

# Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease

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**Abstract** Increased arterial stiffness associated with diabetes and the metabolic syndrome may in part explain the increased cardiovascular disease risk observed in these conditions. Arterial stiffness can be estimated by quantifying pulse pressure but is better described by distensibility and compliance coefficients, pulse wave velocity and wave reflection. The most common non-invasive methodologies used to quantify these estimates of arterial stiffness (e.g. ultrasonography and applanation tonometry) are also described. We then review and summarise the current data on the associations between diabetes, the metabolic syndrome and insulin resistance on the one hand and greater arterial stiffness on the other, and identify and discuss some unresolved issues such as differential stiffening of central vs peripheral arterial segments, the impact of sex, and the pathobiology of increased arterial stiffness in diabetes and the metabolic syndrome. Finally, some considerations with regard to treatment options are presented.

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At present the most powerful therapy available for reducing arterial stiffness is to vigorously treat hypertension using pharmacological agents. New pharmacological strategies to reduce arterial stiffness are likely to be especially relevant to individuals with diabetes.

**Keywords** Arterial stiffness · Cardiovascular disease · Diabetes · Insulin resistance · Metabolic syndrome · Pathophysiology

## Abbreviation

AGEs advanced glycation end-products

## Introduction

Cardiovascular disease is the main cause of death in both type 1 and type 2 diabetes mellitus [1]. The pathophysiological mechanisms underlying these associations are incompletely understood. Increased arterial stiffness may be one important pathway linking diabetes to the increased cardiovascular risk, as it commonly occurs in these conditions [2]. Indeed, increased arterial stiffness predicts the development of cardiovascular disease and mortality in the general population [3] and in type 2 diabetes [4].

To illustrate the problem of arterial stiffness in the context of clinical practice we introduce a clinical case (see text box: Arterial stiffness—the clinical problem). Mrs T's main problem was not obesity or poor glycaemic control, but, rather, severe systolic hypertension and relatively low diastolic blood pressure (i.e. elevated pulse pressure). We explain below that Mrs T's underlying cause of death may have been arterial stiffening.

### Arterial stiffness—the clinical problem

Mrs T

At the age of 70 years:

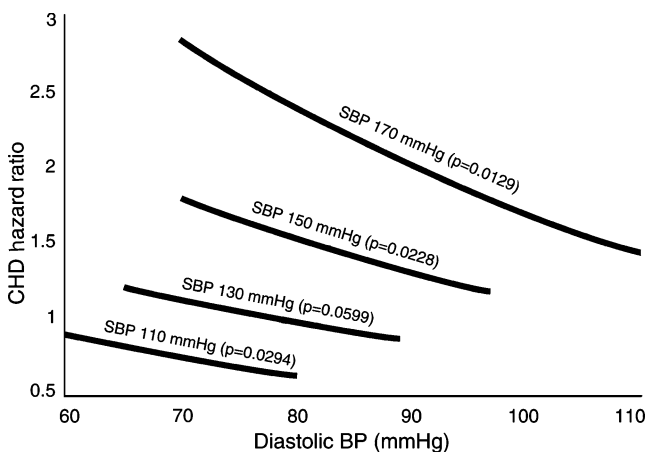
- duration of diabetes 12 years
- BMI 28 kg/m<sup>2</sup>
- HbA<sub>1c</sub> 7.1%
- blood pressure 186/68 mmHg
- five antihypertensives

At the age of 72: myocardial infarction and heart failure

At the age of 74: death from stroke

Arterial stiffness—why is it important?

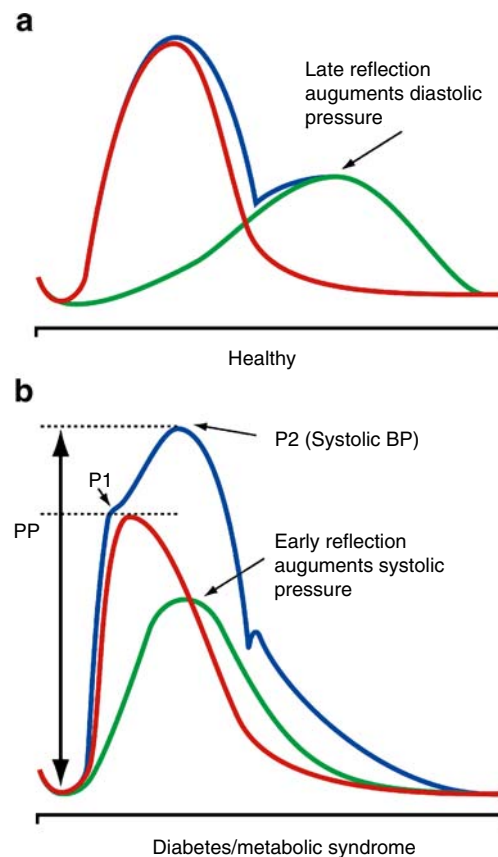
Pulse pressure is now recognised as a strong predictor of cardiovascular disease, particularly in older people. This is illustrated by data from the Framingham Heart Study showing that the risk of coronary heart disease increased with increasing levels of systolic blood pressure, but, and at the same time, for each level of systolic blood pressure the risk was actually higher at the lowest levels of diastolic pressure (i.e. at the widest pulse pressure) [5] (Fig. 1). Pulse pressure depends on the stroke volume ejected by the left ventricle, the cushioning capacity of the arterial system (i.e. the ability of arteries, mainly the aorta, to smooth flow pulsations imposed by the intermittent contracting heart so that the blood is directed through the organs and tissues in an almost steady stream), and the amplitude and timing of arterial wave reflection [6, 7]. Arterial stiffness (i.e. impairment of the cushioning capacity) leads to an increase in systolic blood pressure because hearts ejecting into a stiffer arterial bed must generate



