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Review

Arterial stiffness in diabetes mellitus

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ABSTRACT

Arterial stiffness is an age-related process that is a shared consequence of numerous diseases including diabetes mellitus (DM), and is an independent predictor of mortality both in this population and in the general population. While much has been published about arterial stiffness in patients with DM, a thorough review of the current literature is lacking. Using a systematic literature search strategy, we aimed to summarize our current understanding related to arterial stiffness in DM. We review key studies demonstrating that, among patients with established DM, arterial stiffness is closely related to the progression of complications of DM, including nephropathy, retinopathy, and neuropathy. It is also becoming clear that arterial stiffness can be increased even in pre-diabetic populations with impaired glucose tolerance, and in those with the metabolic syndrome (METS), well before the onset of overt DM. Some data suggests that arterial stiffness can predict the onset of DM. However, future work is needed to further clarify whether large artery stiffness and the pulsatile hemodynamic changes that accompany it are involved in the pathogenesis of DM, and whether interventions targeting arterial stiffness are associated with improved clinical outcomes in DM. We also review of the potential mechanisms of arterial stiffness in DM, with particular emphasis on the role of advanced glycation endproducts (AGEs) and nitric oxide dysregulation, and address potential future directions for research.

Contents

1. Background

Arterial stiffness is an age-related progressive process that is a shared consequence of numerous diseases including diabetes

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mellitus (DM), hypertension, the metabolic syndrome (METS) and chronic kidney disease (CKD), among others. DM is as an increasingly prevalent disease with well-recognized short and long-term cardiovascular consequences. In this paper, we discuss recent findings from clinical and population-based studies assessing arterial stiffness in diabetic cohorts. There is a particular emphasis on the impact of arterial stiffening on microvascular and macrovascular complications of the disease. We additionally review the pathophysiologic basis of arterial stiffness in DM and discuss the outcomes of interventions targeting these processes.

2. Methods

We searched Medline (from 1946 to 2013) and Embase (from 1947 to 2013) databases, using detailed search strategies, as detailed in the online supplement. We developed search methods to capture publications related to arterial stiffness and DM, AGEs, and microvascular complications of DM. This search generated 1700 articles and abstracts which were reviewed in their entirety and discussed by the authors to establish their relevance to this review. When appropriate, we discuss major contributions to the field in text, and use tables to summarize individual studies. This review focuses on conceptual syntheses of data, rather than detailed descriptions of original research.

3. Human studies of DM and arterial stiffness

Arterial stiffness represents a subclinical marker of cardiovascular risk. Arterial stiffness has been shown to be an independent risk factor for adverse cardiovascular events and all-cause mortality in the general population [1]. Markers of large artery stiffness such as pulse pressure (PP), pulse wave velocity (PWV), and aortic characteristic impedance (Zc), have been widely studied over the past two decades. With improvements in techniques to non-invasively measure these hemodynamic parameters, the literature relating arterial stiffness and pulsatile hemodynamics to various disease states has grown significantly. Table 1 provides a brief summary of common indices of arterial stiffness and related pulsatile hemodynamics. Most of these indices are based on either: (1) the velocity of pulse transmission time between 2 arterial points (i.e., PWV, which is considered the non-invasive "gold standard" measurement of arterial stiffness) or (2) aortic distensability. In addition, indices of wave reflections (such as augmentation index or reflection magnitude) are commonly reported in studies of arterial stiffness. Augmentation index is a composite measure of wave reflections and arterial stiffness.

3.1. Arterial stiffness in prediabetic states and the metabolic syndrome

In this section we summarize the major studies that assessed arterial stiffness in patients with "pre-diabetes" i.e., impaired glucose tolerance (IGT), insulin resistance, as well as patients with the metabolic syndrome. Studies assessing the relationship between arterial stiffness and/or related hemodynamic indices in impaired glucose tolerance, insulin resistance, the metabolic syndrome, and DM are summarized in Table 2.

There is recent increasing evidence that, even before the onset of DM, signs of abnormal arterial stiffness are evident in patients with pre-diabetic states including impaired fasting glucose, glucose intolerance, and insulin resistance. Numerous studies have examined the impact of these states on vascular function. The Hoorn study, a large population based-cohort study of nearly 2500 subjects in the Netherlands, showed that after adjusting for age and blood pressure (BP), impaired fasting glucose (IFG) was associated with increased arterial stiffness that was intermediate between that of normal controls and patients with type 2 DM [2]. In another study of 232 previously healthy Japanese adults, brachial-ankle PWV was shown to increase linearly with increasing fasting blood glucose and hemoglobin A1C, and to increase stepwise in patients with normal, IFG, and DM respectively [3]. Interestingly, it has been demonstrated that even within the normal glucose range, stepwise increases in fasting glucose from 65 mg/dL to 100 mg/dL were associated with increased arterial stiffness in 697 patients without DM [4]. Most recently, among 872 adults with normal glucose tolerance, insulin resistance was independently associated with increased brachial-ankle PWV [5]. This suggests that even early insulin resistance that develops prior to impairment in glucose tolerance is associated with arterial stiffness.

However, the finding of increased arterial stiffness in "prediabetes" has not been universal. A recent large study in 1927 middle-aged men and women (Asklepios cohort) suggested that after controlling for age, sex and mean arterial pressure (MAP), IFG was not associated with intrinsic arterial stiffness [6]. Other studies have shown conflicting results. Li et al. showed that in a large study of 4938 patients, subjects with IGT, but not isolated IFG, exhibit increased arterial stiffness compared to normal controls [7]. Accordingly, the relationship between insulin resistance, IGT, and arterial stiffness requires more investigation and longitudinal studies.

Increased arterial stiffness has also been associated with the METS. As part of the Bogalusa Heart study, Li et al. examined arterial stiffness in 806 asymptomatic adults between 22 and 44 years of age. Brachial-ankle PWV increased significantly with the increasing number of METS components. Furthermore, the rate of change

Table 1
Key definitions related to arterial stiffness.

Index	Definition
Arterial pulse wave velocity (PWV)	Velocity with which the pulse wave travels throughout the arterial tree and a measure of arterial stiffness. PWV is proportional to the square root of the incremental elastic modulus of the vessel wall (a measure of the stiffness of the wall material, see below), given constant ratio of wall thickness to vessel radius.
Characteristic impedance (Zc)	Impedance to pulsatile flow imparted by a specific arterial segment. It is a *local* arterial property influenced by wall stiffness and thickness, but also strongly influenced by vessel size.
Compliance	Change in arterial volume relative to the change in arterial pressure.
Distensibility	Fractional (relative) change in arterial volume relative to the change in arterial pressure. In our study, it was assessed via the distensibility coefficient, which is the fractional (relative) change in arterial cross-sectional area relative to the change in arterial pressure.
Incremental elastic modulus (E_{inc})	Measure of wall material stiffness. It is defined as the local slope of the incremental change in circumferential stress and the incremental change in circumferential length (strain) of the wall material at the operating range of stress and strain. It is not measured directly *in vivo*, but can be inferred from measurements of PWV, Zc or compliance when the diameter and wall thickness of the vessel are known.
Ascending aortic Zc	Proximal aortic property that determines the amount of proximal aortic pressure increase for any given flow increase during early systole. It is an important determinant of aortic pulse pressure.
Total arterial compliance	Summed compliance of the arterial tree. It is an important determinant of arterial pulse pressure.
Reflection magnitude	Ratio of the amplitude of the reflected wave/amplitude of the incident (forward) wave.
Augmentation index (AIx)	The augmentation index is defined as the proportion of central pulse pressure due to the late systolic peak, which is in turn attributed to the reflected pulse wave.