The Role of Visfatin in Diabetic Nephropathy

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As a result of the energy overload in obesity, insulin resistance, type 2 diabetes, dyslipidemia, hypertension, and atherosclerosis develop, which together comprise the metabolic syndrome. Although the kidney becomes a victim of hyperglycemia in diabetes mellitus, recent work has shown that the abnormalities of lipid and glucose metabolism in the kidney are similarly important to those in adipose tissue. Interestingly, obesity triggers the release of adipokines such as leptin, resistin, and visfatin, and these can then be associated with the progression of diabetic nephropathy and other vascular complications. These adipokines, which are also synthesized in the kidney, appear to have an important role in renal injury associated with insulin resistance. Our studies found that visfatin is not only a surrogate marker of systemic inflammation in type 2 diabetic patients but is also up-regulated in diabetic kidney through the uptake of glucose into renal cells, which leads to the activation of the intracellular insulin signaling pathway and pro-inflammatory mechanisms. However, we also observed a beneficial effect of visfatin administration to type 2 diabetic mice. Visfatin injection improved diabetic nephropathy *in vivo*, in contrast to our previous *in vitro* study of cultured renal mesangial cells. These results suggest the possibility of multiple cross-talk between adipose tissue and kidney in the metabolic syndrome, particularly in diabetic nephropathy. Further study should be undertaken to understand the role of adipose tissue and kidney as major organs in the metabolic syndrome.

Key Words: *Nicotinamide phosphoribosyltransferase; Diabetic nephropathy*

INTRODUCTION

The kidney is a major target organ in the metabolic syndrome, such as in diabetes mellitus. Although the kidney becomes a victim of hyperglycemia, its central role in glucose metabolism and insulin resistance has not been identified. However, it was recently considered that the kidney plays an important role in glucose metabolism, and there are frequently abnormalities in glucose metabolism in patients with chronic kidney disease.[1] There is also considerable evidence from animal studies for renal glucose production and utilization.[2-4] The roles of the kidney in glucose metabolism and energy homeostasis have recently been discussed under the development of new antidiabetic drugs.[5,6]

Recent studies have shown that adipose tissue is a highly metabolic organ with pleuripotent functions far beyond the mere storage of energy. Adipose tissue is now known to be an endocrine organ that secretes a large number of bioactive proteins, called adipokines, that have essential roles in energy homeostasis, glucose and lipid metabolism, insulin resistance, inflammation, and atherosclerosis.[7,8] These include several active molecules released by adipocytes, such as leptin, resistin, and adiponectin, as well as cytokines released by inflammatory cells, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, macrophage/ monocyte chemoattractant protein (MCP)-1, and interleukin (IL)-1. Interestingly, the circulating levels of these adipokines have been found to be altered in experimental animals and patients with chronic kidney disease, which is an independent risk factor of cardiovascular mortality. Furthermore, their production, secretion, and regulatory actions are not limited to adipose tissue, but are described in other organ tissues as well. For example, it is now recognized that the kidney itself can alter the clearance of adipokines and produce them.

Among these adipokines, visfatin is a ubiquitous intra-

cellular enzyme, also called nicotinamide phosphoribosyltransferase (NAMPT)/pre-B cell colony-enhancing factor (PBEF)-1. It was originally characterized from lymphocytes, and its enzymatic biochemical basis and structure have been established.[9-11] NAMPT constitutes a nuclear nicotinamide adenine dinucleotide (NAD⁺) salvage/recycling pathway, which regulates the functions of NAD⁺-dependent enzymes, such as the protein deacetylase sirtulin (SIRT)-1.[12] NAMPT, a unique rate-limiting enzyme encoded by a single gene, catalyzes the conversion of nicotinamide (NAM) to nicotinamide mononucleotide (NMN), which in turn is converted into NAD⁺ by nicotinamide mononucleotide adenylyltransferase (NMNAT)-1. NAD⁺ is an important signaling molecule and a coenzyme in metabolic processes and redox reactions; it is consumed as a donor of ADP-ribose with the release of NAM as a byproduct. NAMPT has been proved as a critical NAD biosynthetic enzyme that regulates the activity of SIRT-1 in mammalian cells.[11] Finally, SIRT-1 and NAMPT-mediated systemic NAD⁺ biosynthesis together play an important regulatory role in glucose homeostasis, particularly in the glucose-stimulated insulin secretion of pancrease in the pathophysiology of type 2 diabetes.[13] The insulin-mimetic effect of NAMPT, referred to as visfatin, has recently been studied in obesity and type 2 diabetes mellitus. In this review, the role of visfatin in diabetic nephropathy will be summarized and discussed.

