8% of the population. Forty-three percent of end-stage kidney disease patients in the US have diabetes mellitus, and more than 90% of these diabetics have type 2 diabetes; these statistics are similar to the situation in Korea (ESRD Registry Committe, 2010). Type 2 diabetes mellitus, hypertension, obesity, and dyslipidemia are components of metabolic syndrome and are all major risk factors for cardiovascular disease. With the availability of excess food in many parts of the world, obesity is a growing problem that is increasing at an alarming rate in adults as well as in children. Obesity increases the risk for type 2 diabetes mellitus, cardiovascular disease, cancer, musculoskeletal disorders, and pulmonary disease (Kramer, 2006). Although obesity is an important risk factor for diabetes and hypertension, the two most common etiologies of chronic kidney disease, obesity itself may also potentiate kidney damage.

The important etiologic factor of metabolic syndrome is insulin resistance, which leads to hyperinsulinemia; activation of the renin-angiotensin-aldosterone system (RAAS); increased syntheses of transforming growth factor beta 1 (TGF-β1), insulin-like growth factor-1 (IGF-1) and connective tissue growth factor (CTGF); and collagen production in the kidney. These changes cause renal mesangial cell proliferation, extracellular matrix (ECM) expansion and renal fibrosis (Sarafidis & Ruilope, 2006). In addition to its proliferative actions in the kidney, insulin likely influences renal function at the tubular level because its sodium-retaining action results in hypertension. Insulin may also contribute to glomerulus injury by increasing the glomerular filtration rate (GFR), intraglomerular pressure and urinary albumin excretion. Moreover, insulin resistance and hyperinsulinemia are directly associated with low endothelial nitric oxide synthesis, altered endothelin-1 secretion and high oxidative stress production. Although the kidney is affected by hyperglycemia in patients with diabetes mellitus, the role of altered renal lipid metabolism has not yet been extensively studied in obesity-related kidney disease, including diabetic nephropathy. However, previous reports have revealed that abnormalities in lipid and glucose metabolism in the kidney are also important in the development of organ injury, as is

adipose tissue (Drury et al., 1950; Rubenstein et al., 1975; Schoolwerth et al., 1988; Stumvoll et al., 1997).

Obesity is a risk factor for the development of hypertensive nephrosclerosis, and focal and segmental glomerular sclerosis is considered to be independent risk factors for the progression of renal disease. Recent experimental and human clinical trials suggest that obesity can influence renal injury through various mechanisms, including hemodynamic changes in the glomeruli, alteration of renal lipid metabolism, increased oxidative stress, and inflammation via alteration of adipocytokines induced by adipose tissue changes in obesity. Additionally, circulating adipocytokines can also positively or negatively influence systemic insulin resistance, leading to organ injury and endothelial dysfunction. Recent insights about adipose tissue biology suggest that adipose tissue is not an energy storage tissue but an active endocrine organ that interacts with major target organs of metabolic syndrome, such as the liver, muscles and kidneys. A better understanding of adipose tissue biology will help researchers develop new therapeutic strategies for managing metabolic syndrome as well as diabetic vascular complications.

2. Adipose tissue and kidney

2.1 Adipose tissue as an endocrine organ

During the development of obesity, multiple functional and structural changes occur in the adipose tissue (called "adiposopathy"), such as an increase in the number and size of adipocytes, an increase in the infiltration of mononuclear cells, rarefaction of blood vessels, and apoptosis (Wellen & Hotamisligil, 2003). Because leptin, the first identified adipocytokine, has a systemic effect in the body, adipose tissue is now considered to be an active endocrine organ (Zhang et al., 1994). While many adipocytokines have been proposed, few have been studied in detail, and even fewer have been investigated in the kidney. These adipocytokines include several active molecules released by adipocytes, such as leptin, resistin, adiponectin or visfatin, as well as cytokines released by inflammatory cells, such as tumor necrosis factor alpha (TNF-α), interleukine-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and interleukine-1 (IL-1). Interestingly, the circulating levels of these adipocytokines have been found to be altered in experimental animals and patients with kidney disease, which is an independent risk factor for cardiovascular diseases. Moreover, the production, secretion and regulatory actions of these proteins are not limited only to adipose tissue but are also described in other organ tissues. It is now recognized that the kidney itself can alter the clearance of adipocytokines as well as produce them. Recent experimental and clinical evidence has demonstrated possible molecules that cross-talk between adipose tissue and the kidney in the pathogenesis of obesity-related renal disease.

