# Obesity and Metabolic Syndrome

# 17

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Obesity, in particular central obesity, is a major risk factor for cardiovascular disease (CVD) [1]. A great portion of the adverse impact of (central) obesity on cardiovascular health may be explained through related haemodynamic and metabolic mediators such as blood pressure (BP), cholesterol and glucose [2]. These risk factors tend to cluster within individuals forming the metabolic syndrome (MetS) [3]. Obesity and/or MetS-related adverse changes in the arterial wall provide a structural and functional background for clinical events such as myocardial infarction, stroke and peripheral artery disease, all known to occur at higher rates in these conditions [4–7]. This chapter revises the current epidemiological evidence around the adverse effects that (central) obesity and the MetS may exert on large artery properties, particularly, arterial stiffening. Focus is put on evidence derived, whenever available, from representative prospective observational and intervention studies conducted over the last decade.

## 17.1 Body Fatness/Fat Distribution and Arterial Stiffness: An Early Phenomenon

Many studies have shown that higher levels of body fatness, in particular, a central pattern of fat distribution, are associated with arterial stiffness (reviewed in [6, 8]). These primarily cross-sectional studies may be fairly summarised into two key observations: firstly, deleterious adaptations related to increased adiposity seem to occur across all age categories [9–11]; secondly, such adaptations are observed with

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higher levels of adiposity even when within the ranges of normal weight and are thus not confined to obesity. Indeed, the increased levels of arterial stiffness observed already among children/adolescents [12–17] and young adults [9, 18, 19] suggest that higher levels of (central) adiposity do not need to be long lasting to have deleterious effects on the arterial system. In addition, the fact that higher levels of (central) adiposity at young(er) ages are associated with higher arterial stiffness later in life [18, 20–22] and that a favourable change in obesity status from childhood to adulthood is associated with less arterial stiffness in adulthood [23] emphasise the importance of healthy lifestyle promotion early in life. The strong tracking of (central) obesity throughout the life course [20] further corroborates this need because early and cumulative exposures to adverse levels of (central) body fatness may hamper considerable and sustainable improvements in arterial properties resulting from interventions targeting obese adults, given that such interventions will invariably be much shorter than a person's lifetime.

## 17.2 Do Changes in Body Fatness Affect Arterial Stiffness?

The extent to which changes in body fatness affect changes in arterial stiffness remains unclear because most of the longitudinal (observational or intervention) studies available thus far have been restricted to the appreciation of the impact of changes in body weight, which does not discern fat from lean body mass. Indeed, some observational studies have shown that increases in weight were associated with increases in arterial stiffness among young and healthy [24] and overweight middle-aged adults [25]. Several small intervention studies, all confined to individuals with obesity or diabetes, have shown that weight loss led to arterial de-stiffening [26–30]. More recent and larger randomised controlled trials (RCTs) confirmed the beneficial effects of weight loss attained by means of behavioural interventions (diet and/or exercise) among nondiabetic overweight/obese individuals with (e.g. the ENCORE study [31]) or without hypertension (e.g. the SAVE trial [32, 33]). Assuming that the weight loss attained indeed reflected reductions in body fatness, these findings support the view that body fatness may impact on arterial stiffness independently, at least in part, of related changes in BP. Still, it remains that arterial adaptations related to weight changes do not clarify the extent to which any of the favourable effects observed could be attributed to reductions in specific types of fat depots (e.g. *visceral* vs. *subcutaneous*) and/or its distribution (e.g. *central* vs. *peripheral*) or even be attenuated by concomitant loss of muscle mass.