**Fig. 1** Coronary heart disease (CHD) risk according to systolic, diastolic and pulse pressure in the Framingham Heart Study. The figure depicts that any increase in systolic blood pressure (SBP) is associated with an increase in CHD risk; however, and at the same time, for each SBP the highest CHD risk is actually observed at the lowest DBP level, i.e. at the highest pulse pressure (PP) level. Reproduced with permission from Lippincott Williams & Wilkins [5]

higher end-systolic pressures for the same net stroke volume. This leads to increased decay of arterial pressure and volume during systole, causing a reduced arterial volume at the onset of diastole, which in turn causes an enhanced fall in diastolic blood pressure [8]. Greater arterial stiffness also increases systolic and decreases diastolic pressure through increasing pulse wave velocity and through arterial wave reflection (see below). The direct clinical consequences of increased arterial stiffness are an increased risk of stroke as a result of increased systolic pressure; the development of left ventricular hypertrophy as a result of increased cardiac afterload; and a decrease in coronary perfusion and heart failure owing to the decrease in diastolic blood pressure.

Systolic blood pressure increases progressively with increasing age, whereas a decrease in diastolic blood pressure is observed particularly from the 5th decade onwards [9]. Because ventricular ejection decreases with age, arterial stiffness assumes a critical role in the explanation of the age-related



**Fig. 2** Illustration of the combination of forward (red line) and the sum of many reflected waves (green line) and its impact on the measured pulse wave (blue line). In elastic vessels (e.g. healthy individuals) reflection occurs during diastole (a), whereas in stiff vessels (e.g. diabetes and the metabolic syndrome) wave reflection occurs during systole leading to an amplification of the systolic BP and pulse pressure (PP) (b). P1, systolic peak of the forward (first) wave; P2, systolic peak of the augmented (measured) wave. Adapted from [11]

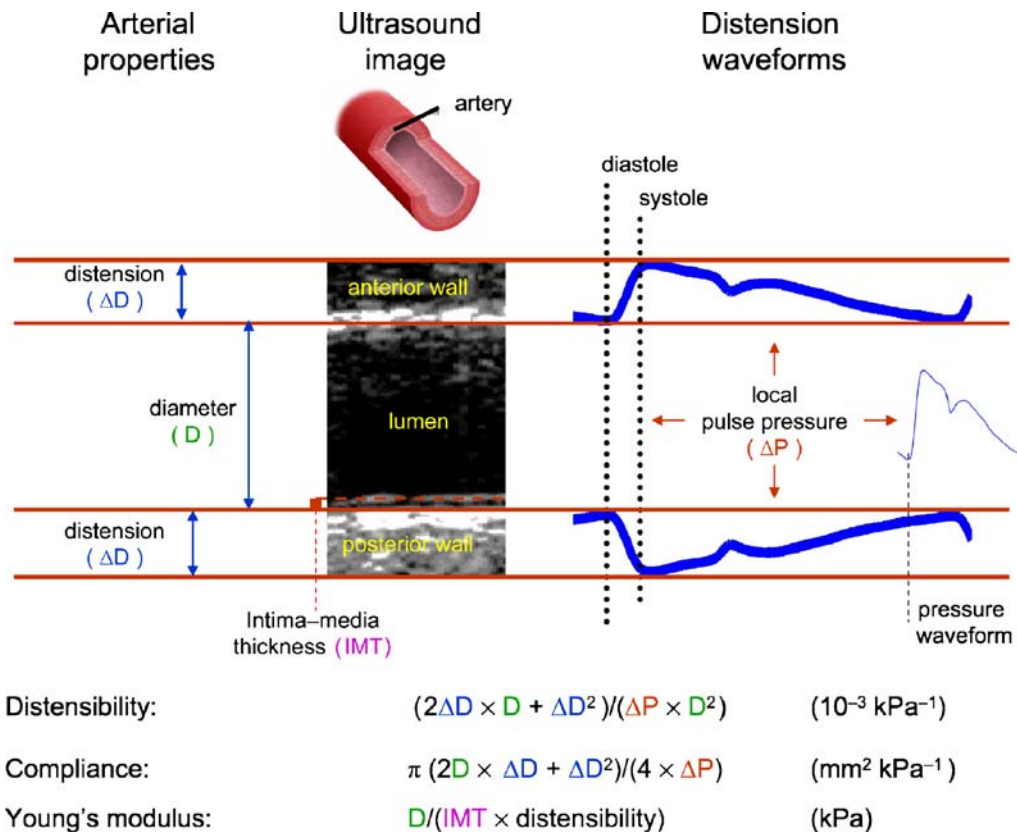
increases in systolic and pulse pressure and related mortality, and this therefore explains why brachial pulse pressure is commonly used as a marker of arterial stiffness [7].