2.2 Role of leptin in kidney disease

Leptin is a representative adipocytokine that is primarily produced in adipose tissue and that plays an important role in appetite control and regulation of energy expenditure. The plasma leptin concentration is positively increased according to the degree of adiposity (Friedman & Halaas, 1998), and hyperleptinemia has been reported to be an independent risk factor for cardiovascular disease (Ren, 2004; Soderberg et al., 1999). However, recent experimental data imply that leptin may directly influence renal function through the small isoform of the leptin receptor (Ob-Ra) in the kidney (Wolf & Ziyadeh, 2006). Infusion of

leptin in normal rats induced glomerulosclerosis and proteinuria, and transgenic mice overexpressing leptin also showed increased renal expressions of fibronectin and type IV collagen (Wolf et al., 2002). Several *in vitro* experiments using glomerular endothelial and mesangial cells also demonstrated that leptin stimulates the proliferation of endothelial cells, increases glucose uptake into mesangial cells and finally increases the productions of TGF-β1 and collagen (Wolf et al., 1999). In addition, leptin plays an important role in the progression of atherosclerosis, such as platelet aggregation and thrombosis, production of inflammatory cytokines (including TNF-α and IL-6) and calcification of vascular smooth muscle cells (Konstantinides et al., 2001). Leptin is also associated with sympathetic activation and can lead to hypertension and renal injury (Henegar et al., 2001; Kambham et al., 2001). Collectively, these data suggest that leptin contributes to the development of renal injury through both direct and indirect effects.

2.3. Role of adiponectin in kidney disease

Adiponectin is an important anti-diabetic adipocytokine produced in adipose tissue (Scherer, 2006). A large body of evidence has shown that adiponectin improves insulin sensitivity and exerts an anti-inflammatory effect in vascular cells (Scherer, 2006; Axelsson, 2008; Goldstein & Scalia, 2004). Adiponectin-null mice show increased susceptibility to insulin resistance when fed a high-fat diet, and treatment with adiponectin improves insulin sensitivity (Maeda et al., 2002). Studies of the genetic modulation of adiponectin receptors also suggest that representative adiponectin receptors 1 and 2 are involved in insulin resistance through the activation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor (PPAR) (Kadowaki et al., 2008; Mao et al., 2006). Interestingly, serum levels of adiponectin are lower in obese patients compared with those in lean patients (Kanaya et al. 2006; Laughlin et al. 2007). Although the association between adiponectin level and renal disease is still controversial, recent clinical studies have reported that serum adiponectin and albuminuria levels were inversely correlated (Tsioufis et al., 2005; Sharma et al., 2008; Yano et al., 2007). Considering that adiponectin is produced in adipose tissue and shows an inverse relationship with the amount of adiposity, these findings support the possibility of adiponectin as a candidate molecule that connects obesity and kidney disease.

Sharma et al. first reported the link between adiponectin and albuminuria in an adiponectin-null mouse (Sharma et al., 2008). The C57BL/6 adiponectin-null mouse exhibits albuminuria and pathologic changes in foot process effacement of podocytes (Sharma et al., 2008). This study observed that podocytes express the adiponectin R1 receptor, and that treatment with adiponectin normalized the albuminuria and pathologic changes of the foot process through adiponectin stimulation of the AMPK pathway, a key regulator of intracellular energy status with potent anti-proliferative and anti-oxidative effects. In addition, renoprotective effects of adiponectin have also been reported in the subtotal renal ablation model of adiponectin-knockout mice (Ohashi et al., 2007). An increase in visceral fat increases the productions of proinflammatory adipocytokines, which leads to an increase in oxidative stress in various target organs. Furthermore, the increase in adipose tissue oxidative stress results in further aggravation of systemic oxidative stress and inflammation, which positively affect the development of insulin resistance. Taken together, these data suggest that adiponectin is a possible mechanistic link between adipose tissue and renal disease. However, it is not yet clear whether adiponectin receptor 2 has a role in obesity-related kidney disease.