VISFATIN IN DIABETIC NEPHROPATHY

1. The role of visfatin as an adipokine

Visfatin is increased in inflammatory conditions such as acute lung injury, sepsis, and rheumatoid arthritis.[14-16] Thus, it is considered to be a proinflammatory adipokine via either a compensatory response or an epiphenomenon. Of note, visfatin was recently reported to be expressed almost exclusively in visceral adipose tissue rather than subcutaneous adipose tissue. Adipokines, which are secreted by adipocyte tissue, have been studied in association with insulin resistance and the metabolic syndrome, including obesity, glucose intolerance, and dyslipidemia.

However, studies of visfatin in human populations have obtained conflicting results. Elevated plasma visfatin levels have been reported in patients with type 2 diabetes mellitus.[17-20] On the other hand, other investigative results showed decreased plasma visfatin levels in patients with type 1 diabetes, liver cirrhosis, exercise in type 2 diabetes, and 3rd trimester gestational diabetes.[21-25] Elevated visfatin levels were also shown in hemodialysis patients[26,27] and a positive correlation of visfatin levels with all stages of chronic kidney disease was observed.[28] Yilmaz et al.[29] published that visfatin levels were positively associated not only with insulin resistance but also with the degree of albuminuria in type 2 diabetic patients. They suggested that the endothelial dysfunction in early diabetic nephropathy is associated with altered circulating levels of visfatin. However, in another experimental study, visfatin was shown to activate endothelial nitric oxide synthase (eNOS) via Akt and mi-

togen-activated protein (MAP) kinase and MCP-1 and improve endothelial cell function, angiogenesis, and atherosclerosis.[30,31] Thus, controversy exists among clinical studies and experimental data for the role of visfatin in diabetic nephropathy. Whether this phenomenon primarily arises from direct vascular defects or is secondary to the presence of visceral obesity and a deranged metabolic milieu that is characteristic of many patients with diabetes remains unclear.

Consistent with several reports, we observed that plasma visfatin levels were elevated in patients and animals with type 2 diabetic nephropathy.[32,33] Interestingly, in our *in vitro* study,[34] visfatin was synthesized in renal glomerular mesangial cells, upregulated by high glucose stimulation. In addition, exogenous visfatin stimulation in renal cells upregulated the synthesis of profibrotic molecules, including transforming growth factor (TGF)-β1, plasminogen activator inhibitor (PAI)-1, and type I collagen. Given these findings, the pathophysiologic relevance of visfatin seems to be as a proinflammatory adipokine regarding type 2 diabetes and other metabolic complications.

2. The insulin-mimic effect of visfatin

Despite the insulin-mimic effect of visfatin, controversy exists over its role insulin resistance. The exciting paper of Fukuhara et al., which had described the insulin-mimetic effect of visfatin and its naming, has been finally retracted. Several studies failed to show an association of circulating visfatin with insulin sensitivity.[19,35-37] There has been no report of whether the relation between visfatin and insulin is synergistic. However, it is still interesting whether visfatin binds directly to the insulin receptor at a site distinct from insulin and has hypoglycemic effects by reducing glucose release from hepatocytes and stimulating glucose utilization in peripheral tissue.[38] Insulin receptor expression has been ascertained in renal cells such as proximal tubular cells, mesangial cells, and podocytes. However, the affinity of visfatin for the insulin receptor and other receptors such as insulin-like growth factor receptor and insulin-receptor like receptor is unclear. In fact, insulin also binds with low affinity to insulin-like growth factor receptor and insulin-receptor like receptor in kidney. A recent study reported that insulin receptor expression was shown to be reduced in the kidney of an insulin-resistant rat animal model.[39] Despite a high plasma insulin level, decreased insulin receptor expression has been explained to correlate with insulin resistance in various tissues such as liver, skeletal muscle, and adipose tissue. However, this finding in the kidney can be different among renal cells and may be distinct depending on the organ type, i.e., whether liver, skeletal muscle, or adipose tissue. On the other hand, another study suggested that visfatin does not have insulin-mimetic actions but rather has a regulatory role in glucose-stimulated insulin secretion in pancreatic β-cells *in vitro* and *in vivo*.[40] Those authors demonstrated that mice lacking visfatin synthesis develop impaired glucose tolerance and defective insulin secretion, which are restored by admin-

istration of visfatin. Taken together, these results suggest that visfatin may act as a multiplayer in either a cell- or tissue-dependent manner.