Despite their utility in clinical practice, cuff sphygmomanometer measures of blood pressure are not sufficient to understand the underlying processes explaining the increase in pulse pressure for two main reasons: first, they do not depict the phenomenon of arterial wave reflection, and second, they are not appropriate for the detection of artery stiffening in early stages because of the phenomenon of pulse pressure amplification between central and peripheral arteries observed in young individuals [10]. As the pressure wave generated by cardiac ejection is transmitted forward from the central aorta to the periphery and is reflected back from any point of impedance discontinuity (e.g. arterial branching and arterial–arteriolar junctions), the arterial pressure waveform recorded in any arterial site (e.g. the ascending aorta or brachial artery) is thus the result of the summation of the forward and backward pressure waves at that specific site. In elastic arteries, reflected waves arrive at the aorta during diastole, as usually observed in young and healthy subjects, whereas in stiff arteries the reflected pressure wave returns during early systole, adding to the forward wave and augmenting the systolic and pulse pressure, as usually observed in the elderly

and in hypertensive individuals [11] (Fig. 2). In addition, elastic properties of large conduit arteries vary along the arterial tree, owing to cellular and histological differences in the structure of the arterial wall): proximal arteries (e.g. aorta) are more elastic and distal arteries (e.g. brachial or femoral) are stiffer. This heterogeneity is important because the pressure wave propagated along the arterial tree is progressively amplified from central to peripheral arteries as a result of wave reflections. In peripheral arteries, wave reflection can amplify pressure because the reflection sites are closer than in central arteries, which explains why, particularly in young individuals, brachial pulse pressure is higher than aortic pulse pressure. However, because ageing stiffens central arteries to a greater extent than peripheral arteries, the amplification between central and peripheral arteries is attenuated. Therefore, in the young, the use of brachial pulse pressure as a marker of arterial stiffness is not appropriate [7].

Estimates of arterial stiffness

An overview of methods and calculation details is shown in the text box ‘Definitions of the most commonly used indices of arterial stiffness’. Arterial stiffness can either be estimated locally at specific arterial sites (e.g. carotid, radial, brachial



**Fig. 3** Ultrasound-derived arterial properties to determine local arterial stiffness. The two thick blue lines represent the vessel wall movement during the cardiac cycle

and femoral) or regionally over a given arterial segment length (e.g. the aorta or the upper or lower limb) [3]. Local estimates of arterial stiffness are most often described in terms of compliance and distensibility coefficients, and are usually obtained through measurement of arterial changes in diameter or area and local distending pressure by means of ultrasound imaging (Fig. 3). Regional estimates of arterial stiffness are obtained through measurement of the speed of pulse pressure wave propagation, i.e. pulse wave velocity along an arterial segment. Pressure sensors (i.e. mechanotransducers or applanation tonometers) are applied at two arterial sites to record pressure waveforms and the transit time that the pressure wave took to travel between the two arterial sites; pulse wave velocity is then calculated as the distance/travel time. Pulse wave velocity measured along the aorto–iliac pathway, i.e. carotid–femoral pulse wave velocity, is the most commonly used measure of arterial stiffness, given its proven value as a predictor of cardiovascular disease and mortality. The local and regional stiffness estimates described above are, however, closely related conceptually. This is illustrated by the fact that if arterial diameter falls while distending pressure is kept constant (i.e. an increase in stiffness), the speed with which the pressure wave travels increases [3]. In addition, analysis of the arterial pulse waveform using applanation tonometry is used to measure the augmentation in pulse pressure that is due to pulse wave reflection. Good quality registration of the arterial pressure waveform is obtained by applanating (flattening) a superficial artery (usually the radial) supported by bone using an external tonometer. This peripheral pressure waveform is then transformed, usually with the use of a transfer function, into a central arterial shape, i.e. that of the ascending aorta, which represents the true load imposed to the left ventricle. Analysis of this central waveform identifies the systolic peak of the forward wave and the systolic peak of the augmented wave; the difference between these two values expressed relative to pulse pressure represents the augmentation of the pulse pressure due to wave reflection [3] (Fig. 2).

The stiffness of an arterial site or segment is dependent on its background level of distending pressure, i.e. mean arterial pressure—a greater recruitment of relatively inelastic collagen fibres occurs with increasing distending pressures, enhancing stiffness. Therefore, to fully appreciate arterial stiffness estimates in clinical studies, adjustment for mean arterial pressure levels is imperative so that the distending pressure effects can be differentiated from true differences in viscoelastic properties of the arterial wall [12].

For an extensive theoretical review of the haemodynamic principles and models underlying the definitions and assessment methods of the arterial stiffness estimates described above, the reader is referred to the recent Expert Consensus document on arterial stiffness recently published by Laurent et al. [3], as this is beyond the scope of this review.