2.4 Role of visfatin in kidney disease

Among the adipocytokines, visfatin is a ubiquitous intracellular enzyme; it is also known as nicotinamide phosphoribosyltransferase (NAMPT)/pre-B cell colony-enhancing factor (PBEF-1). Visfatin is a newly identified adipocytokine that is secreted by adipocytes and that mimics insulin in animals (Fukuhara et al., 2005); however, its role in kidney disease is not yet known. In humans, early data have suggested that visfatin concentrations are increased in patients with type 2 diabetes mellitus (Chen et al., 2006), but that it is not in itself a mediator of insulin resistance (Lopez-Bermejo et al., 2006). Plasma visfatin concentrations were recently found to increase in patients with diabetes mellitus compared with those in healthy control participants (Kang et al., 2010c). These data did not show any significant relationships between plasma visfatin concentration and metabolic parameters, including the homeostasis model assessment of insulin resistance (HOMA-IR), HbA1c, or body-mass index (BMI). However, plasma levels of visfatin were markedly increased in patients with diabetic nephropathy irrespective of the stage of nephropathy. Visfatin level was associated with systemic inflammatory markers (such as MCP-1), and its levels were positively associated with systolic blood pressure, fasting blood glucose and carotid intima-medial thickness (IMT). These findings suggest that the plasma concentration of visfatin is elevated when inflammatory conditions exist.

Another experiment reported that plasma concentration of visfatin was increased in animals as well as humans during the early stages of diabetic nephropathy in type 2 diabetics (Kang et al., 2010d). The present study found that visfatin expression was markedly up-regulated in both the glomeruli and proximal tubules of the diabetic kidney. In another experiment, the synthesis and physiological action of visfatin in renal cells (such as mesangial cells) were studied to investigate the role of visfatin in diabetic nephropathy (Song et al., 2008). Visfatin was found to be synthesized in renal mesangial cells as well as adipocytes and stimulated glucose uptake in glomerular mesangial cells mediated by glucose transporter-1 (GLUT-1). In glomerular podocytes and tubular cells as well as mesangial cells, high glucose stimulation up-regulated marked visfatin synthesis but did not increase the response to angiotensin II stimulation (Kang et al., 2010d; Song et al., 2008). Exogenous visfatin administration induced synthesis of pro-fibrotic molecules, including TGF-β1, PAI-1 and type I collagen. Endogenous visfatin produced from renal cells, such as mesangial cells, podocytes and tubular cells, seems to stimulate glucose uptake and intracellular metabolic abnormalities.

Hyperglycemia in diabetes is associated with increased glucose uptake into cells and causes intracellular metabolic alterations, which are considered an important pathogenesis for diabetic microvascular complications. Consistently, previous studies have suggested that glucose uptake into mesangial cells promotes mesangial extracellular matrix protein accumulation, which is characteristic of diabetic nephropathy (Ayo et al., 1991; Haneda et al., 1991; Heilig et al., 1995).

However, in diabetic animals, exogenous visfatin administration interestingly improved diabetic nephropathy (Song et al., 2008). These results were in opposition to previously obtained observational data of humans and animals. First, visfatin treatment improved urinary albumin excretion in diabetic animals irrespective of plasma glucose concentration. Second, dramatic improvements in plasma lipid concentration and insulin resistance were observed. Third, visfatin regulated the balance of lipid metabolism in the diabetic kidney as well as in the liver and adipose tissue. Several possibilities may explain these paradoxical results. Visfatin may have a compensatory effect via both the autocrine and paracrine

