Chapter 6

Arterial Stiffness: A Review in Type 2 Diabetes

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http://dx.doi.org/10.5772/56582

1. Introduction

Diabetes is a growing health problem worldwide in [1]. In a prospective study the risk of cardiovascular death in patients with diabetes, without previous coronary heart disease (CHD) is equal to that of patients with CHD without diabetes, with a higher risk factor in women in [2]. This excessive risk is not explained by classic risk factors for cardiovascular disease such as smoking, LDL-cholesterol, hypertension in [3]. This has led to a search for early markers of vascular dysfunction (arterial stiffness) in diabetic patients that may pre-date the development of overt clinical disease, offer a target for early intervention and delay the progress of cardiovascular disease complications. Arterial walls stiffen with age. Once, the aging-associated changes in arterial structural and functional changes were thought to be part of natural aging, but this concept changed when data emerged showing that these changes are accelerated with coexistent cardiovascular disease. For example, patients with diabetes exhibit increased stiffness even after adjusting for age in [4] and this 'accelerated' arterial aging is well confirmed to be a risk. Several non-invasive methods are currently used to assess vascular stiffness. An extensive theoretical review of models underlying the definitions and assessment methods of arterial stiffness estimates have been recently published in [5].

Pulse wave velocity is a recognized marker of large artery stiffness. Increased arterial stiffness may be an important pathway linking diabetes to increased cardiovascular risk in [6]. Indeed, increased arterial stiffness predicts the development of cardiovascular disease and mortality in several groups of patients in [7] and has been shown to be elevated and predict premature mortality in patients with type 2 diabetes (T2DM) in [8]. Abnormalities in rigidity markers have been reported in patients with T2DM in [9,10] although not in all the arteries in [11], and also without T2DM though predisposed to diabetes suggesting that genetic influences operate through a mechanism different from structural alterations where body mass index (BMI), and

glucose metabolism may be involved in [12,13,14]. Diabetic patients are subject to a myriad of abnormalities (poor glycaemic control, dyslipidaemia etc) and it is difficult to determine which abnormality accounts for arterial stiffening in [15]. We present the results of an analysis that examined the independent association of PWV c-f with cardiovascular risk factors. This may be useful to interpret its variations and is of clinical relevance, as arterial stiffening is an independent predictor of an increase in cardiovascular risk in [16]. For this reason we used PubMed for bibliographic research from 1990 to 2012 using the key words : diabetes non-insulin dependent, T2DM, "PWVc-f," "aortic pulse wave velocity," and "aortic stiffness," which were combined with the terms determining and predictive. Articles with multiple regression analysis were included to evaluate factors independently associated with PWV c-f without any restriction on sample size or type. Variables not included in the regression analysis model were considered not independently associated with PWV c-f. Pathogenetic mechanisms, pathophysiological implications and strategies to reduce arterial stiffening will be discussed.

2. Pulse wave velocity carotid-femoral measurement

Pulse wave velocity carotid-femoral (PWVc-f) is currently considered the "gold standard" in [5] of aortic distensibility, a biophysical property of the arterial wall that allows the pressure waves generated by the left ventricle (buffering function) to be absorbed. PWVc-f, the velocity of arterial wave propagation between two arterial sites, can be measured non-invasively, is simple to determine, precise and reproducible in [17,18]. PWVc-f is calculated by dividing the distance between the carotid and the femoral artery by the time delay of the arterial pulse between these two arterial sites. The speed at which the pulse wave travels through an arterial segment increases with increasing stiffness in [19].

3. Factors associated with Pulse wave velocity carotid-femoral

Age is a powerful determinant of PWVc.f in [20,21]. The results of this review confirm that this is also the case for patients with T2DM. In particular, age is the main determinant of PWV c-f in the multiple regression analysis in 89% of nineteen studies (Table 1). Age exposes the aortic wall to degenerative phenomena such as collagen accumulation, fragmentation of elastic fibers and calcification of the media responsible for the increase in aortic rigidity in [22,23,24]. This interpretation gives a possible explanation of the relationship with arterial blood pressure that is another major determinant of PWVc-f in 95% of the included studies. Longstanding arterial pulsation in the central artery has a direct effect on the structural matrix proteins, collagen and elastin in the arterial wall, disrupting muscular attachments and causing elastin fibers to fatigue and fracture in [25]. This would explain why age and blood pressure are major determinants of PWV c-f in [26]. It should be stressed that aortic stiffening is not only a consequence of hypertension but is also in itself a pathogenetic mechanism of the disease. Several studies report an independent association between heart rate (HR) and PWVc-f. The