### 17.2.1 Visceral Fat as Main Determinant of Arterial Stiffness

Abdominal visceral fat is thought to be more strongly associated with arterial stiffness than abdominal subcutaneous fat [34–37]. In an important proof of concept study, and despite its small sample and highly experimental setting, Orr et al. indeed showed that abdominal visceral (VAT), not subcutaneous adipose tissue (SAT), was

associated with the increases in arterial stiffness resulting from 5 kg weight gain induced by overfeeding nonobese young adults for 6–8 weeks [38]. In addition, in a recent study in which the biopsies from visceral (greater omentum) and subcutaneous (abdominal) white adipose tissue samples were obtained from obese subjects scheduled for bariatric surgery, the visceral fat cell size (i.e. volume), but not number, was strongly associated with arterial stiffness, whereas no such association was found with SAT (volume or number) [39]. It must be mentioned that recent studies suggest that the adverse effect of VAT on arterial stiffness (as on metabolic disturbances relating central obesity to poorer cardiovascular outcome) may not only be due to the effects of omental hypertrophy of adipose tissue but also due to adipose tissue accumulating specifically around the epicardium [40–42] and/or in the liver (a typical feature of non-alcoholic fatty liver disease) [43–45]. Because this evidence derives from cross-sectional studies, the interrelations, relative contributions and specific pathobiological mechanisms through which these fat depots may impact on general and local arterial stiffening, and haemodynamic factors still need to be further investigated in prospective studies.

### 17.2.2 The Beneficial Role of Peripheral Fat on Arterial Stiffness

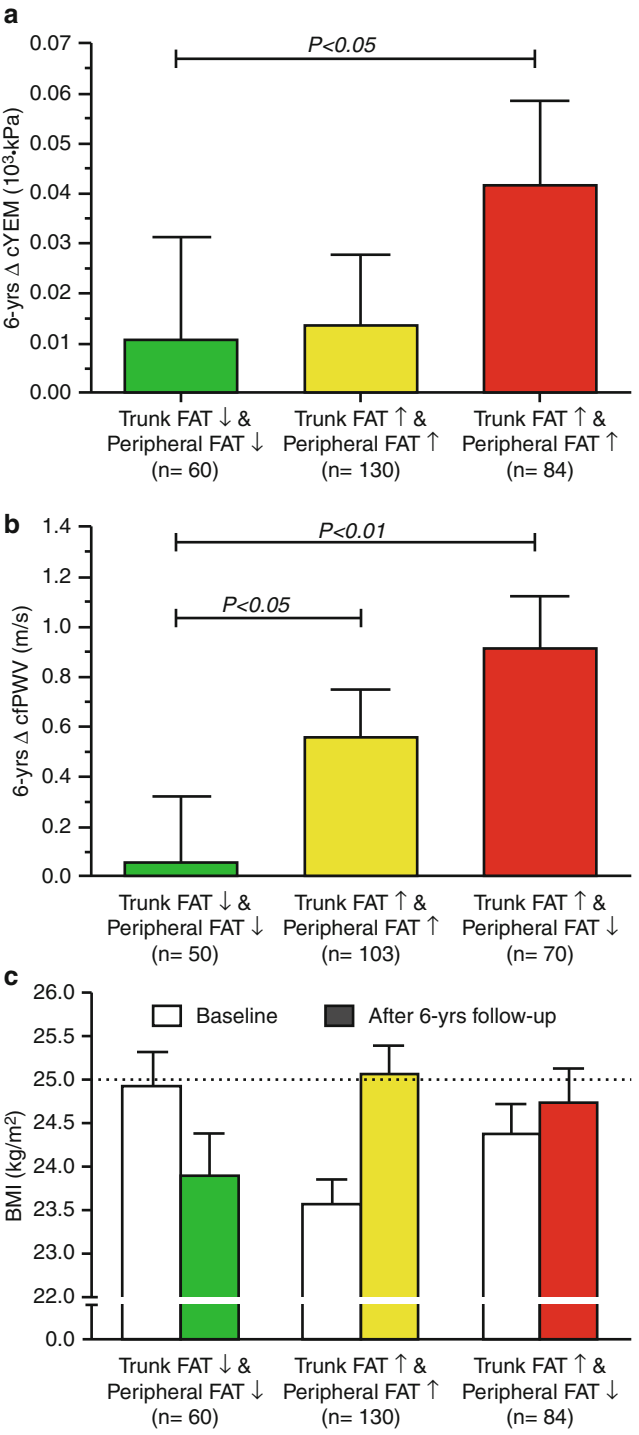
Studies examining the role of the whole-body fat distribution on arterial stiffness rather than of central fatness only have unveiled a complex scenario: in contrast to central fat (i.e. that accumulated in the trunk/abdominal areas), higher levels of peripheral fat mass (i.e. that accumulated in the limbs and thus stored mainly subcutaneously) may have an independent *favourable* impact on arterial stiffness [19, 46, 47]. Indeed, the different lipolytic activity of the two fat regions/tissues provides biological support for their opposite effects on arterial stiffness. These 'dysfunctional' [1] vs. 'functional' [48] effects of fat could explain why, in general, central fat estimates correlate more strongly with health outcomes than estimates of total body fatness. As such, adverse changes in *body fat distribution* may occur with ageing (i.e. increases in central accompanied by decreases in peripheral fat mass) without being detected by appreciable changes in total body weight or body mass index (BMI), though both contributing, additively, to accelerated arterial stiffening. This hypothesis was tested in the *Amsterdam Growth and Health Longitudinal Study*, in a first study to have examined in detail, how naturally occurring changes in body fat and its distribution (assessed by dual x-ray absorptiometry) correlated with changes in arterial stiffness indexed by a large set of valid estimates throughout the arterial tree [49]. The study had three key findings: first, throughout the 6-year longitudinal study (between the ages of 36 and 42), greater levels of central fat were *adversely* associated with carotid, femoral and aortic stiffness, whereas greater levels of peripheral fat were *favourably* associated with these stiffness estimates; these associations reflected the more 'chronic' (deleterious) effects of persistent adverse fat distribution over time. Second, increases in trunk fat were *adversely* associated with 6-year changes in carotid and aortic, though not femoral, stiffness, whereas increases in peripheral fat were *favourably* associated with changes in these stiffness