## Arterial stiffness in diabetes and the metabolic syndrome: the evidence

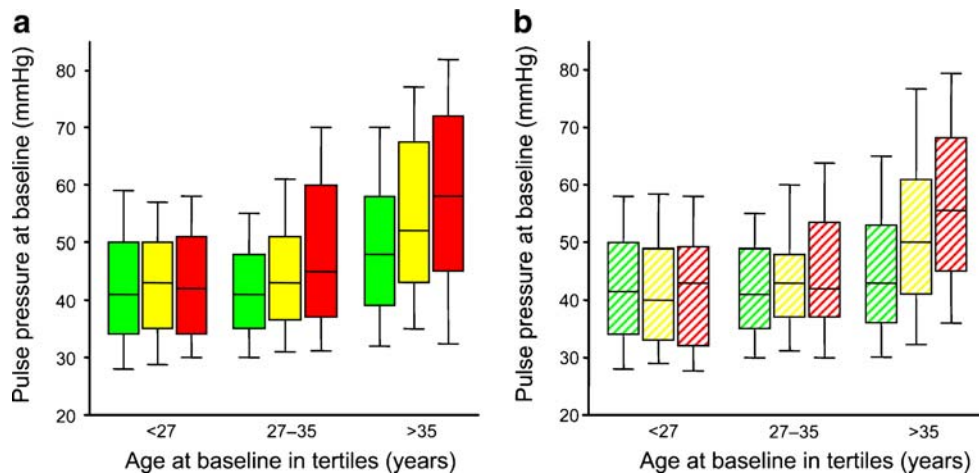
As the literature up to 1999 has been extensively reviewed [13], we shall focus on recent developments. In addition, and in the context of type 2 diabetes, we also review the evidence with regard to the association between the metabolic syndrome and arterial stiffness, as clustering of cardiovascular risk factors precedes the development of diabetes [14, 15], and understanding their impact on arterial stiffness may be critical for the primary prevention of diabetes-related macrovascular disease. Finally, we discuss the evidence with regard to the role of insulin resistance.

*Type 1 diabetes mellitus* A large body of evidence supports the concept of increased arterial stiffness in type 1 diabetes [16–26] [Electronic supplementary material (ESM) Table 1]. This is an early phenomenon that occurs before the onset of clinically overt micro- or macrovascular disease [17, 18, 22, 24, 26–29], and arterial stiffness is further enhanced in the presence of microvascular complications (e.g. nephropathy, microalbuminuria or retinopathy) [17, 25, 30]. Similar findings have been reported with regard to pulse pressure: in individuals with type 1 diabetes an increase in pulse pressure can be detected as early as the third and fourth decade of life, i.e. there is accelerated arterial ageing, and the age–pulse pressure relationship is even steeper in the presence of microvascular complications [31, 32] (Fig. 4). It is, however, not clear whether increased arterial stiffness is a cause (because greater arterial stiffness is associated with greater pressures in small arteries and capillaries) or a consequence (because microvascular dropout will increase wave reflection and thus increase pulse pressure [33]) of microangiopathy, or alternatively, that both phenomena derive from a common antecedent (e.g. endothelial dysfunction or inflammation) [34, 35]. Importantly, greater pulse pressure in type 1 diabetic patients is associated with incident cardiovascular mortality [32]. Taken together, these data support the concept of accelerated arterial ageing in type 1 diabetes and may explain, at least in part, the increased cardiovascular risk in these patients.

*Type 2 diabetes mellitus* Similar to type 1 diabetes, a large body of evidence supports the concept of increased arterial stiffness in type 2 diabetes [36–53] (ESM Table 2). This again is an early phenomenon as much already occurs in the impaired glucose metabolism state (i.e. impaired fasting glucose and/or impaired glucose tolerance) [42, 44, 48, 53, 54] (Fig. 5). These findings support the so-called ‘common soil’ or ‘ticking clock’ hypothesis, which suggests that macrovascular disease associated with type 2 diabetes begins in the pre-diabetic state [15, 55]. In addition, the presence of micro- and macrovascular complications in type 2 diabetes is associated with a further increase in arterial stiffness [37, 41,

**Definitions of the most commonly used indices of arterial stiffness**

Method of measurement	Estimate	Definition	Calculation details (units)	Site of measurements	Comments
Arterial wall ultrasonography (echo-tracking) (see Fig. 3)	Compliance coefficient (CC)  Distensibility coefficient (DC)  Young's (or incremental) elastic modulus (YEM or $E_{inc}$ )	Absolute change in lumen area for given increase in pressure  Relative change in lumen area for a given change in pressure  The pressure step per squared centimetre required for (a theoretical) 100% stretch from resting length, determined by the arterial diameter (D) divided by DC multiplied by the thickness of the intima-media complex (IMT).	$\Delta A/\Delta P$ ( $\text{mm}^2 \text{kPa}^{-1}$ )  $\Delta A/A \times \Delta P$ ( $\text{kPa}^{-1}$ )  $D/DC \times \text{IMT}$ (kPa)	Locally, most often at the carotid (an elastic artery) or the brachial, radial and femoral (muscular) arteries; (all peripheral sites)	These estimates are determined directly from simultaneous changes in (local) pulse pressure ( $\Delta P$ ) and arterial diameter ( $\Delta D$ ) or area ( $\Delta A$ ). This method has the advantage of allowing the concomitant assessment of arterial wall thickness (IMT), thereby enabling the calculation of the Young's elastic modulus (an estimate of the intrinsic elastic properties of the arterial wall material). The lower the DC or CC and the higher the YEM of an artery the higher its stiffness.
Pressure sensors such as mechanotransducers or applanation tonometers (with ECG triggering)	Pulse wave velocity	The speed of the pressure wave travelling along an arterial segment, determined by the length (L) of the arterial segment under study divided by the time it takes for a pressure wave to travel from arterial location A to arterial location B within this segment ( $\Delta t$ )	$L/\Delta t$ (m/s)	Regionally over a given arterial segment, e.g.: carotid–femoral (central), or carotid–radial or femoral–dorsalis pedis (both peripheral)	The 'gold standard' for arterial stiffness. Greater values indicate greater stiffness.
Pulse wave analyses (radial applanation tonometry) (see Fig. 2)	Augmentation index (Aix)	The supplementary increase in blood pressure during systole due to the reflection of the forward travelling pressure waves from the peripheral circulation	$((P2 - P1)/PP) \times 100$ (%)	At the radial or carotid artery from which the central aortic pressure and waveform are derived with the use (or not) of a transfer function	Aix is thus estimated from the difference between second (P2) and first (P1) systolic peaks of the arterial pulse wave expressed as a % of pulse pressure (PP). Aix is an estimate of stiffness and wave reflection and therefore provides indirect information on arterial stiffness.



