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**The role of endothelial dysfunction driven by adipocytokines in the development and progression of microvascular complications in patients with type 1 and type 2 diabetes**

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## Abstract

Micro and macrovascular complications are the leading cause of morbidity and mortality in diabetic patients. During the last decades attention has been focused on their early diagnosis and prevention. Diabetes related metabolic abnormalities: insulin resistance, hyperglycaemia and dyslipidaemia along with oxidative stress and low- grade inflammation contribute to the development of endothelial dysfunction and macrovascular complications. Recent investigations indicate a potential role of adipocytokines originating from visceral adipose tissue: adiponectin, leptin, resistin and dipeptidyl peptidase- 4 (DPP-4) activity in the development of microvascular complications in diabetes. The association of these adipocytokines with the activity of endothelial synthetase (eNOS) involved into the metabolism of nitric oxide (NO) was documented in animal and cell culture studies. We hypothesize that lower adiponectin and higher leptin and resistin plasma concentration and DPP-4 activity are associated with the development and progression of diabetic microvascular complications by endothelial function impairment.

A possible identification of new markers of the complex pathophysiology development and progression of microvascular complications in diabetes will contribute to improved diagnosis followed by an individualized patients approach.

## **Background**

The estimated prevalence of diabetes mellitus (DM) is currently about 382 million, or 8.3% of the world population aged 20-79 years (1). Due to the high impact on morbidity and mortality the prevention and early diagnosis of diabetic vascular complications is in the focus of scientific and professional interest. Diabetic retinopathy is the leading cause of blindness (2), diabetic nephropathy is the most important cause of renal failure (3), and macrovascular complications are the leading cause of death in more than two-thirds of diabetic patients (4). Endothelial cell dysfunction (ECD) is pathophysiologically related to all vascular complications of diabetes (5). Reduced bioavailability of nitric oxide (NO) (6) indirectly contributes to metabolic disorders of diabetes: hyperglycaemia and dyslipidaemia along with oxidative stress and low grade inflammation in the microvascular complications development (7).

Visceral adipose tissue represents a hormonally active organ by secreting various adipocytokines implicated in the regulation of metabolic homeostasis (8). Studies demonstrating the effects of insulin resistance (IR) related adipocytokines: adiponectin, leptin, resistin and dipeptidyl peptidase-4 (DPP4) on endothelial NO sintetase (eNOS) have implicated their possible contribution to the development and progression of microvascular complications independently of traditional risk factors. However, their association with retinopathy, nephropathy and neuropathy through modulation of endothelial physiology has not been extensively studied.

## **The hypothesis**

We hypothesis that lower plasma concentration of adiponectin, while higher concentration of leptin, resistin and serum DPP4 activity contribute to the development and progression of diabetic microvascular complications through endothelial function impairment. Insulin

resistance (IR) contributes directly to the development of ECD modulating the activity of eNOS (9) and impairing other metabolic processes in diabetes (10). Prospective clinical studies have shown that abnormalities associated with ECD were causally related with the development and progression of microvascular complications in DM (11-13). Stehouwer et al. (2012) in longitudinal study in 328 patients with type 2 diabetes (T2DM) has shown that the level of ECD was associated with progression of nephropathy both in relation to and independently of traditional risk factors (14). The results of cross-sectional studies in patients with type 1 diabetes (T1DM) have also indicated that ECD might be more strongly associated with the development of microvascular complications in comparison with traditional risk factors (15). For that reason it seems to be of special scientific and clinical interest to investigate for new ECD related risk factors associated with the development and progression of microvascular complications in diabetes.

### **Evaluation of the hypothesis**

Leptin is the oldest known adipocytokine (16). A higher plasma concentration of leptin is associated with the development and progression of microvascular complications in patients with T2DM (17-19). At the molecular level the effect of leptin on endothelial function is unclear as leptin both stimulates the activity of eNOS and reduces the bioavailability of L-arginine required for NO synthesis (20-22). In addition, the results of studies exploring the relationship between leptin and microvascular complications in patients with T1DM are controversial (23).

Adiponectin is the most extensively studied adipocytokine in the context of their association with microvascular complications in diabetes. In T2DM plasma concentration is inversely associated with retinopathy (25) and urinary albumin excretion rate (UAE), an early marker of renal microvasculature (26). However, in T1DM the relation of adiponectin with retinopathy,

albuminuria and nephropathy is not fully understood (20,29-31). In some studies a positive correlation of adiponectin with retinopathy and albuminuria in T1DM was found (29, 30). In animal and cell culture studies adiponectin increased the bioavailability of NO directly, stimulating eNOS, and indirectly, by reducing the concentration of superoxide products (27-29). Sharma et al. (2008) have shown in an animal model of T1DM that the retraction of podocyte cells representing the primary changes in diabetic nephropathy correlated with the superoxide concentrations (32). To explain elevated concentrations of adiponectin in patients with T1DM and microvascular complications the author hypothesized that an increase in adiponectin level might represent a protective mechanism aimed to suppress superoxide effects on eNOS (31, 33).

An elevated plasma concentration of resistin was also found in T1DM and T2DM. Its effect on IR is thought to be mediated through proinflammatory activity (34). The association of resistin with the prevalence of microvascular complications has not been extensively investigated. Azab et al. (2012) (35) have recently demonstrated in 30 patients with T2DM that resistin concentrations were associated with retinopathy. This is in support to the results of Osawa et al. (2007) who previously showed resistin relations with all microvascular complications in T2DM (37). However, other studies have not confirmed their results (36). It was not clarified whether resistin effect on inhibition of eNOS activity (37) and the development and progression of microvascular complications is independent of low-grade inflammation and IR (38).

The results of recent experimental studies suggest an increased expression of DPP-4 in adipocytes of visceral fat and increased serum enzymes in patients with IR and T2DM (39, 40). In vitro studies also suggest a possible link between DPP4 activity and renovascular protective effect (41, 42). However, the role of the serum DPP-4 enzyme in the pathogenesis of chronic microvascular complications in diabetes has not been systematically investigated.

Inhibition of DPP4 activity leads to increased eNOS activity, although it is not clear whether this represents a direct effect of DPP4 activity (43-45).

## **Conclusion**

We hypothesize that lower plasma concentration of adiponectin, while higher concentration of leptin, resistin and serum DPP4 activity contribute to the development and progression of diabetic microvascular complications mediating endothelial function impairment. Our assumption represents the first interdisciplinary approach in order to clarify the complex pathogenesis of microvascular complications in diabetes. This novel approach aims to acquire the development of an individualized approach to diagnosis, prevention and treatment of diabetes related vascular complications.

Conflict of interest

None declared.

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