Endothelial Dysfunction and Large Artery Stiffness

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12.1 Introduction

Common to both diabetes and hypertension are abnormalities in blood vessel structure and function. While individuals with type 1 diabetes display abnormalities in vascular structure and function compared to their healthy counterparts [1], this chapter will predominantly focus on those with type 2 diabetes (T2D) due to the common coexistence (and bidirectional relationship) with hypertension.

Arterial ageing commences in early life and is a normal ageing phenomenon in most populations. However, pathological arterial ageing, as evident in conditions such as hypertension and T2D, results in accelerated vascular changes related to *atherosclerosis* in the arterial intima and *arteriosclerosis* in the arterial media. Exposure to adverse environmental and genetic factors as early as during childhood or even during foetal life promotes the development and accumulation of subclinical vascular changes that direct an individual towards a trajectory of early vascular ageing (EVA) [2]. Emerging evidence suggests that early life programming is also an important player in vascular remodelling mainly because the architecture of the vascular system is programmed in utero and elastin, the major structural component underlying arterial wall elasticity, is synthesised and deposited during this time. The EVA phenomenon is also evident among offspring with a positive family history of cardiovascular disease (CVD) or T2D [3, 4].

The ageing process affects the entire arterial wall and includes endothelial dysfunction, a decrease in nitric oxide (NO) production and local inflammation in the intima [5]; decreased levels of elastin and a relative increase in collagen content in the media [6]; and impairment of neuronal control, a loss of function of the vasa vasorum [7] and development of perivascular fat deposits that may increase local

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inflammation and adversely impact vasodilation in the adventitia [8]. This leads to structural changes in the arterial wall which manifest as an increase in intima-media thickness (IMT) [9–12], accompanied by lumen enlargement [10–12] and increased stiffness (*arteriosclerosis*) in the large, proximal elastic arteries [13]. The ageing process involves the entire vascular system including remodelling of the small arteries.

Alterations in vascular structure and function have been observed in patients with prediabetes or impaired fasting glucose as well as overt T2D, suggesting that the abnormalities in carbohydrate metabolism form a continuum that progressively worsens vascular health. An early feature of this adverse sequence of events that leads to atherosclerosis is believed to be endothelial dysfunction. Individuals with hypertension and T2D also display accelerated large artery stiffness compared to healthy individuals, of which endothelial dysfunction may be a key contributor [14].

In this chapter, literature on the association between T2D and hypertension with a particular focus on the changes that occur in relation to the endothelium and large arteries are summarised. The haemodynamic and biomechanical pathways involved in the bidirectional relationship between hypertension and T2D are discussed.

12.2 Endothelial Function and Large Artery Stiffness in Health and Disease

The vascular endothelial cells play an important role in maintaining vascular homeostasis. The endothelium provides a physical barrier between the vessel wall and lumen and actively secretes several mediators that regulate platelet aggregation, coagulation, fibrinolysis and vascular tone. The endothelial cells secrete mediators that cause vasoconstriction (endothelin-1 and thromboxane A2) or vasodilation (NO, prostacyclin and endothelium-derived hyperpolarising factor). NO plays a major role in endothelium-dependent relaxation in conduit arteries, while hyperpolarising factor predominates in the smaller, resistance vessels.

Endothelial dysfunction is characterised by a shift towards reduced vasodilation and a proinflammatory and prothrombotic state. Free radicals disrupt the balance of NO, damaging the endothelium leaving it permeable to toxins [15]. When NO action is impaired, endothelial signal is also impaired, leading to several systemic diseases. Endothelial dysfunction is associated with hypertension, coronary artery disease, heart failure, peripheral vascular disease, diabetes, kidney dysfunction as well as severe viral infections including the recent SARS-CoV-2 infection [16]. A number of factors can contribute to increased free radicals including obesity, hyperglycaemia, smoking, sleep deprivation and infection.