http://dx.doi.org/10.5772/56582

underlying mechanism is unknown, however several observations indicate that the rate of elastin fatigue fracture depends on the number of stress cycles that is, the number of heartbeats experienced which may explain the relationship between HR and PWVc-f in [27,28]. The relationship between HR and PWV c-f suggests that HR may be a confounding factor that should be incorporated into any analysis relating to PWVc-f. T2DM was associated with an increase in PWVc-f in some studies in [29,30,31,32,33] but not in others in [34,35,36,37]. One explanation for the variable association of PWVcf with diabetes mellitus is that it is gender dependent, with a stronger association in women than in men in [38]. A relation between duration of diabetes and PWV c-f has also been described in [39,40] although other authors have failed to show this in [41]. Glycaemia and glycate hemoglobin (HbA1c) were associated with an increase in PWV c-f in [42] that persisted in the multivariate analysis. In the study by Smith et al [43] there was a weak association between PWV c-f and fasting plasma glucose that persisted in the multivariate analysis. PWV c-f was unrelated to elements of the metabolic syndrome (waist circumference, BMI, and triglycerides) and smoking. Only in [44] BMI was associated to PWVc-f and waist-hip ratio in Strain et al [45]. More importantly, fasting glucose concentration, 2 h post-challenge glucose and homeostasis model assessment for insulin resistance (HOMA-IR) were independently related to PWV c-f after adjustment for age, gender, mean arterial pressure, HR, BMI, renal function and antihypertensive medication in [46]. Implying hyperglycaemic excursion and insulin resistance play important roles in the pathogenesis of atherosclerosis. Possible contributors to increased arterial stiffening in T2DM include impaired glycaemic control and the formation of advanced glycation. The aforementioned are end products which lead to structural changes in the vessel walls. Kimoto et al 2006 showed that gender is a determinant of PWV c-f. In the study by Smith et al women have greater age-related aorta stiffening than men, a finding consistent with the enhanced vascular risk in women with diabetes. In the study by Taniwaki et al aortic stiffness while increased in females, was not a risk factor of PWV c-f in the multiple regression analysis. None of the selected studies report smoking as a determining factor in patients with T2DM. Dyslipidaemia did not play an important role in atherosclerosis therefore it is plausible that hyperlipidaemia and foam-cell-driven plaque formation may affect vascular wall integrity at a later stage in the pathogenic process in [47]. Increased aortic stiffness was associated with retinopathy and peripheral neuropathy after adjusting for possible confounding variables. Other variables associated with increased aortic stiffness were old age, HR, diabetes duration, 24 h pulse pressure, dyslipidaemia and physical inactivity in [48].

4. Coefficient of determination (R^2) values

Thirteen studies (68%) reported R^2 values, representing the amount of variability in PWVc-f. Furthermore, regression models could predict a part of the variability of PWVc-f (22–73%) indicating that other factors (e.g. insulin resistance, advanced glycation end-products, genetic factors) may play a more important role in arterial stiffness in T2DM.

5. Pathogenetic mechanism of arterial stiffening

Arterial stiffness depends on the structure and function of the vessel wall. Alterations in the extracellular matrix of the media and adventitia have long been implicated in the pathogenesis of age and blood pressure-related increase in arterial stiffness in [49,50]. Data suggest that such alterations may be caused not only by short-term hyperglycemia, but also by carbonyl and oxidative stress and endothelial dysfunction in [51,52]. Impaired glucose tolerance also enhances nonenzymatic glycation of proteins with covalent cross-linking of collagen (AGEs) and alters the mechanical properties of interstitial tissue of the arterial wall in [53,54]. Chronic hyperglycemia and hyperinsulinemia increases the local activity of renin-angiotensin-aldosterone system (RAAS) and expression of angiotensin type I receptor in vascular tissue in [55] promoting development of wall hypertrophy and fibrosis in [56,57]. In recent years there has been growing evidence of the important role played by inflammation which can influence, by different mechanisms, the increase in arterial stiffness (endothelial dysfunction, smooth muscle proliferation and activation, changes in composition of extracellular matrix) in [58].