pathways, resulting in improved insulin resistance and lipid metabolism. Long-term visfatin infusion may restore the decreased availability of insulin receptors in the kidney. The next possibility is the benefit of a more physiologic route of intra-peritoneal visfatin injection compared to vascular infusion, which directly accumulates in the liver and visceral adipose tissue (the main organs regulating lipid and glucose metabolism) before achieving adequate concentration levels in the systemic circulations of the plasma, heart and kidney. Therefore, the secondary beneficial effects (improving insulin resistance and dyslipidemia) of visfatin on the kidney may be more effective than the direct renal effects. However, it is equally possible that a difference in the models of insulin resistance may have accounted for this apparent discrepancy. Despite the paradoxical effect of visfatin in this study, visfatin was shown to have beneficial effects on lipid metabolism and insulin resistance in diabetic animal experiments (Song et al., 2008). Long-term therapy with intraperitoneal visfatin injection eventually induced various organ-protective effects in type 2 diabetic nephropathy. Based on these results, visfatin might play some crucial role in the pathogenesis of insulin resistance and diabetic nephropathy.

2.5 Role of Renin-Angiotensin-Aldosterone System (RAAS)

Several clinical trials of hypertension have demonstrated a lower incidence of diabetes mellitus among patients treated with renin-angiotensin-aldosterone system (RAAS) inhibitor compared to that of those given other classes of anti-hypertensive drugs (Dahlof et al., 2002; Hansson et al., 1999; Yusuf et al., 2000). Although these studies were mostly performed among patients with hypertension or congestive heart failure, a relative risk for new-onset diabetes mellitus was reduced in patients using RAAS in a meta-analysis of randomized controlled trials. Furthermore, the activity of RAAS is also associated with metabolic syndrome (Engeli, 2006). These findings suggest that RAAS may have an important role in the development of diabetes mellitus. Interestingly, mature adipocytes express all components of RAAS, including angiotensinogen, angiotensin-converting enzyme and angiotensin type 1 (AT1) and angiotensin type 2 (AT2) receptors (Engeli et al., 2000). For these reasons, the anti-diabetic effect of RAAS inhibition was recently evaluated, and the effects of these drugs on adipocyte function were observed to occur via the modulation of adipocytokines (Kang et al., 2010a; Lee et al., 2008). Administration of an AT receptor antagonist (ARB) improved insulin resistance simultaneous to an improvement in diabetic nephropathy in an animal experiment. ARB augmented lipid accumulation, differentiation of adipocytes and improvement in adipocytokine synthesis in type 2 diabetic animals. In animals with diabetic nephropathy, ARB improved alterations in renal lipid metabolism and subsequently reduced renal cholesterol and triglyceride contents with decreased albuminuria. Importantly, in both adipocytes and renal cells, AT2 increased the synthesis of pro-inflammatory molecules in adipose tissue, such as plasminogen activator inhibitor-1 (PAI-1), MCP-1, and nuclear factor kappa B (NF-κB) activation, and then their synthesis was suppressed by ARB treatment.

The mechanisms linking obesity to hypertension are important for identifying specific treatments for these patients, and some evidence suggests that obesity is associated with increased aldosterone levels. Obesity induces activation of the RAS system in adipose tissue, and weight reduction often restores RAS activity to basal levels in lean healthy participants (Engeli et al., 2005). Proposed mechanisms for these interesting findings are the role of adipose-tissue-derived products called mineralocorticoid stimulating factor (MSF) and free fatty acids. An *in vitro* experiment showed the presence of MSF in conditioned media of

adipocytes, which increased the production of aldosterone in cultured adrenal gland cells. Increased fatty acid production (especially non-esterified fatty acids) from adipose tissue in obese patients might stimulate aldosterone production in the adrenal gland. Metabolic syndrome and the cardiovascular and renal abnormalities associated with insulin resistance are mediated in part by aldosterone activity on the mineralocorticoid receptor (MR). In addition, recent research has shown that aldosterone promotes adipocyte differentiation *in vitro* through specific activation of the MR; a pro-inflammatory role for MR activation in adipose tissue has also been reported (Hirata et al., 2009). Patients with primary hyperaldosteronism (PA) showed differences in glucose metabolism compared with that of essential hypertensive patients; patients with PA have a lower beta-cell function that is influenced by aldosterone levels. This association was initially described in individuals with primary hyperaldosteronism and impaired glucose tolerance (Conn, 1965). Increased plasma aldosterone levels are associated with insulin resistance. It is also of interest that plasma aldosterone levels appeared to be positively correlated with plasma glucose levels in diabetic rat models of our previous study (Han et al., 2006). Aldosterone impairs lipid metabolism and insulin signaling in cardiovascular and renal tissue, as well as in fat, skeletal muscle and the liver (Sowers et al., 2009). Since aldosterone is also associated with glucose metabolism and dyslipidemia, selective aldosterone blockade may represent a particularly attractive therapeutic strategy in obese patients who have a cluster of cardiovascular risk factors.