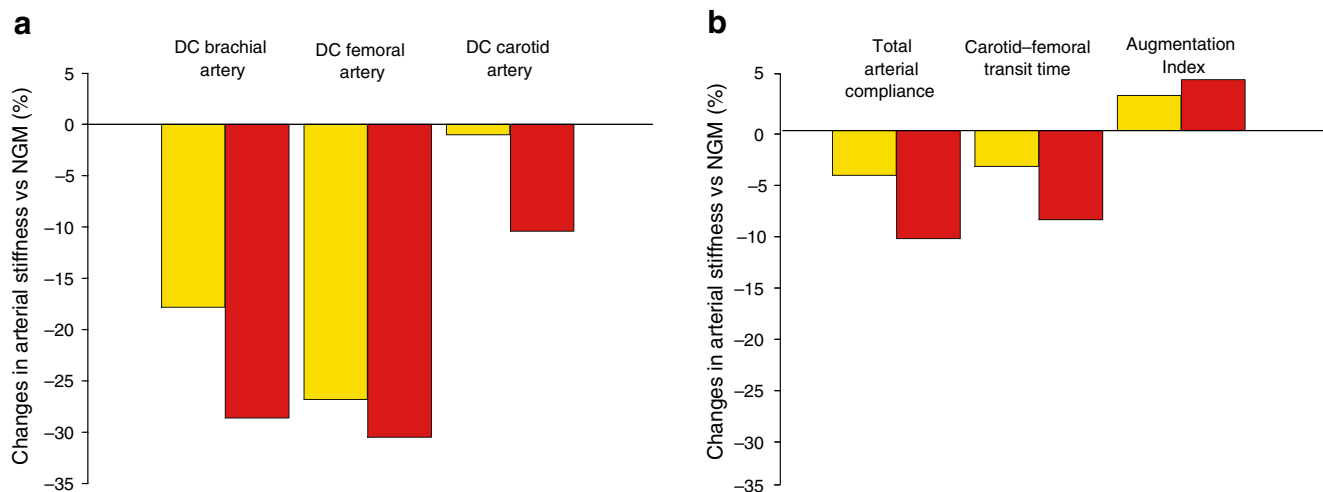
**Fig. 4** The association of pulse pressure with age among type 1 patients is stronger in the presence of micro- or macroalbuminuria (a) or proliferative or proliferative retinopathy (b) than in their absence (The EURODIAB Study). Green boxes, normoalbuminuria; yellow boxes, microalbuminuria; red boxes, macroalbuminuria; hatched green

boxes, no retinopathy; hatched yellow boxes, non-proliferative retinopathy; hatched red boxes, proliferative retinopathy. The box plots show the median, interquartile range and standard error. Reproduced from [32] with the permission of Lippincott Williams & Wilkins

50, 56–59]. Furthermore, as in type 1 diabetes, the age-related increase in arterial stiffness is steeper in individuals with type 2 diabetes than in their non-diabetic counterparts [36, 40, 43, 46]. This is consistent with observations of steeper increases in pulse pressure with ageing in these patients [60] (Fig. 6): these increases are further amplified in the presence of micro- and macrovascular complications [61–63]. Importantly, the increased pulse pressure observed in type 2 diabetic patients has been found to be predictive of future cardiovascular mortality [60, 64].

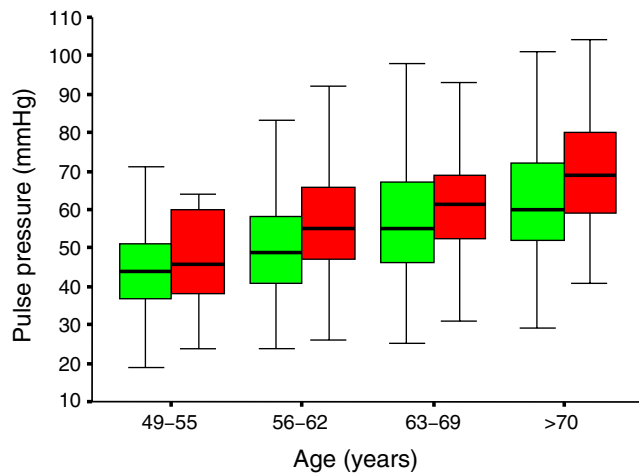
*Metabolic syndrome* Studies investigating the association between the metabolic syndrome and arterial stiffness have

consistently shown increased arterial stiffness in individuals with the metabolic syndrome or with increasing number of traits of the metabolic syndrome [45, 65–87] (ESM Table 3). Importantly, such deleterious arterial changes have been shown at a very young age (e.g. in obese [78] and apparently healthy adolescents [76] and young adults [70, 71, 84]) (Fig. 7). The increased stiffness in the metabolic syndrome thus appears to be caused by subtle metabolic abnormalities (and not by fully developed diabetes), which supports the ticking clock hypothesis mentioned above. In addition, prospective studies have shown that the increase in arterial stiffness with age is greater in individuals with the metabolic syndrome as compared with those without [66, 81]. Impor-