estimates; these observations suggested a more 'acute' component to the deleterious effects of changes in body fat distribution on arterial stiffness of predominantly elastic arterial segments. Finally, the detrimental effects of *increases* in central fat and *decreases* in peripheral fat on arterial stiffness were independent of one another and concomitant changes in lean mass and other risk factors (including mean BP) and were accompanied by only minor increases in body weight [49]. Noteworthy, increases in trunk but decreases in peripheral fat mass formed a relatively prevalent phenotype (one third of the study population) that displayed the steepest rates of progression in carotid and aortic stiffness (Fig. 16.1a, b, *respectively*) despite changes in BMI that ranged within the limits assigned to normal weight (Fig. 16.1c). This phenotype is consistent with the existence of a relative prevalent subgroup of individuals at the population level designated as 'metabolically obese but normal weight', who are often characterised by elevated visceral adiposity (despite a BMI <25) and a more atherogenic lipid and/or glucose metabolism profile and who thus may be at a particular high risk for metabolic and arterial disease and in need of appropriate screening and preventive measures [50, 51].

### 17.2.3 The Role of Muscle Mass: The Need for Comprehensive Whole-Body Composition Studies

Adopting a whole-body composition (i.e. examining also the independent contribution of muscle mass in addition to body fat) rather than a body fat/fat distribution-only model has revealed that also appendicular muscle mass may be an independent beneficial determinant of arterial stiffness, particularly though not confined to the elderly [19, 46, 49, 52–55]. Currently, there is a great concern about the cardiometabolic consequences of the increasing prevalence of (central) obesity and sarcopenia (i.e. the degenerative loss of skeletal muscle mass and strength) associated with ageing, especially when occurring in combination – i.e. *sarcopenic obesity* [56]. How decreases in lean mass may affect arterial stiffness is not clear as the evidence so far has been mainly derived from cross-sectional studies [19, 46, 52–55]. It is possible that the relationship is not causal in the sense that higher muscle mass may simply reflect higher (lifelong) physical activity and/or less sedentary habits, better nutrient intake status and/or better glucose uptake/insulin sensitivity, all of which protect against arterial stiffness [57–61]. Alternatively, arterial stiffness may promote sarcopenia by reducing limb blood flow and inducing rarefaction and

