

Treating Arterial Stiffness in Metabolic Syndrome and Type 2 Diabetes Mellitus

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Abstract: Arterial stiffening characterizes ageing and several diseases related to increased cardiovascular (CV) risk such as the metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), hypertension, obesity and smoking. Several studies have shown that arterial stiffness is a strong, independent predictor of CV morbidity and mortality risk in such patient populations. Lifestyle measures and drugs frequently prescribed in MetS and T2DM patients such as hypolipidaemic, antihypertensive, hypoglycaemic and antiplatelet agents, may improve arterial stiffness, thus further reducing vascular risk. The current review considers the effects of these drugs and lifestyle changes on arterial stiffness in MetS and T2DM patients. The potential clinical implications of such effects on treatment decisions in clinical practice remain to be established. Multifactorial interventions may be even more beneficial in terms of CV risk reduction and thus their impact on arterial stiffness should also be evaluated.

Keywords: Antihypertensive, antiplatelet drugs, arterial stiffness, hypoglycaemic, hypolipidaemic drugs, metabolic syndrome, type 2 diabetes mellitus.

INTRODUCTION

Arterial stiffening characterizes ageing and several diseases related to increased cardiovascular (CV) risk such as the metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), hypertension, obesity and smoking [1-6]. Pulse wave velocity (PWV), a marker of arterial stiffness, can be non-invasively estimated by the evaluation of waveforms in the carotid and femoral or radial artery using certain devices (Sphygmocor and Complior are the most widely used) [7]. The carotid-femoral PWV (cfPWV) is currently considered the 'gold standard'; the recent 2013 guidelines of the European Society of Hypertension/European Society of Cardiology recommend the measurement of cfPWV in hypertensive patients to detect large artery stiffening (IIa-B level of evidence) [8].

Previous large long-term studies showed that increased arterial stiffness, as assessed by PWV, can independently predict CV morbidity and mortality, as well as all-cause mortality in different patient groups including those with MetS [9] and T2DM [10] as well as in the general population [11,12]. These associations were also supported by meta-analyses [13]; an increase in PWV by 1 m/sec was related to 15% increments in CV morbidity and mortality as well as all-cause mortality. Furthermore, arterial stiffness evaluation was reported to lead to the re-classification of patients into different CV risk categories, thus contributing a significant

additive value in CV risk prediction beyond traditional risk factors, including the SCORE and Framingham risk scores [8,14,15].

Based on the above data, there is increasing interest about arterial stiffness in the pathophysiology and management of patients with MetS and T2DM. The present review considers the effects of lifestyle measures as well as hypolipidaemic, antihypertensive, hypoglycaemic and antiplatelet drugs, that are frequently prescribed to these patients, on arterial stiffness. The potential clinical implications of such effects on treatment decisions in clinical practice remain to be established.

LIFESTYLE MEASURES AND ARTERIAL STIFFNESS

Weight reduction by diet and exercise was reported to improve arterial stiffness in patients with MetS, even after a short period of time (i.e. 3 months) [16]. A greater reduction in arterial stiffness was observed when a low-calorie diet was combined with an intensive training course (2 sessions of 90 min, 3 days per week) after only 7 weeks in morbidly obese individuals as compared with diet alone [17]. Of note, low-intensity exercise beneficially affected PWV only when combined with diet in obese postmenopausal women [18].

In an animal model, diet-induced obesity led to arterial stiffening within a month which preceded the development of hypertension by 5 months; weight loss resulted in normalization of both arterial stiffness and blood pressure [19]. Weight loss maintenance is also important for protecting the vasculature; among obese patients that successfully completed a 6-month weight reduction program, arterial stiffness was decreased only in those who maintained or even lowered

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their weight and not in those who regained weight within a period of 30 months [20].

The Amsterdam Growth and Health Longitudinal Study [21] showed that lower lifetime consumption of fiber, fruits, vegetables and whole-grains in young ages was associated with stiffer carotid arteries in adulthood. Similar results were obtained in the Cardiovascular Risk in Young Finns Study (duration = 27 years) with regard to lifetime fruit and vegetable intake [22]. Milk and dairy products, except butter, seem to protect against increased arterial stiffness as shown in a cohort of the Caerphilly Prospective Study [23] and in a subset analysis of the Maine-Syracuse Longitudinal Study [24]. Salt substitutes with reduced-sodium and increased-potassium content can reduce arterial stiffness over a 12-month period [25]. Cranberry juice and ginseng have been also reported to improve arterial stiffness in some studies [26,27].

Physical activity and especially vigorous habitual exercise was related to decreased arterial stiffness in the Amsterdam Growth and Health Longitudinal Study population [28]. In the same context, fit men with MetS (mean age = 52 ± 6 years) had similar PWV with unfit men without MetS [29]. Short-term aerobic physical activity (i.e. 3 weeks) improved arterial stiffness in T2DM patients [30]. Overall, exercise training has been shown to ameliorate arterial remodeling and stiffening in MetS, hypertensive, T2DM and obese patients [31]. However, it was recently reported that PWV reductions induced by aerobic exercise of 3 months duration in older patients (mean age 69.3 ± 0.6 years) with T2DM, hypertension and hyperlipidaemia were attenuated in 6 months [32]. Similarly, PWV did not change after a 6-month supervised exercise program (3 days per week) in T2DM hypertensive individuals, thus possibly suggesting a resistance in exercise-induced vascular benefits [33].

Smoking is associated with several risk factors for CV disease such as dyslipidaemia, hypertension, T2DM, chronic kidney disease (CKD), non-alcoholic fatty liver disease (NAFLD), peripheral arterial disease (PAD) and MetS [2,34,35]. Similarly, smokers as well as passive smokers have increased arterial stiffness [3]. Statin treatment can decrease the high CV risk of current smokers [36]. Furthermore, smoking cessation may improve arterial elasticity [37,38].