While the structural components within the arterial wall of large arteries (i.e. the aorta) such as elastin and collagen influence wall stiffness, arterial smooth muscle and locally derived, circulating factors also contribute to the regulation of large artery stiffness [17]. Vasoconstrictors (such as noradrenaline or angiotensin II)

increase large artery stiffness, whereas vasodilators have an opposing effect [18]. In a healthy cardiovascular system, the compliant properties of the large arteries ensure that pulsations in pressure and flow generated by cyclic left ventricular contraction are dampened at the site of the ascending aorta into a continuous pressure (and flow) downstream at the site of arterioles. This allows for the delivery of a steady flow of blood during organ perfusion, and the microvasculature of target organs is protected from the damaging effects of pressure pulsatility [18]. The dampening of the pressure/flow wave is achieved via the windkessel effect whereby the aorta expands during systole and temporarily stores a portion of the stroke volume, which is then propelled into the systemic circulation during diastole via recoil of the elastic arterial wall. However, in response to ageing [19, 20], hypertension and other disease states such as diabetes mellitus [14, 21], arterial stiffening limits the buffering capacity of the elastic arteries. A reduction in NO availability may explain why patients with T2D demonstrate arterial stiffening before overt atherosclerosis is apparent.

The stiffness gradient between the proximal elastic arteries and distal muscular arteries leads to an impedance *mismatch*, generating backward pressure wave reflection (i.e. towards the heart) that reduces the forward transmission of pressure pulsatility to the small arteries of target organs. In the healthy vasculature, most of the backward wave travels at a low velocity and does not superimpose on the incident pressure wave and central blood pressure (BP) remains normal. However with increasing arterial stiffening and due to a lack of age-induced stiffening in the muscular arteries [22] , the stiffness gradient between the proximal and distal arteries is reduced, thus exposing the microvasculature to increased pulsatile stress [22, 23]. The backward travelling pulsatile energy travels at high velocity and superimposes on the incident pressure wave, increasing central systolic BP.

Arterial stiffening has a number of consequences for cardiovascular health. Firstly, the arterial pressure waveform is a composite of the forward and backward travelling pressure wave. In the case of stiff arteries, because the pressure wave propagation (i.e. pulse wave velocity, PWV) is high, the backward travelling wave arrives back at the central arteries sooner than if PWV was lower (i.e. in more compliant vessels) adding to the forward wave, augmenting pressure pulsatility and systolic BP. This results in isolated systolic hypertension at the central level and increased left ventricular afterload, ventricular remodelling, hypertrophy, dysfunction and failure [24, 25]. Secondly, arterial stiffening and the consequent loss of diastolic recoil and lower aortic diastolic BP reduce coronary perfusion pressure. Thirdly, the increased transmission of elevated pulsatile pressure/flow to the microvasculature of target organs may be particularly harmful to high flow/low resistance organs such as the brain and kidney, damaging capillary networks and resulting in target organ damage [26–32]. Indeed, arterial stiffness per se is a mechanism inducing cardiac, renal and brain microcirculatory damage, favouring CVD events [33]. Together, this may explain why the brain and kidney are more often affected by microvascular disease than are other organs in patients with both T2D and hypertension [34].

12.3 The Interplay Between Hypertension, Type 2 Diabetes, Endothelial Function and Large Artery Stiffness

Vascular abnormalities are common to both T2D and hypertension. A number of studies have shown that compared to their nondiabetic counterparts, patients with T2D display endothelial dysfunction [35–37] and accelerated arterial stiffness [38–41]. In patients with T2D, endothelial dysfunction is a consistent finding as hyperglycaemia and T2D lead to an impairment in NO production and bioavailability [42]. T2D exerts an additive deleterious effect on endothelial function, beyond other risk factors [43]. Individuals with both T2D and hypertension have elevated arterial stiffness compared to healthy controls or individuals with either T2D or hypertension alone [44]. In sub-Saharan populations, large artery abnormalities are significantly worse in those with coexistent T2D and hypertension but does not differ in those with either T2D or hypertension alone [45]. On the other hand, recent work has suggested that vascular changes may precede both T2D and hypertension [36, 46–54]. Thus, a bidirectional relationship between T2D and hypertension exists and is likely exacerbated by endothelial dysfunction and large artery stiffness [55] (Fig. 12.1). Importantly in people with T2D, large artery stiffness is independently related to CVD risk, mortality and all-cause mortality [56–58], and endothelial dysfunction is associated with adverse cardiovascular health and mortality [59–61].