Interestingly, in our *in vitro* study,[34] high glucose stimulation upregulated visfatin synthesis and then visfatin stimulated glucose uptake via the glucose transporter (GLUT)-1 in renal mesangial cells. However, angiotensin ll stimulation did not induce visfatin synthesis. We found that exogenous visfatin stimulation in renal mesangial cells upregulated the insulin signaling pathway and induced synthesis of its downstream components of profibrotic molecules.

In contrast, another study published data indicating that life span extension in mice is associated with reduced insulin receptor signaling cascade, which upregulates the expression of SIRT-1 proteins.[41] Therefore, there could be possible cross-talk between the visfatin-mediated and insulin signaling pathways via various physiologic mechanisms.[42]

3. Visfatin as a nicotinamide adenine dinucleotide (NAD) biosynthetic enzyme

Recent studies have shown that disturbances in the circadian clock feedback cycle through NAMPT/visfatin-mediated NAD^+ biosynthesis may cause an imbalance in energy metabolism and homeostasis.[13] Other data showed that this optimizing of SIRT1-mediated p53 degradation by visfatin induces the extension of human cell life span, such as smooth muscle cells, and the resistance to oxidative stress.[43] If visfatin is impaired in the aging-dependent circadian cycle and this leads to the decline of pancreatic cell function in type 2 diabetes, visfatin could be an effective target for the treatment and prevention of type 2 diabetes.

Furthermore, a recent study suggested that angiotensin ll plays a role in the prolongation of the life span in mice.[44] Agtr1a-/- mice developed a longevity phenotype and upregulation of visfatin expression in the kidney. Although high glucose stimulation induces renal cell visfatin synthesis and intracellular glucose transport, which leads to increased pro-fibrotic molecular expression as demonstrated in our previous *in vitro* study,[34] angiotensin ll did not induce visfatin synthesis and mice lacking angiotensin receptor expressed visfatin upregulation. Taken together, these data suggest that visfatin may have multiple actions in the kidney, even in the regulation of NAD-consuming enzymes such as sirtuins. In fact, we examined the effect of intraperitoneal visfatin administration on diabetic nephropathy in mice. In our *in vivo* study, visfatin had a protective effect on the albuminuria of diabetic nephropathy in mice (data not published). Exogenous visfatin infusion did not show a large glucose-lowering effect through glucose uptake into renal cells. Besides, the plasma visfatin concentration is much lower than the insulin concentration, although the affinity of visfatin for the insulin receptor appears to be similar to that of insulin.[45] Although high glucose stimulates intrarenal cellular visfatin synthesis, and then glucose taken up by renal cells activates the intracellular signaling pathway leading to injury in diabetic nephropathy,

plasma visfatin elevated by autocrine action may act via a different regulatory pathway. The enzymatic and functional role of visfatin remains unknown in the kidney.[42] Therefore, visfatin has a compensatory effect via both autocrine and paracrine pathways to improve insulin resistance and lipid metabolism. Particularly, one study showed that long-term visfatin infusion does not decrease the abundance of insulin receptors in the kidney of insulin-resistant rats, which is different in other tissues, such as liver, skeletal muscle, and adipose tissue.[39] It is also possible that a more physiologic route of intraperitoneal visfatin injection may have benefit compared with vascular infusion, which is directly accumulated in the liver and visceral adipose tissue, which are the main organs regulating lipid and glucose metabolism, before sufficient concentration levels are reached in the systemic circulation of plasma, heart, and kidney. In addition, an unknown receptor for visfatin may exist, which could indirectly affect the insulin signaling pathway. For example, the enzymatic regulatory action of NAMPT/visfatin-mediated NAD synthesis might have a major effect on diabetic nephropathy through a different pathway. Nonetheless, it is equally possible that differences in the models of insulin resistance studied may have accounted for this seeming discrepancy.

CONCLUSION

Controversy remains concerning the pleiotropic roles of visfatin, although its enzymatic regulatory functions have already been identified with energy metabolism. The interesting point is that visfatin appears to act as a multiplayer adipokine in inflammation, obesity, the metabolic syndrome, and cardiovascular disease, including diabetic nephropathy. Particularly in humans and animals with type 2 diabetic nephropathy, the results of several studies suggest that visfatin could be a surrogate marker. On the other hand, its direct administration might be beneficial or harmful depending on species, organs, and cell types. There is no doubt about its different effects on various diseases. Therefore, further studies need to be performed to clarify the effects of visfatin on cellular metabolism and physiology, ultimately leading to adjustments of therapeutic strategies for metabolic and other diseases in humans.

DISCLOSURES

None.

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