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# THE PROGRESSION OF DIABETIC MICROVASCULAR COMPLICATIONS AND INCREASED VASCULAR STIFFNESS

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## Abstract

*In patients with type 2 diabetes mellitus it might be helpful to use, for risk stratification, non-invasive techniques as markers of early atherosclerosis. Arterial stiffness shows the functional vascular properties and can be estimated by pulse wave velocity (PWV) and augmentation index (AIX). Typical for type 2 diabetes is premature arterial stiffening which appears before the onset of clinically micro or macrovascular disease and is increased in the presence of microvascular complications. Further studies are needed to determine whether therapeutic interventions for reducing vascular stiffness may decrease the cardiovascular mortality in patients with type 2 diabetes.*

**key words**: *type 2 diabetes, arterial stiffness, chronic complications*

### Background and Aims

Cardiovascular disease remains the leading cause of mortality in patients with type 2 diabetes mellitus. Non-invasive techniques used as markers of atherosclerosis may be helpful for risk stratification in patients with type 2 diabetes. It is already known that vascular stiffness is modified before the onset of diabetes. Therefore, the vascular tools which estimate arterial stiffness could be useful in identifying the high risk patients in the early stages of atherosclerosis [1].

Arterial stiffness shows the functional vascular properties and can be estimated by surrogate markers as pulse wave velocity (PWV) and also by augmentation index (AIX). PWV is the velocity of the pulse wave through the arterial tree. PWV increases with stiffness and gradually with age. AIX is the augmentation of aortic pressure expressed as percentage of pulse pressure. The reproducibility of PWV is higher than that of AIX, therefore it is the most accepted method for estimating vascular stiffness. PWV has been shown also to predict cardiovascular mortality [2]. A number of studies have investigated the effects of age on aortic PWV and AIX. Changes in AIX were more pronounced in younger subjects (<50 years), whereas the changes in aortic PWV were more marked in those older than 50 years. Therefore, central AIX might be a more sensitive marker of arterial aging in younger individuals and aortic PWV is more sensitive in those over 50 years of age [2].

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Usually, insulin resistance appears before the onset of type 2 diabetes and can be often accompanied by different risk factors. Some studies have suggested that higher vascular stiffness could be a feature of insulin resistance [1]. A positive relationship between insulin-mediated glucose uptake and vascular distension was observed in healthy subjects. This effect was more pronounced in women. An inverse correlation between insulin sensitivity and arterial stiffness in the carotid and also in the femoral arteries were observed in a diabetic population [1]. Impaired glucose tolerance and impaired insulin sensitivity have been associated with increased arterial stiffness measured by the distension of the common carotid artery [3]. Therefore, premature arterial stiffening is typical for type 2 diabetes. Regarding sex differences, it was observed that type 2 diabetes is associated with a greater age-related stiffening of the aorta in women compared with men [2].

Some strong evidence supports the theory of higher vascular stiffness as an early phenomenon which appears before onset of clinically micro-or macrovascular disease in diabetes and is increased in the presence of microvascular complications such as diabetic renal disease or retinopathy. The arterial stiffness is more age-related increased in patients with type 2 diabetes than in those without, and the increases are amplified in the presence of microvascular complications [1].

Various studies have shown that patients with diabetes have higher vascular stiffness compared with healthy subjects, starting from the age of 20 years [2]. It is also known that PWV increases with age both in females and males. Also the frequency of chronic complications increases with duration of diabetes.

In order to established in the future some therapeutic strategies that lead to slowing the progression of chronic complications, the purpose of this review is to analyze the pathophysiological implications of arterial stiffness inducing diabetic microvascular complications.

**Diabetic peripheral neuropathy**

Diabetic peripheral neuropathy (DPN) is a common microvascular complication with high mortality rates. A recent Korean study [4] investigated the association between DPN and vascular wall properties in patients with type 2 diabetes by measuring cardio-ankle vascular index (CAVI) and carotid intima–media thickness (IMT). Subjects with DPN were older, had a longer duration of diabetes, had higher systolic blood and pulse pressure and were more likely to have albuminuria and retinopathy than subjects without neuropathy. In the same time, subjects with DPN had a lower glomerular filtration rate, HDL cholesterol level, and body mass index (BMI). After adjusting for age, sex, diabetes duration, BMI, $HbA_{1c}$, pulse pressure, glomerular filtration rate, hyperlipidemia, autonomic neuropathy and use of insulin or antihypertensive drugs, CAVI was significantly higher in subjects with DPN than in subjects without DPN. In multivariate logistic regression models, CAVI was also a significant predictor of DPN. After further adjusting for other microvascular complications, DPN remained a significant determinant of abnormal CAVI [4].