**Fig. 17.1** Comparisons of (**a**) changes in carotid Young's elastic modulus (cYEM), (**b**) changes in carotid-femoral pulse wave velocity (cfPWV) and (**c**) baseline and follow-up body mass index (BMI), between different phenotypes of change in body fat distribution as observed in a 6-year follow-up from the *Amsterdam Growth and Health Longitudinal Study*. BMI data were adjusted for sex; arterial data were adjusted for sex, body height and changes in mean arterial pressure, lean mass and other biological risk factors. Error bars indicate the standard errors of the means (Reproduced from Schouten et al. [49] with permission from the American Society of Nutrition)


a
P<0.05
6-yrs Δ cYEM (10³•kPa)
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
Trunk FAT ↓ & Peripheral FAT ↓ (n= 60)
Trunk FAT ↑ & Peripheral FAT ↑ (n= 130)
Trunk FAT ↑ & Peripheral FAT ↑ (n= 84)
b
P<0.01
P<0.05
6-yrs Δ cfPWV (m/s)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Trunk FAT ↓ & Peripheral FAT ↓ (n= 50)
Trunk FAT ↑ & Peripheral FAT ↑ (n= 103)
Trunk FAT ↑ & Peripheral FAT ↓ (n= 70)
c
Baseline
After 6-yrs follow-up
BMI (kg/m²)
26.0
25.5
25.0
24.5
24.0
23.5
23.0
22.0
0.0
Trunk FAT ↓ & Peripheral FAT ↓ (n= 60)
Trunk FAT ↑ & Peripheral FAT ↑ (n= 130)
Trunk FAT ↑ & Peripheral FAT ↓ (n= 84)

dysfunction in the microcirculation, thereby affecting muscle contraction and ultimately leading to muscle mass rarefaction. This hypothesis was supported by a recent prospective study from the *Health*, *Aging and Body Composition Study*, showing that older individuals with higher cfPWV at baseline had poorer levels of leg lean mass and sarcopenic index at baseline and over a 6-year follow-up period, independently of age, BMI, BP, diabetes, physical activity, smoking, total fat mass, low-grade inflammation, peripheral artery disease and CHD status [62]. Further longitudinal and intervention studies are needed to clarify the role of muscle mass on arterial stiffening (or vice versa), if any. Nevertheless, the existence of a link between muscle mass and arterial stiffness retains relevant clinical implications because it stresses the need to carefully monitor and secure that weight-loss interventions do not occur at the expense of muscle mass, particularly among the elderly.

## 17.3 Metabolic Syndrome and Arterial Stiffness: An Early Phenomenon

Increased arterial stiffness has been consistently reported in individuals with the MetS or with increasing clustered load or number of traits of the MetS (reviewed in [7]). Like for (central) fatness, a major force underlying the MetS risk factor clustering, such adverse arterial changes have been shown across all ages [63, 64], including young children and adolescents, with [65] or without overt obesity [12, 66], and young [67–71] and older adults [72], including those treated [73] or untreated for hypertension [74, 75]. The increased arterial stiffness in the MetS thus seems to be caused by subtle metabolic abnormalities that characterise prediabetic states but not necessarily fully developed diabetes. In addition, the recent findings from *the Cardiovascular Risk in Young Finns Study* showing higher levels of arterial stiffness among young adults who had the MetS during youth but also of arterial stiffness reduced to levels similar to those who had never had the MetS throughout the life course among those who, by adulthood, recovered from the MetS [76], support the potential reversibility of the adverse effects of the MetS if prevented/targeted early in life.