**Fig. 5** Relative changes in peripheral arterial stiffness (local arterial distensibility coefficients [DC] of the brachial, femoral and carotid arteries) (a), and central arterial stiffness (systemic compliance, carotid–femoral transit time and aortic augmentation index) (b) in individuals with type 2 diabetes and impaired glucose metabolism

compared with those with normal glucose metabolism (the Hoorn Study). Yellow bars, impaired glucose metabolism, red bars, type 2 diabetes. NGM, normal glucose metabolism. Reproduced with permission from Lippincott Williams & Wilkins [48]



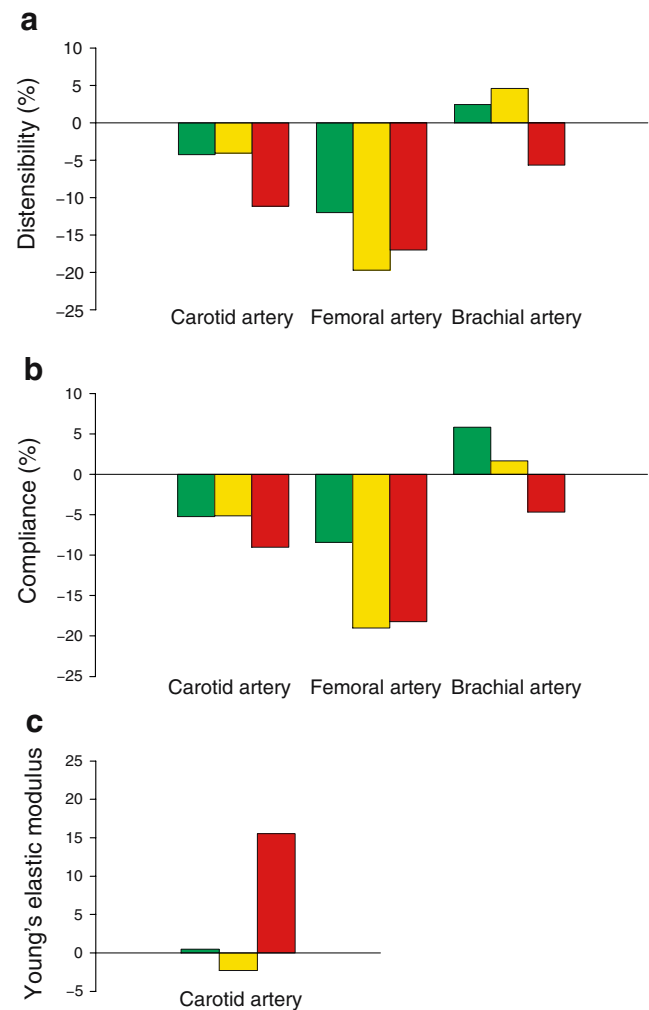
**Fig. 6** Arterial ageing in type 2 diabetes. There is a steeper increase in pulse pressure with age in type 2 diabetic (red boxes) than in non-diabetic individuals (green boxes). The box plots show the median, interquartile range and standard error. Reproduced with permission from Lippincott Williams & Wilkins [60]

tantly, individuals whose metabolic syndrome status has regressed or remained negative over time show lower rates of increase in arterial stiffness [82].

Taken together, these data support the concept of increased arterial stiffness in the metabolic syndrome, which may explain, at least in part, the increased cardiovascular risk in these individuals, and emphasise the importance of primary prevention. It is important to stress that the association between (traits of) the metabolic syndrome and arterial stiffness is not only related to higher blood pressure; in addition to (and independently of) blood pressure, (central) obesity and increased fasting glucose levels were the traits consistently associated with arterial stiffness, whereas dyslipidaemia was less so. These are the three traits that are most often observed in combination, and this clustering is associated with the greatest mortality risk [88]. Analyses of the metabolic syndrome traits and their clustering expressed as a continuous score and the close examination of each trait (and/or combination of traits) in relation to increased arterial stiffness may therefore be a more appropriate approach in aetiological studies (for an example, see [84]).

*The role of insulin resistance* Insulin resistance usually precedes the development of type 2 diabetes and is often accompanied by a clustering of the risk factors characteristic of the metabolic syndrome. Recent mechanistic studies performed in humans have suggested that increased stiffness could be yet another feature of insulin resistance [89]. Insulin, at physiological concentrations, has acute vasodilatory effects that lead to increased arterial distensibility; however, these beneficial effects are blunted in insulin-resistant states such as obesity/the metabolic syndrome and type 1 diabetes and type 2 diabetes, and are closely related to whole-body glucose uptake

[89]. The chronic effects of insulin resistance on arterial stiffness have also been examined. In healthy individuals, a positive association between insulin-mediated glucose uptake and arterial distensibility was observed, although this effect was confined to the femoral artery and was more pronounced in women [90]. In a large population-based study, insulin concentrations (a more indirect measure of insulin sensitivity) were associated with carotid artery stiffness, and this association was also stronger in women than in men [91]. Also in diabetic patients, inverse associations were observed between clamp-measured insulin sensitivity and arterial stiffness in the carotid [92, 93] and femoral [93] arteries. Importantly, because arterial stiffness is highly dependent on blood pressure and hypertension itself affects the stimulation