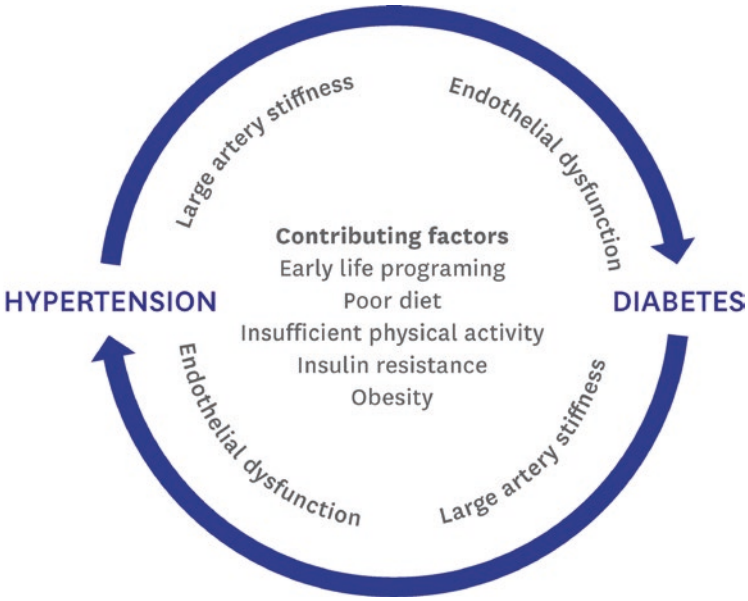

Fig. 12.1 The bidirectional relationship between diabetes and hypertension, perpetuated by endothelial dysfunction and large artery stiffness

12.3.1 Hypertension and Endothelial Dysfunction

Given that NO and endothelins are major regulators of vascular tone, they play a significant role in regulating BP. In hypertension, the balance between vasodilators and constrictors is disturbed, resulting in a predominance of vasoconstrictors such as endothelin-1. In patients with hypertension, impairment in vasodilation in the small resistance vessels in response to acetylcholine has been observed [62], and impaired flow-mediated dilation (FMD, a measure of endothelial function) distinguishes patients with hypertension at increased risk of fatal and non-fatal cardiovascular events [63]. Treatment with angiotensin-converting enzyme inhibitors, which act to increase NO bioavailability, improves endothelial function in patients with hypertension [64].

Whether endothelial dysfunction is a cause or a consequence of hypertension remains unclear [65]. Traditionally, it is believed that CVD risk factors including chronic inflammation, atherosclerosis, plaque instability and hypercoagulation preceded endothelial dysfunction. Normotensive offspring of parents with hypertension demonstrate impaired endothelial dysfunction [66], and the Cardiovascular Risk in Young Finns Study demonstrated that elevated BP in adolescence predicted future impaired endothelial function [67]. On the other hand, research in 952 postmenopausal women free from hypertension and risk factors showed that after 3.6 years of follow-up, there was a 5.77 increased risk of incident hypertension in those with the lowest flow-mediated dilation [68]. Interestingly, data from the Multi-Ethnic Study of Atherosclerosis cohort showed that FMD measured at baseline was not related to incident hypertension after 4.8 years of follow-up [69]. Furthermore, endothelial NO deficiency can occur via a number of non-hypertension-related insults that increase oxidative stress, such as hypercholesterolaemia. In the apolipoprotein E knockout mouse, where endothelial dysfunction results due to a hypercholesterolaemic diet, BP is not elevated.