Recently, a new RAAS inhibitor, direct renin inhibitor (DRI), has been used to manage hypertensive patients. While DRI has been primarily been studied in diabetic nephropathy, its effects have been extended into insulin resistance and metabolic syndrome in animal experiments (Kang et al., 2010a). DRI, which is independent of blood pressure lowering effects, showed a beneficial influence on the diabetic vascular complications of renal and cardiac injury. More importantly, its direct effect on pro-inflammatory molecules, such as MCP-1, TGF-β1, type Ⅳ collagen, PAI-1, and vascular endothelial growth factor (VEGF), may occur in the presence of target organ injury and not via RAAS activation. Additional findings have also revealed that DRI improved lipid parameters and insulin resistance with no effect on blood glucose level in the modulation of lipid metabolism in adipose, hepatic and renal tissues. Therefore, the RAAS inhibitor improved insulin resistance and lipid metabolism via anti-inflammatory actions on adipose tissue and also improved diabetic nephropathy.

2.6 Role of the MCP-1/CCR2 pathway

The kidney has been regarded as a target organ of critical complications in patients with metabolic syndrome, obesity, hypertension, dyslipidemia, and type 2 diabetes mellitus. While its important role in altering energy and glucose metabolism has been reported in patients with chronic kidney disease (Rubenstein et al., 1975), there is also considerable evidence of renal glucose production and utilization in animal models (Drury et al., 1950; Mather and Pollock, 2011; Schoolwerth et al., 1988; Stumvoll et al., 1997). The kidney contributes to glucose homeostasis through gluconeogenesis, glucose filtration, glucose reabsorption, and glucose consumption (Gerich, 2010). The human liver and kidneys release approximately equal amounts of glucose via gluconeogenesis in the post-absorptive state. Traditionally, pharmacotherapeutic interventions have been aimed at stimulating insulin secretion or addressing peripheral insulin resistance. A novel drug class currently being

studied targets another pathophysiological process in the kidney of type 2 diabetes mellitus (Mather & Pollock, 2010; Neumiller et al., 2010). Therefore, the development of glucose-lowering drugs involving inhibition of renal glucose reabsorption, such as the sodium-glucose co-transporter 2 (SGLT2) inhibitor, has recently begun for use in type 2 diabetes mellitus.

The pathophysiology of diabetic nephropathy is multifactorial; it involves metabolic factors including hyperglycemia, genetic factors and hemodynamic factors such as hypertension and glomerular hyperfiltration (Han et al., 2006; Kang & Cha, 2009; Kang et al., 2009). Diabetic nephropathy was initially considered a non-inflammatory glomerular disease, and the inflammatory process has been largely ignored as a mechanism of diabetic nephropathy. However, recent animal and human clinical studies have provided evidence of the important role of inflammation in the development and progression of diabetic nephropathy (Han et al., 2010; Han et al., 2006; Ko et al., 2008). Hyperglycemia induces monocyte/macrophage infiltration in the kidney and contributes to the deposition of fibrotic molecules, which can lead to glomerulosclerosis. Moreover, there is abundant experimental evidence that inhibiting macrophage recruitment or macrophage activation can ameliorate renal inflammation and fibrosis. The MCP-1/C-C chemokine receptor 2 (CCR2) pathway has been reported to be an important mediator for inflammatory glomerular disease. The act of MCP-1 binding to the CCR2 receptor induces infiltration of inflammatory cells and proliferation of resident glomerular cells, such as epithelial and endothelial cells (Kato et al., 1999; Viedt et al., 2002). In addition, glomerular podocytes are the major glomerular cells that express MCP-1 in various proteinuric conditions, including diabetic and membranous nephropathies (Hartner et al., 2005; Prodjosudjadi et al., 1995). Blockade or loss of MCP-1 has been shown to provide renoprotective effects in experimental diabetic nephropathy (Chow et al., 2006; Kanamori et al., 2007), which suggests an influential role of the MCP-1/CCR2 pathway for the inflammatory process in diabetic injury. In addition, urinary MCP-1 excretion is increased in patients with early diabetic nephropathy, and acute-phase markers of inflammation are associated with the nephropathic state in type 2 diabetic patients (Dalla Vestra et al., 2005; Wada et al., 2000). However, CCR2, a seven-transmembrane protein-coupled receptor, is a receptor for MCP-1 and is expressed by monocytes. Local recruitment of monocytes is considered to be the predominant mechanism by which MCP-1 contributes to renal damage.