6. Pathophysiological implications

The principal function of the arterial system is to deliver an adequate supply of blood to tissues and organs. In performing this primary conduit function, the arteries transform the pulsatile flow generated by ventricular contraction into a continuous flow of blood in the periphery. This latter cushioning function is dependent on the mechanical properties of the arterial walls. Increased aortic stiffness has several detrimental effects on cardiovascular performance. A less distensible aorta cannot efficiently accommodate the blood volume ejected by the left ventricle, which results in high systolic pressure. In addition, diastolic pressure is decreased and pulse pressure (PP) is thus increased. These haemodynamic modification influence ventricular afterload and impair coronary perfusion in [59]. Indeed, PP is more closely predictive of mortality in individuals with T2DM than systolic (SBP) and diastolic blood pressure (DBP) in [60]. PWVc-f seems closely related to PP. Excessive pressure pulsatility enhances regional stress and flow abnormalities in the central aorta and proximal large arteries and may contribute to the propensity for focally severe atherosclerosis in these regions. Thus, excessive aortic stiffness and increased pressure pulsatility contribute to damage the arterial wall and may represent both a cause and a consequence of atherogenesis in [61]. Increased local pulsatile pressure and strain increase the likelihood of plaque rupture and thereby contribute to the increased risk of overt clinical events in individuals with atherosclerotic disease. In addition, high pulsatility may be transferred down to arterioles, resulting in disruption of microcirculation leading to stroke, dementia, and to renal failure in [62,63]. A positive relationship between PP and proteinuria has been observed in [64,65]. Such microvascular disease is accentuated in patients with T2DM.

http://dx.doi.org/10.5772/56582

7. Strategies to reduce arterial stiffening in type 2 diabetes

In patients at high risk of developing CVD, such as diabetic patients, it is important to improve arterial stiffness. There are many studies reporting changes in arterial stiffness after various interventions, either non-pharmacological or pharmacological. Non-pharmacological treatment able to reduce arterial stiffness include exercise training, weight loss, and various dietary modifications, including low-salt diet, moderate alcohol consumption, α-linoleic acid, dark chocolate, and fish oil in [66]. It is still debated whether the reduction in arterial stiffness after antihypertensive treatment is only attributable to blood pressure (BP) lowering, or if additional BP-independent effects are involved. However, renin–angiotensin–aldosterone system (RAAS) inhibitors, such as ACE inhibitors and angiotensin II receptor blockers (ARBs), have been widely suggested to have a BP-independent effect on arterial stiffness in [66,68]. Currently, ARBs are recommended as first-line drugs for hypertension treatment in T2DM patients. Several studies have reported that angiotensin receptor blockers (ARBs) also reduce arterial stiffness in patients with hypertension and T2DM in [69,70]. Fish oil ingestion improved vascular compliance in patients with T2DM by increasing nitric oxide (NO) production or release in [71]. Aerobic exercise has been reported to restore the loss of central arterial compliance and would likely improve arterial stiffening in patients with T2DM in [72]. A combined nutrition and walking program in [73] as well as a pure walking intervention in [74] have also demonstrated prospectively a decrease in arterial stiffness in the middle-aged diabetic population. In T2DM, 3 months of pioglitazone treatment reduced PWVc-f while increasing adiponectin in [75] and lowering C-reactive protein. Interestingly, the decrease of PWVc-f and C-reactive protein levels occurred irrespective of improved diabetic control, suggesting that vascular and antidiabetic effects of glitazones may be partially independent. Studies have shown reduction of arterial stiffness using compounds that affect or break the structure of advanced glycation end-product crosslinks (AGEs) in [76].

8. Conclusions

Arteries stiffen with advancing age, even in the absence of clinically detectable atherosclerotic disease. Diabetes has been shown to accelerate this age associated stiffening in [77] mainly through nonenzymatic glycation, the reaction between glucose and the extracellular matrix proteins in the arterial wall. Nonenzymatic glycation leads to the formation of increased collagen crosslinks that result in increased arterial stiffness in [78]. The results of this review show that in T2DM, the increase in aortic stiffness is independent from other common atherosclerotic risk factors. The principal determinants of PWV c-f are age and arterial blood pressure suggesting that an increase in aortic stiffness could be explained in terms of age and blood pressure. This review has certain limits: First, the studies were cross-sectional, and could not reveal causal relationships. Future studies should include prospective studies to elucidate the contribution of environmental-genetic factors over time to arterial stiffening. Secondly, only studies reporting PWV c-f as a measure of arterial stiffness were included. There is considerable variability in agreement between measures of stiffness and PWVc-f is clinically