**Fig. 7** Relative change in arterial stiffness estimates according to number of risk factors (RFs) of the metabolic syndrome (MetS) as compared with no risk factors; distensibility (a) and compliance (b) of the carotid, femoral and brachial arteries, and (c) Young's elastic modulus of the carotid artery (The Amsterdam Growth and Health Longitudinal Study). Green bars, 1 RF; yellow bars, 2 RFs; red bars, ≥3 RFs (MetS). Reproduced from [70] with permission from the American Medical Association

### Arterial stiffness in diabetes and the metabolic syndrome—review of the evidence

- Arterial stiffness is increased in type 1 diabetes  
—this is an early phenomenon that occurs before the onset of clinically overt micro- or macrovascular complications
- Arterial stiffness is increased in type 2 diabetes  
—this is an early phenomenon, as much occurs in the impaired glucose metabolism state  
—the presence of micro- and macrovascular complications is associated with a further increase in arterial stiffness
- Arterial stiffness is also increased in the metabolic syndrome and in insulin-resistant states  
—subtle changes in metabolic variables (not fully developed diabetes) affect arterial stiffness from an early age

Diabetes is a disease of accelerated arterial ageing, as shown by stiffer arteries and consequent steeper increases in pulse pressure with age in these subjects

of glucose uptake by insulin, it is noteworthy that the studies mentioned above have shown insulin resistance to be associated with estimates of arterial stiffness even after adjustments for mean arterial pressure levels. In this respect, recent studies have shown additive adverse effects of insulin resistance on arterial stiffness in the context of hypertension [94, 95]. Notably, in the only longitudinal study that has addressed the individual and combined effects of raised blood pressure and raised glucose levels on the progression of arterial stiffness, the estimated rate of increase in arterial stiffness was higher in individuals with both abnormalities than in those with either abnormality alone [96]. Most importantly, persistence of both abnormalities synergistically accelerated the rate of increase in arterial stiffness such that it was three times higher than in those who persisted with elevated levels of blood pressure or glucose alone. In conclusion, insulin resistance contributes to increased arterial stiffness independently of blood pressure in type 2 diabetic patients but also in apparently healthy individuals.

Unresolved issues in diabetes- and metabolic syndrome-related arterial stiffening

#### *Preferential stiffening of peripheral over central arteries?*

One important issue is whether the association between diabetes (or the metabolic syndrome) and arterial stiffening differs between central and peripheral arteries. This question has been raised by the conflicting results published by the relatively few studies examining arterial stiffness in several arterial territories within the same individual. Discrepancies

detected may be due to the use of different methods (i.e. regionally or locally) in the assessment of estimates of arterial stiffness and/or the different histological features (i.e. the elastin to collagen ratio that decreases from proximal to distal sites) of the arterial tree, which may have different susceptibilities to risk factors.

Studies in which regional stiffness estimates have been compared in different arterial segments have shown diabetes or the metabolic syndrome to preferentially affect the central rather than the peripheral part of the arterial tree [43, 50, 73] or to have a similar impact on the stiffness of central and peripheral segments [47, 51, 84]. In contrast, in studies where stiffness estimates have been assessed locally at different (mainly peripheral) arterial sites, the deleterious effects of diabetes or the metabolic syndrome were stronger at the more muscular (i.e. radial, brachial and femoral) rather than the more elastic (i.e. the carotid) arteries [17, 42, 48, 70, 90]. However, preferential stiffness of elastic over muscular arteries has also been shown [21, 97]. Because most of the studies reviewed herein have investigated one particular vascular territory only (see ESM Tables 1, 2, 3), no consistent picture has as yet emerged with regard to preferential central or peripheral stiffening in either diabetes or the metabolic syndrome, which hampers pathophysiological interpretation of these data. Preferential stiffness of peripheral arterial segments or sites would suggest that the cushioning function of the central circulatory system would be relatively preserved over the peripheral conduit function, which would facilitate cardiac stroke volume expulsion into a circulatory system that increasingly stiffens with age.



*Central vs peripheral stiffness as cardiovascular risk factor* Studies demonstrating the prognostic value of arterial stiffness in the prediction of cardiovascular events have been almost all confined to estimates of stiffness of elastic arterial segments or sites (i.e. aortic pulse wave velocity and carotid distensibility) [3]. Whether stiffness of muscular segments or sites has the same predictive value is largely unknown. So far, this has been investigated in one study only, where central but not peripheral arterial stiffness was an independent predictor of death in a cohort of haemodialysis patients [98]. Similarly, a recent study showed that central rather than peripheral arterial stiffness was elevated in type 2 diabetes patients with ischaemic heart disease [99]; however, its cross-sectional design does not allow the conclusion of a greater prognostic value of central over peripheral stiffness in the diabetic population. Nevertheless, peripheral arterial stiffness may be clinically relevant as it has been shown to be closely associated with prevalent peripheral vascular disease [100, 101], which is a clinically important outcome in the (pre-)diabetic population. Additional studies to clarify these issues are needed.

*The impact of sex* Several studies suggest that the cardiovascular morbidity associated with diabetes [102, 103], like that associated with the metabolic syndrome [104, 105], is greater in women than in men. Moreover, unlike men with diabetes, it seems that women with this disease have not experienced a decline in coronary heart disease mortality [106]. Potentially, this discrepancy could be explained by greater arterial stiffness in women with diabetes or the metabolic syndrome, although this is not clear from the current literature. The majority of previous studies have either undertaken sex-adjusted analyses or have been performed in single-sex cohorts (ESM Tables 1, 2, 3). Studies that have examined the strength of the associations between diabetes or the metabolic syndrome and arterial stiffness in men and women separately have disclosed no sex differences [21, 72, 83] or have shown these associations to be somewhat stronger in women than in men [23, 46, 67, 71, 80, 84, 85, 97]. Overall, these findings suggest that analyses of data in men and women separately may be more appropriate.