Many tissues, such as the pancreas, liver, skeletal muscle, heart, and vessels, are adversely affected by obesity (Matsuzawa, 2006). Although multiple molecular mechanisms contribute to the development of obesity-related complications, recent data (Ferrante, 2007) suggest that inflammation, especially that involving monocytes and macrophages, is a central axis in the pathophysiology of many obesity-related disorders. Obesity is accompanied by infiltration and activation of macrophages in adipose tissue, leading to the chronic inflammation of adipose tissue. Adipose tissue has been reported to be an important organ of obesity-induced inflammation as determined by measurement of its expressions of pro-inflammatory molecules (Hotamisligil et al., 1993). Obesity induces phenotypic changes in adipocytes, such as hypertrophy, and also induces an inflammatory response in adipocytes in an autocrine or paracrine fashion, resulting in impaired adipocyte function, including insulin signaling (Hotamisligil et al., 1996).

Several studies have reported that overexpression of MCP-1 causes macrophage recruitment in adipose tissue and insulin resistance (Kamei et al., 2006; Kanda et al., 2006). Adipocytes express CCR2, the primary receptor for MCP-1, which causes the expressions of

inflammatory genes and impaired uptake of insulin-dependent glucose (Charo & Ransohoff, 2006). Obese mice with a CCR2 deficiency have shown improved insulin resistance, attenuated hepatic steatosis, increased adiponectin expression, and reduced macrophage content in adipose tissue when the mice were induced into obesity by a high-fat diet (Weisberg et al., 2006). Several CCR2 antagonists also resulted in decreased macrophage accumulation in adipose tissue with an accompanying improvement in insulin resistance (Kang et al., 2010b; Tamura et al., 2008). These results propose the possibility of an expanded role of the CCR2 genotype in adipose and hepatic tissues against insulin resistance in metabolic syndrome. Therefore, the MCP-1/CCR2 pathway might have an important role in insulin resistance with macrophage infiltration into adipose tissue, leading to systemic inflammatory and metabolic consequences.

Considering that inflammation in both adipose tissue and the kidney has an important role in insulin resistance and metabolic syndrome, common mechanisms between adipose tissue and the kidney should be identified. There may be cross-talk between adipose tissue and the kidney with obesity-induced inflammatory injury in metabolic syndrome, particularly in diabetic nephropathy. We performed mutual epididymal fat transplantation between diabetic and non-diabetic animals to support this hypothesis (Kim et al., 2010). We observed that diabetic db/db mice who received epididymal fat from normal db/m mice showed a significant decrease in urinary albumin excretion. In addition, there was significant improvement in renal pathologic changes, including decreases in TGF-β1, type IV collagen and PAI-1 protein expressions. The beneficial effect of non-diabetic epididymal fat transposition into diabetic animals supports the possibility of this same type of cross-talk in type 2 diabetic nephropathy. Functional and phenotypic changes in adipose tissue in obesity might have an impact on renal function through the various mechanisms of metabolic and hormonal effects, such as the MCP-1/CCR2 pathway and those of numerous adipocytokines.