HYPOLIPIDAEMIC DRUGS AND ARTERIAL STIFFNESS

Statin-induced beneficial effects on arterial stiffness have been reported in several patient populations [39,40] including MetS and T2DM patients [9]. In this context, atorvastatin [41,42], fluvastatin [43] and pitavastatin [44] were previously shown to improve arterial elasticity in diabetic individuals. Data on fibrates are scarce; in one study fenofibrate did not affect arterial stiffness in T2DM patients [45]. A recent study reported decreased arterial stiffness following treatment with extended-release niacin in MetS patients [46]; to our knowledge there are no data in diabetics. Overall, there is a need for further randomized trials investigating the impact of statins on arterial stiffness as conflicting results also exist [47].

Omega-3 polyunsaturated fatty acids when supplemented after experimental ovariectomy prevented arterial stiffening and hypertension development [48]. Similarly, they can reduce arterial stiffness in humans as reported in a previous systematic review [49].

ANTIHYPERTENSIVE DRUGS AND ARTERIAL STIFFNESS

Several studies have shown that antihypertensive drugs can reduce arterial stiffness [6,50] both after acute and long-term (12 months) antihypertensive therapy [51,52].

Calcium antagonists, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), diuretics and vasodilating beta-blockers have been reported to improve PWV without significant differences between drug categories [53-60]. Similar results are supported by meta-analyses for ACEi [61-63]; such improvements in arterial hemodynamics are independent of blood pressure lowering. In contrast, when augmentation index (AIx) is used to assess arterial stiffness, the effects of beta-blockers are markedly different than that of other antihypertensive drugs; beta-blockers increase AIx, partly due to reductions in heart rate, whereas other agents decrease AIx [64]. Interestingly, conventional beta-blockers (such as atenolol), although equally reducing PWV, are less beneficial on central hemodynamics and AIx, whereas the newer vasodilating beta-blockers (such as nebivolol, carvedilol, and labetalol) seem to share the benefits of the other antihypertensive drugs [55,59]. Aliskiren (a direct renin inhibitor), spironolactone and eplerenone were also reported to decrease PWV [53].

This theme is extensively discussed in another review of this special issue [65]. There is an unmet need for further large, randomized controlled trials to compare the effects of different antihypertensive agents on arterial stiffness. Furthermore, novel antihypertensive agents such as aldosterone synthase and neprilysin inhibitors, as well as new devices/procedures, including renal denervation and baroreceptor stimulation, are currently being investigated with regard to arterial remodeling [66].

HYPOGLYCAEMIC DRUGS AND ARTERIAL STIFFNESS

Hemoglobin A_{1c} (HbA_{1c}) has been related to increased PWV in a dose-dependent way in the general population [67] as well as in patients with pre-diabetes [68], T2DM [69] or MetS [70], although conflicting results exist for older non-diabetic adults [71] and Korean T2DM patients [72]. Metformin was associated with improvements in arterial stiffness in patients with NAFLD [73] or polycystic ovary syndrome (PCOS) [74]; only one study evaluated the impact of metformin therapy on arterial stiffness in T2DM individuals, reporting no significant changes [75]. Insulin [76] as well as pioglitazone [77-79] and glimepiride [80] (but not glibenclamide [81,82]) were shown to decrease arterial stiffness in T2DM patients.

With regard to the incretins, sitagliptin [81] and liraglutide [83] did not affect arterial stiffness in T2DM individuals. However, data are scarce and further studies are needed with other gliptins and glucagon-like peptide-1 (GLP-1) analogues/agonists.

ANTIPLATELET DRUGS AND ARTERIAL STIFFNESS

There are no data on the effect of antiplatelet drugs (such as aspirin, clopidogrel, prasugrel and ticagrelor) on arterial stiffness. Only one recent study [84], evaluated the effects of cilostazol (vs placebo) on arterial stiffness in T2DM patients with MetS; no significant differences were found after 8 weeks of treatment in terms of both PWV and other inflammatory biomarkers except for soluble vascular cellular adhesion molecule-1 (sVCAM-1) which was reduced.

Anticoagulants including warfarin, heparins, direct factor Xa inhibitors (rivaroxaban, apixaban) and direct thrombin inhibitors (dabigatran) have also not been studied with regard to arterial stiffness.

MULTIFACTORIAL TREATMENT

Several studies have shown the beneficial effects of multifactorial interventions (including lifestyle changes, hypolipidaemic, antihypertensive, antiplatelet, hypoglycaemic and antiobesity drugs) on CV risk reduction in different patient populations such as those with CKD [85], MetS [86,87] and T2DM [88,89].

With regard to arterial stiffness, only one recently published study compared intensive multifactorial treatment versus routine care in T2DM patients [90]; after a mean follow-up of 6.2 years, those receiving multifactorial interventions had significantly lower PWV than those on routine care.

CONCLUSIONS

There is increasing interest in the role of arterial stiffness in the pathophysiology and management of patients with MetS and T2DM. Several studies have shown that arterial stiffness is a strong, independent predictor of CV risk in such patient populations. Lifestyle measures, hypolipidaemic, antihypertensive, hypoglycaemic and antiplatelet drugs, frequently prescribed in MetS and T2DM patients, may improve arterial stiffness, thus further reducing vascular risk. However, future research is needed to establish the role of arterial stiffness in clinical practice as well as in selecting the appropriate drugs when treating high-risk patients such as those with MetS and T2DM. Multifactorial interventions may be even more beneficial in terms of CV risk reduction and thus their effects on arterial stiffness should also be evaluated.

CONFLICT OF INTEREST

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