12.3.2 Hypertension and Large Artery Stiffness

Hypertension is related to increased stiffness of the aorta for any given level of BP [70]. The enlargement of large proximal arteries is suggested to be a compensating mechanism, ensuring that a certain level of arterial compliance is maintained [18, 71, 72]. The effect of pulsatile mechanical load on arterial remodelling has been observed in large elastic arteries but not in more distal, muscular arteries (radial). The changes in the large arteries are generally due to the fracture of the load-bearing elastin fibres due to the fatiguing effect of both the steady and pulsatile tensile stress. Collagen replaces the loss of elastin, and advanced glycation end products (AGEs) formation is accelerated, promoting cross-linking of structural proteins [73]. Vascular smooth muscle cell (VSMC) growth and apoptosis may also be involved, as the cyclic, pulsatile strain on the vessels is also a determinant of gene expression and growth of VSMCs in vitro [74, 75]. The structural alterations associated with arterial stiffness may also impair the vasodilatory function and alter

pulsatile haemodynamics, blood flow pattern and shear stress resulting in decreased NO bioavailability. Under conditions of increased oxidative stress, increased production of reactive oxygen species (ROS) leads to endothelial dysfunction and large elastic artery stiffening [76, 77]. Other molecular mechanisms associated with hypertension can also influence the stiffness of the arterial wall and are described in detail elsewhere [58]. Briefly, chronic activation of the renin-angiotensin system stimulates VSMC proliferation, low-grade inflammation, increased AGEs formation and collagen content which all promote arterial stiffening. Low-grade inflammation can lead to increased infiltration of VSMC, macrophages and mononuclear cells, media calcifications and cellular infiltration around the vasa vasorum which may result in ischaemia. Finally, sympathetic nervous system overdrive which occurs in individuals with hypertension [63] is an additional mechanism linking hypertension and increased large artery stiffness [64].

Although arterial stiffness has traditionally been viewed as a consequence of hypertension, the reverse may also be true, as recent studies have shown that arterial stiffness may contribute to the pathogenesis of hypertension [25, 46–49]. In mice who were fed a high-fat, high-sucrose diet and developed characteristics mirroring metabolic disease (insulin resistance, chronic inflammation and oxidative stress), aortic PWV increased within 2 months by 2.4-fold, while BP remained unchanged and only increased after 4–6 months [46]. In the Framingham offspring cohort, arterial stiffness (determined via carotid to femoral PWV) was associated with BP worsening and incident hypertension 4–10 years later [25]. Similarly, Zheng et al. [47] showed that after 27 months of follow-up, brachial to ankle PWV was associated with incident hypertension in Chinese adults, independent of traditional CVD risk factors. Furthermore, in young adults from the Young Finns Study, arterial stiffness (aortic arch to popliteal PWV) was independently associated with incident hypertension 4 years later [78].

12.3.3 Type 2 Diabetes and Endothelial Dysfunction

Hyperglycaemia, insulin resistance, dyslipidaemia, hyperuricaemia, increased dietary fructose and fat all predispose to endothelial dysfunction. People with T2D are particularly susceptible to the detrimental effects of endothelial dysfunction [36, 60]. T2D impairs the vasodilating properties of the endothelium via a number of mechanisms such as formation of AGEs and increased oxidative stress. Indeed, in patients with diabetes, exposure to acetylcholine causes vasoconstriction rather than vasodilation [79]. T2D may also amplify the detrimental effect of endothelial dysfunction on atherothrombosis via overproduction of ROS, inflammation, increased procoagulant activity and platelet aggregation [80]. Similar mechanisms have also been observed in those with impaired glucose metabolism or insulin resistance. Studies [60, 81] have shown that endothelial dysfunction is most strongly associated with incident CVD events in those with T2D compared to those without, suggesting the co-occurrence of T2D and endothelial dysfunction exacerbates CVD risk.

On the other hand, endothelial dysfunction exacerbates T2D by impairing the timely access of glucose and insulin in target tissues [54]. The Framingham Heart Study found that high levels of endothelial cell-derived Willebrand factor increased the risk of developing T2D, independently of other risk factors for T2D [81]. Similarly, in a large prospective study, higher levels of circulating E-selectin and intercellular adhesion molecule-1 (markers of endothelial dysfunction) were associated with increased risk of incident T2D after 5.9 years of follow-up [82]. Furthermore, hyperinsulinaemia and systemic insulin resistance stimulates the production of endothelin-1 (a vasoconstrictor) and, therefore, has been suggested to be a mechanism linking insulin resistance to the development of T2D. The combination of systematic insulin resistance and T2D accelerates endothelial cell dysfunction, thereby setting up a vicious, bidirectional cycle that promotes CVD.