## 17.4 Do Changes in Metabolic Syndrome Status Affect Arterial Stiffness?

Confirming the suggestions derived from cross-sectional observations showing that the increases in arterial stiffness with advancing age were accentuated in the presence of the MetS [68, 64], recent prospective cohort studies have shown that individuals with the MetS not only have higher arterial stiffness at baseline but also display *steeper* increases in arterial stiffness with ageing as compared with those without the MetS [70, 77–80]. In addition, analyses of the impact of changes in MetS status among young [80, 81] and middle-aged [82] adults showed that those with incident and persistent MetS over the course of time displayed the steepest

increases in arterial stiffness as compared with their peers who remained MetS-free throughout. Importantly, increases in arterial stiffness with ageing among those who recovered from the MetS tended to be somewhat less steep than those with persistent MetS [80] or even comparable to those who remained MetS-free throughout [82, 81]. An important observation in one of these longitudinal studies was that the MetS-related increase in carotid stiffness seemed to have preceded structural and local haemodynamic changes consistent with maladaptive (outward) carotid remodelling, an important process that may explain the increase risk of stroke in individuals with the MetS [80]. Taken together, the longitudinal data reviewed above [70, 76–82] demonstrate *accelerated arterial stiffening and maladaptive remodelling*, which may explain, at least in part, the increased CVD risk in individuals with the MetS [7]. These findings also emphasise the importance of primary prevention given the observed reversibility of the adverse impact of MetS on arterial structural and functional properties among those individuals who recovered from the MetS.

### 17.4.1 Specific Clusters of the Metabolic Syndrome's Traits and Arterial Stiffness

It is important to stress that the association between the MetS and arterial stiffness seems not only to be attributable to elevated BP, one of its most common traits and a main determinant of arterial stiffness. Indeed, in addition to (and independently of) elevated BP, (central) obesity and increased glucose levels are traits often associated with arterial stiffness [70, 72, 80, 83], whereas dyslipidaemia (as ascertained by elevated triglycerides and/or decreased HDL cholesterol) has been less or not consistently so. The clustering of central obesity, increased glucose levels and BP appears to be the most prevalent across several populations in the western world [64, 84, 83], and this phenotype is not only associated with the highest arterial stiffness levels [64, 83] but also with the greatest mortality risk [84].

## 17.5 Pathobiological Mechanisms Linking (Central) Obesity and the Metabolic Syndrome to Arterial Stiffening

The adverse association of the critical axis (central) obesity - MetS with arterial stiffness raises important questions about the potential underlying molecular processes. These may include some of the effects central obesity and related insulin resistance are known to exert at the vascular wall level, for instance, through inflammatory reactions, endothelial dysfunction and sympathetic activation [34, 32, 85]. These abnormalities are interrelated and affect vascular tone and stimulate vascular smooth muscle cell proliferation. In addition, changes in the type or structure of elastin and/or collagen in the arterial wall due to hyperglycaemia, particularly the formation of cross-links through nonenzymatic glycosylation of proteins that generate advanced glycation end products, could constitute another mechanism [7]. Several of these putative mediators are thus likely to account for the obesity- or MetS-related increases in arterial

stiffness, but currently we have only fragments of insight among a likely large set of players involved [5]. Teasing apart their individual contribution and/or identification of predominant operative pathways may provide key information for tailored interventions aiming at the treatment of arterial stiffening and related cardiovascular *sequelae* [6]. A comprehensive analysis of these issues in the context of representative prospective cohort studies or RCTs is still lacking and thus most warranted.

## 17.6 Summary

In this chapter, recent epidemiological evidence pertaining to the role of (central) obesity and the MetS on arterial stiffness was reviewed. Reinforced by recent prospective data, there is convincing evidence that these interrelated risk factors increase arterial stiffness, a mechanism that may explain the associated higher CVD risk. However, there is still relatively few data on (1) the molecular basis of greater arterial stiffness associated with these risk factors, (2) the prognostic significance of arterial stiffness indices in individuals with these risk factors and (3) the extent to which intervention on these risk factors improves cardiovascular outcome through beneficial impact on arterial stiffness. Given the high and increasing prevalence of obesity and the MetS, these questions constitute an important research agenda.

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