The pathobiology of increased arterial stiffness in diabetes and the metabolic syndrome

Increased arterial stiffness is primarily determined by the properties of the extracellular matrix (elastin, collagen) and vascular smooth muscular cell function [107, 108]. These variables are strongly affected by aging and blood pressure, which cause repetitive pulsatile stress upon the arterial wall, leading to both structural and functional disruption of the arterial pressure load-bearing elastin–collagen network within the media (e.g. fracturing of elastin fibres resulting from mechanical fatigue and altered pressure-dependent recruitment of [excessive] collagen fibres) [11]. How arterial stiffness is increased in diabetes and the metabolic syndrome is largely unknown [11, 34, 108, 109]. One of the main mechanisms thought to be involved, particularly in diabetic individuals, is the formation of advanced glycation end-products (AGEs) on the arterial wall, causing cross-linking of collagen molecules, which may lead to loss of collagen elasticity and a subsequent increase in arterial stiffness [110]. Indeed, AGEs have been associated with greater stiffness in diabetic patients [111, 112], and cross-link breakers have been demonstrated to decrease arterial stiffness in humans [113]. Chronic hyperglycaemia and hyperinsulinaemia also increase the local activity of the renin–angiotensin–aldosterone system and expression of angiotensin type I receptor in vascular tissue, promoting development of wall hypertrophy and fibrosis [109]. In addition, low-grade inflammation and endothelial dysfunction, which are inter-related, may also explain, at least in part, the increases in arterial stiffness related to diabetes and the metabolic syndrome [75, 84, 114]. Indeed, low-grade inflammation and endothelial dysfunction are common in diabetes and the metabolic syndrome [34, 35, 109] and partially explain the increased cardiovascular risk in these conditions [115, 116]. Endothelial dysfunction may lead to functional stiffening of large arteries as the reduced availability of nitric oxide and increased activity of vasoconstrictors such as endothelin-1 affect vascular smooth muscle cell tone [117–119]. In addition, endothelial dysfunction may lead to smooth muscle cell proliferation and increased synthesis of structural

### Arterial stiffness—unsolved issues and questions for the future

- Does diabetes preferentially affect the stiffness of peripheral over central arteries (or vice versa)?
- What is the prognostic value of an increased peripheral arterial stiffness observed in diabetes?
- Is the diabetes-related increase in arterial stiffness more pronounced in women?
- What are the pathophysiological mechanisms that underlie the associations between diabetes and metabolic syndrome and arterial stiffness?

proteins such as collagen. Low-grade inflammation impairs endothelial function, which may therefore result in increased arterial stiffness [120]. However, prospective data to test the mediating role of endothelial dysfunction and/or inflammation on the metabolic syndrome and diabetes-related arterial stiffening are still lacking.

### Treatment

At present the most powerful therapy to reduce arterial stiffness is vigorous treatment of hypertension with pharmacological agents. Indeed, many, but not all, of the current pharmacological strategies reduce arterial stiffness, but this is an indirect effect resulting from lowering of mean arterial pressure (for review see [121]). In fact, because anti-hypertensive drugs were primarily designed to reduce peripheral resistance, they may not alter the pathological process of arterial stiffening itself or electively reduce systolic blood pressure. This may explain why isolated systolic hypertension is so often resistant to pharmacological intervention. Whether some anti-hypertensives are more effective than others in this respect constitutes a current important area of investigation (cf. the Conduit Artery Function Evaluation [CAFÉ] study [122] and Regression of Arterial Stiffness in a Controlled Double-Blind Study [REASON] [123]). In addition, new strategies to reduce arterial stiffness [e.g. so-called AGE breakers such as Alagebrium (ALT 711)] are in development and are likely to be especially relevant to individuals with diabetes [124]. These pharmacological agents break down established AGE cross-links between proteins within the arterial wall, thereby reducing arterial stiffness [113], but more evidence is necessary to establish the clinical relevance of such drugs. Alternative strategies to reduce arterial stiffness may involve enhancing NO release from endothelial cells (e.g. by the use of 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors), and/or changes in lifestyle patterns with the aim of increasing dietary intake of n-3 fatty acids and decreasing salt intake, increasing aerobic physical activity levels, and reducing body fatness [108, 125]. None of these strategies, however, has unequivocally been shown to reduce arterial stiffness in diabetes or the metabolic syndrome, and more study of these issues is needed.

### Conclusion

There is convincing evidence that diabetes and the metabolic syndrome are associated with greater arterial stiffness. The underlying pathobiology is complex and remains to be fully elucidated. However, greater arterial stiffness may, at least in part, explain the increased cardiovascular risk in individuals with diabetes and the

metabolic syndrome. For the clinician, it is important to realise that greater brachial pulse pressure, particularly in middle-aged and older individuals but even in relatively young type 1 diabetic individuals, is a marker of greater arterial stiffening and thus a marker of greater cardiovascular risk. However, whether other estimates of arterial stiffness (e.g. aortic pulse wave velocity) can improve risk stratification in diabetes or the metabolic syndrome remains to be shown.

**Duality of interest** The authors declare that there is no duality of interest associated with this manuscript.

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