12.3.4 Type 2 Diabetes and Large Artery Stiffness

While increased arterial stiffness is commonly observed in those with T2D, individuals with prediabetes also display arterial stiffening. A population-based cohort study (the Hoorn Study) in 747 individuals showed that prediabetes was associated with increased local femoral and brachial artery stiffness, but not carotid stiffness [83]. Others have also observed increased arterial stiffness in patients with prediabetes [41, 84] and accelerated progression of arterial stiffness over 4 years in non-diabetics but with elevated glycated haemoglobin or markers of insulin resistance [85]. The relationship between hyperglycaemia and arterial stiffening appears to be stronger in older, compared to younger adults [86]. Interestingly, endothelial dysfunction is related to aortic stiffness in those with hypertension and T2D, but not those without T2D, suggesting that diabetes-related metabolic alterations combined with hypertension may contribute to increased stiffness of large arteries via reduced endothelial function, independently of other confounders [43].

Recent work suggests there may be a bidirectional relationship between large artery stiffening and T2D, whereby arterial stiffening may contribute to the development of T2D. Indeed, Muhammad et al. [50] showed in 2450 individuals that after 4.5 years of follow-up, there was a stepwise increase in incidence of T2D across increasing tertiles of arterial stiffness independent of traditional risk factors. Another study recently showed that arterial stiffness measured via brachial-ankle PWV preceded increases in fasting blood glucose status [51]. Other haemodynamic markers related to large artery stiffness (pulse pressure, central systolic BP and augmentation index) have also been associated with increased risk of T2D [52, 53]. The relationship between arterial stiffness and incident diabetes may be explained via an increase in transmission of pressure and flow pulsatility to the microvasculature of the pancreas [6], which has a relatively high flow [79] and may be susceptible to the damaging effects of arterial stiffness. However, this is yet to be determined.

There are a number of mechanisms that may contribute to arterial changes in T2D which are discussed in detail elsewhere [14]. Briefly, hyperglycaemia contributes to blood vessel alterations early on in the progression of the disease [34], even

prior to the diagnosis of T2D [87]. Hyperglycaemia modifies the structure of the vasa vasorum [88] and may stimulate VSMC proliferation, migration and altered reactivity. Hyperglycaemia also leads to various changes in the glycolytic pathway, the pentose phosphate pathway and tricarboxylic acid cycle, which all lead to the production of ROS and oxidative stress. Oxidative stress impairs endothelial NO synthase activation which reduces NO availability [89]. Chronic low-grade inflammation also leads to a reduction in the bioavailability and activation of NO [90] as well as releasing vasoconstrictor prostanoids, which can result in endothelial dysfunction and increased arterial stiffness [91]. AGEs encourage inflammation, inhibit NO release and further promote oxidative stress [92]. Furthermore, hyperinsulinaemia has direct deleterious effects on VSMCs and endothelial cells and may also induce vascular alterations by inducing sympathetic activation [93].

12.4 Summary and Conclusion

T2D is associated with an increased risk of CVD, which is exaggerated by the coexistence with hypertension. Many of the underlying molecular mechanisms that contribute to macrovascular and microvascular complications in patients with T2D such as oxidative stress, inflammation and fibrosis also cause vascular remodelling and dysfunction in hypertension. Endothelial dysfunction and large artery stiffening are key contributors to the bidirectional relationship between T2D and hypertension. While a genetic predisposition plays a critical role in the development of endothelial dysfunction and arterial stiffness, genetic markers do not seem to overlap between hypertension and T2D at least. Controlling hypertension in those with T2D and targeting strategies to promote vascular health may be especially important in reducing complications, CVD and premature death in patients with T2D.

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