Another study by Cardoso et al. [5], conducted on 482 patients with type 2 diabetes, also demonstrated a close relationship between DPN and vascular stiffness. The significant association between DPN and increased CAVI observed in this study suggests that determinants of cardiovascular disease affecting arterial stiffness may be potential risk factors for DPN. Accordingly, prospective cohort studies have demonstrated that cardiovascular risk factors

predict the development of DPN in patients with type 1 diabetes [6]. Although the mechanism linking DPN to arterial stiffness is not well estabilished, one possible explanation is that large artery stiffness may cause microvascular damage through high pulse pressure, leading to diminished blood flow to nerve tissues vulnerable to hypoxic damage, and thereby to the development of neuropathy [6].

**Diabetic retinopathy**

Several studies have shown that diabetic retinopathy is associated with the atherosclerotic end points, but most of these have looked at the end stages of atherosclerotic process. Since the clock for atherosclerosis starts ticking even before the onset of diabetes, it was of interest to study whether structural changes, such as carotid intima-media thickness (IMT) and functional changes, such as arterial stiffness, are associated with diabetic retinopathy.

An Indian study [7] showed that carotid IMT had a strong association with diabetic retinopathy even after adjusting for age, duration of diabetes, and $HbA_{1c}$ in a group of type 2 diabetes patients. Arterial stiffness, estimated by AIX pulse-wave analysis, has been shown to have good correlation with cardiovascular end points. In this study the mean AIX was higher in subjects with diabetic retinopathy compared to those without. This was the first study to demonstrate an association of diabetic retinopathy with functional change in arteries as measured by arterial stiffness in a population-based study of Asian Indians, a high-risk group for coronary artery disease. In the same study, patients who received laser photocoagulation for advanced forms of retinopathy had a higher vascular stiffness, compared with those in the early stages of retinopathy [7].

Also regarding retinopathy, the purpose of a recent Korean [8] study was to determine the association between macroangiopathy expressed by Common Carotid Artery Intima-Media Thickness (CCA-IMT), brachial-ankle PWV (baPWV), carotid plaque, peripheral arterial disease (PAD) and diabetic retinopathy. BaPWV was significantly associated with diabetic retinopathy, whereas CCA-IMT, carotid plaque, and PAD were not [8].

In a Japanese cross-sectional study [9] in which the purpose was to investigate the association between arterial stiffness (using PWV) and diabetic retinopathy in patients with type 2 diabetes, it was observed that PWV, duration of diabetes, systolic blood pressure and hemoglobin A1c level were all significantly higher in patients with diabetic retinopathy than in patients without this disorder. The association between brachial-ankle PWV and diabetic retinopathy remained significant after statistical adjustments, suggesting that PWV might be a marker of vascular injury caused by chronic hyperglycemia [9].

Although several studies have reported that PWV is associated with diabetic retinopathy, it remains controversial as to which artery segment provides the PWV that might best reflect the presence of retinopathy. A recent Koreean paper [10] found that diabetic retinopathy was most closely associated with the heart-femoral PWV, suggesting that this is the most reliable index of regional arterial stiffness index in retinopathy [10].

**Diabetic chronic kidney disease**

Arterial stiffness also increases in patients with diabetic chronic kidney disease (CKD) and PWV is a strong and independent marker of mortality in these patients [11]. Arterial stiffness in chronic kidney disease is based on several mechanisms. Increased intima-media thickness occurs due to arterial wall response to higher stress in context of arterial hypertension [11].

The increase in collagen content of the extracellular matrix and vascular smooth muscle cell proliferation is determined by local and systemic activation of the renin - angiotensin system. In addition, elasticity of the collagen in the extracellular matrix is low, in response to non-enzymatic glycosylation of proteins which are increased in uremic patients. Arterial stiffness in chronic kidney disease is also caused by diffuse calcifications of the vascular wall. Such calcification is accompanied by minimal inflammation, but the histological aspect is different from that in the common atherosclerosis process [12].

Increased arterial stiffening plays an important role in the etiology of cardiovascular disease in CKD. The strong association between arterial stiffening and mortality in end stage of renal disease was demonstrated over 10 years ago. This process appears to begin during early stages of CKD but the prognostic value of vascular stiffness in this group remains unproven [12].

Potential mediators of cardiovascular disease and kidney disease include disordered bone mineral metabolism and vascular calcification [13]. Thus, several studies shown that disordered bone mineral metabolism was linked to vascular stiffness [13]. Recent work has also highlighted the importance of aldosterone in the etiology of arterial stiffness in CKD [12].

A study of 133 patients with stages III-IV of CKD demonstrated PWV to be a predictor of decline in renal function [14]. However, a larger study of 235 patients with CKD and longer follow-up failed to show an association between PWV and progression of CKD [15].

The different results obtained in these studies highlight the lack of consistent data describing the natural history of the relationship between arterial stiffness and kidney disease and in particular the complex interactions between age, uraemia, blood pressure and medication in patients with CKD [16].

## Conclusions

There is an obvious correlation between arterial stiffness and chronic diabetic complications. Further studies are needed to determine whether therapeutic interventions on reducing vascular stiffness may decrease the cardiovascular mortality in patients with type 2 diabetes mellitus.

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