2.7 Role of the Vitamin D Receptor (VDR)

Vitamin D deficiency is known to be related to cardiovascular disease and chronic kidney disease. Vitamin D improves albuminuria and the progression of renal injury independent of its classic actions (de Zeeuw et al., 2010; Deb et al., 2010; Kang et al., 2010). These animal studies provide rationale for treatment with the vitamin D receptor (VDR) agonist, paricalcitol, in the improvement of type 2 diabetic nephropathy and lipid metabolism. In the present study, there were no differences in the basal characteristics of body weight, fasting plasma glucose, HbA1c, glucose tolerance test, insulin tolerance test, serum creatinine level, or systolic and diastolic blood pressure. However, paricalcitol improved cardiac left ventricular mass index and urinary albumin excretion. Moreover, paricalcitol-treated diabetic mice showed improved plasma lipid profiles of total cholesterol, triglycerides and LDL cholesterol. Interestingly, cholesterol and triglyceride contents in kidney tissue were dramatically decreased by paricalcitol, and a similar result was observed in fat and liver tissues. In addition, plasma and urinary 8-isoprostane levels were markedly inhibited by paricalcitol treatment. Tissue lipid peroxidase (LPO) levels in kidney, fat and liver tissues were significantly improved. Paricalcitol suppressed the pro-inflammatory molecular synthesis and improved the morphological changes in renal glomerulosclerosis, hepatic steatosis and adipose phenotypic change of diabetic mice. The *in vitro* experiment with

cultured VDR-siRNA mesangial cells revealed changes in gene expression and protein synthesis of the enzymes related to the lipid metabolism of fatty acid synthase (FAS), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-Co AR; inducing cholesterol synthesis) and sterol-regulatory element-binding protein-1c (SREBP-1c; inducing cholesterol synthesis). Paricalcitol may have a protective effect on diabetic nephropathy through an improvement of systemic and tissue lipid metabolism and an anti-oxidative effect.

3. Conclusions

The role of the kidney is not only as a target organ during the development of obesity and metabolic syndrome, but also as a regulatory organ that cross-talks with adipose tissue. A large body of evidence has demonstrated that various adipocytokines, RAAS and VDR of the kidney and adipose tissue are associated with one another; alterations of these substances can lead to many complications of metabolic syndrome that develop from obesity-induced inflammation. Eventually, the improvement of insulin resistance through an anti-inflammatory effect on adipose tissue could result in the improvement of diabetic nephropathy, which decreases cardiovascular complications in metabolic syndrome. A better understanding of adipose tissue biology will help researchers develop a new therapeutic strategy to manage metabolic syndrome, including diabetic vascular complications. Future studies should focus on the aforementioned potential targets to improve insulin resistance as well as diabetic nephropathy.

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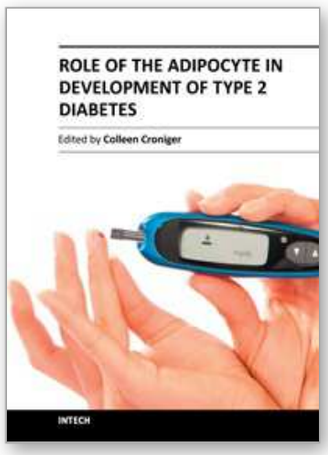

Role of the Adipocyte in Development of Type 2 Diabetes

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Adipocytes are important in the body for maintaining proper energy balance by storing excess energy as triglycerides. However, efforts of the last decade have identified several molecules that are secreted from adipocytes, such as leptin, which are involved in signaling between tissues and organs. These adipokines are important in overall regulation of energy metabolism and can regulate body composition as well as glucose homeostasis. Excess lipid storage in tissues other than adipose can result in development of diabetes and nonalcoholic fatty liver disease (NAFLD). In this book we review the role of adipocytes in development of insulin resistance, type 2 diabetes and NAFLD. Because type 2 diabetes has been suggested to be a disease of inflammation we included several chapters on the mechanism of inflammation modulating organ injury. Finally, we conclude with a review on exercise and nutrient regulation for the treatment of type 2 diabetes and its co-morbidities.

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