References	Sample (n°)	Men %	Age	M	PWVc-f m/s	R2 (%)	Variables associated with PWVc-f	Other variables
Tanokuchi et al 1995 [34]	107 T2DM	54	59	H	9,4	-	Age, SBP,DBP	-
Taniwaki et al 1999 [39]	271 T2DM 285 C	44 51	51 50	U	9 7	33	Age-Diabetes duration	-
Amar et al 2001[4]	247 T2DM,HC	52	54	C	8,8	34	Age.SBP,HR	Apolipoprotein
Aoun et al 2001[41]	122 T2DM 122 Ccontrol	66 66	58 58	C	13 12	-	Age,MBP	-
Kimoto et al 2003 [30]	161 T2DM, 129 Control	53 43	60 59	N	- -	47	Age-SBP-T2DM	-
Lacy et al 2004 [29]	66 T2DM 66 Control	68 68	55 55	S	9,3 7,7	73	Age. SBP,DBP,HR,T2DM	Previous history of cardiovascular disease
Tedesco et al 2004 [42]	50 T2DM 85 T2DM -HT	60 39	53 55	C	11 13,8	22	MBP	FPG
Silva et al 2004 [37]	102 T2DM	37	55	C	12,6	-	Age.24-h SBP	-
Smith et al 2005 [43]	134 T2DM	66	61	S	10,2	55	Age,,PP, Diabetes duration	HT drugs, ACEI/ARB use
Paini et al 2006 [44]	126 T2DM	58	63	C	18,3	33	Age,SBP,	BMI
Kimoto et al 2006 [31]	434 T2DM with and without CKD	56	62 59	H	12,5	55	Age,SBP, T2DM,	Sex male, GFR, non cholesterol HDL
Strain et al 2006 [45]	51 European T2DM 66 African Caribbean T2DM	49 36	57 57	C C	14 15	-	Age,SBP,MBP,HR Age,MBP	Waist:hip ratio
Lee et al 2007 [33]	18 T2DM 20 Control		66 63	MR	8,8 6,2	70	Age,SBP,T2DM	-
Matsumae et al 2008 [40]	94 Hemodialysis with T2DM 148 Hemodialysis without T2DM	59	65	H	11	32	SBP, Diabetes duration Age,SBP,HR,	HbA1c Duration HD, HbA1c
Saez et al 2008 [32]	318 Renal transplant with and without T2DM	49	52	S	9	-	Age,SBP,T2DM	-
Rahman et al 2008 [36]	T2DM 30 IGT 30 NG 30		47 47 47	S	10,4 9,5 8,7	29	Age,SBP	2hPPG
Cardoso et al 2009 [48]	482 T2DM 334 148	38 37	59 67	C	<12 >12	-	Age,24-hPP,HR,Diabetes duration	Dyslipidemia,retinopathy, physical inactivity, peripheral neuropathy
Webb et al 2010 [46]	176 NGM 219 IGR 175 T2DM	58 59 59	55 53 57	U	8,9 9,7 10	51	Age, MBP,HR Sex Female	FPG,2HPG,HOMA-IR
Naka et al 2012 [35]	165 T2DM	30	66	S	10,2	25	Age, SBP	-

Table 1. Characteristic of studies on PWVc-f included in the review

the most relevant. PWV c-f is easy to measure with specifically designed devices. High aortic stiffness doubles the risk of cardiovascular events or mortality compared to low aortic stiffness, and the predictive value of high PWV c-f is greater in high-risk patients, such as patients with T2DM. PWVc-f expresses the cumulative effect of various factors on the arterial system and their interplay with genetic predisposition. In contrast to cardiovascular risk factors, such as blood pressure or cholesterol, that may fluctuate over time, PWVc-f is relatively stable, since it is mostly influenced by alterations of arterial wall structure. The 2007 European Society of Hypertension & European Society of Cardiology guidelines for the management of hypertension rightfully included increased PWVc-f as subclinical target-organ damage, and recommended aggressive management of patients with high PWVc-f in [79]. The World Health Organization estimates that by the year 2025 more than 300 million people worldwide will have diabetes [80]. Measurement of aortic PWV c-f should be integrated in the examination and risk stratification of patients with T2DM.

M, method, C, compilor; S, SphygmoCor; U, ultrasound; H, Hasegawa method MR, magnetic resonance, N, indicates noninvasivepressure recordings. R2,coefficient of determination, SBP, systolic blood pressure, DBP, diastolic blood pressure, PP, pulse pressure, MBP, mean blood pressure, HR, heart rate, FPG, fasting plasma glucose, T2DM, type 2 diabetes; BMI, body mass index, ACE angiotensin-converting enzyme ARB, angiotensin receptor blocker, GFR glomerular filtration rate, HbA1c, glycate hemoglobin, 2HPG, 2 h post-challenge glucose HOMA-IR, homeostasis model assessment for insulin resistance, IGT impaired glucose tolerance IR insulin resistance, IGR, impaired glucose regulation, HT, hypertensive HC, hypercholesterolemia.

Acknowledgements

We would like to thank Mrs Rotolo MR, (Prof. A. Malliani Library, University of Milan) for her help with the bibliographic research.

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