Fat Distribution and Arterial Stiffness

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Summary

Cardiovascular disease (CVD) is a serious health epidemic in Western societies. In the Netherlands CVD is responsible for 30% of death for women and 28% for men. One of the main underlying causes of CVD is arterial stiffness, by its contribution to systolic hypertension, left ventricular hypertrophy and impaired coronary perfusion. Although the clinical consequences (such as myocardial infarction, stroke and heart failure) usually occur in middle-aged or older people, arterial stiffness already begin in childhood and early adulthood, with a pre-clinical phase which is already detectable. Excessive body fat and, in particular, a central pattern of fat distribution (i.e. fat of the trunk), is an independent predictor of cardiovascular risk. In contrast, peripheral fat (i.e. limbs) has been suggested to have a protective effect on cardiovascular risk. Furthermore, it has been demonstrated that individuals with obesity are also likely to have an increase in arterial stiffness. Obesity-related increases in arterial stiffness have been proposed as one of the potential pathways through which (central) obesity could lead to cardiovascular disease.

Central fat and peripheral fat may differ in secretion of adipose derived proteins that influence the metabolism, vascular function, vascular structure and this way arterial stiffness. The pathobiological mechanisms explaining why especially central body fatness is associated with arterial stiffness remains largely unknown, however. One mechanism may be an altered profile of adipokine secretion, such as hyperleptineamia and/or hypoadiponectinaema. As an alternative to the adipokine hypothesis, other adiposity-related factors may in part explain the relationship between central body fatness and arterial stiffness. These include low-grade systemic inflammation and endothelial dysfunction.

The general purpose of this thesis was to gain more insight in the longitudinal associations between body fatness, fat distribution and arterial stiffness. The unique characteristics of the *Amsterdam Growth and Health Longitudinal Study* (AGAHLS), an observational longitudinal study that started in 1976 with a total inclusion of 698 boys and girls, allowed the study of these above mentioned associations.

Main findings

Chapter 2 addressed the associations between changes in central fat versus peripheral fat and lean masses with changes in arterial stiffness over a 6-year follow-up period between 36 and 42 years of age. First, throughout the 6-yr longitudinal study, greater levels of total body fatness, particularly of trunk body fat, were *adversely* whereas peripheral lean mass was *favourably* associated with carotid and femoral stiffness. Trunk and peripheral fat also exhibited opposite associations with aortic stiffness. Second, *changes* in trunk fat were adversely whereas *changes* in peripheral fat and lean masses were favourably associated with *changes* in the carotid and aortic, but not femoral, stiffness. Finally, the detrimental and additive 'effects' of *increases* in trunk and *decreases* in peripheral fat masses on arterial stiffness were independent of one another and of concomitant changes in lean mass and other risk factors, and were accompanied by only minor increases in body weight. Importantly, this pattern of changes in body fat distribution was observed for individuals who were on average in the normal-weight range, who made up about one third of the study population, and who exhibited the steepest increases in arterial stiffness.

Chapter 3 evaluated the relationship between the development of an extensive array of biomarkers of endothelial dysfunction and low-grade inflammation on the one hand and arterial stiffness on the other over a 6-year period. First, endothelial dysfunction and low-grade inflammation were associated with greater arterial stiffness. Endothelial dysfunction was associated with greater femoral artery stiffness, whereas low-grade inflammation was associated with both greater carotid and femoral artery stiffness. However, both endothelial dysfunction and low-grade inflammation were not associated with aortic stiffness. Second, mutual adjustment for low-grade inflammation or endothelial dysfunction showed that the associations between endothelial dysfunction and low-grade inflammation with femoral artery stiffness were interdependent.

Chapter 4 focussed on the associations between leptin, adiponectin, and the leptin-to-adiponectin ratio (LAR) with carotid, femoral and aortic stiffness throughout the 6-year period. We found that lower levels of adiponectin and higher levels of leptin and of the LAR were adversely associated with carotid and femoral stiffness. However, neither the adipokines nor their ratio was associated with aortic stiffness

(as measured by cfPWV). Thus, the adipokines may affect arterial stiffening in a site-specific way, exerting their effect on first and second-generation branches of the aorta, but sparing the aorta itself.

Chapter 5 examined the potential mediating role of adipokines, low-grade inflammation and endothelial dysfunction in the relationship between total fat and trunk fat mass on the one hand and arterial stiffness on the other hand (research question 2 and 3, outlined in Introduction). Adipokines, rather than low-grade inflammation and endothelial dysfunction, to a large extent explained the relationship between overall fatness and arterial stiffness, and also between central fatness and carotid stiffness.

Chapter 6 addressed to what extent the longitudinal development of fatness parameters (BMI, sum of skinfolds and skinfold ratio) from the age of 13 to 36 years precede favourable or unfavourable levels of adipokines at the age of 36 years . It appeared that higher levels of total fatness (as estimated by sum of skinfolds) and BMI during adolescence were adversely associated with unfavourable levels of leptin, but to a lesser extent with adiponectin, in adulthood.

Conclusions

From the results presented in this thesis, it is difficult to estimate the direct implications for public health because the outcome used in the present thesis, arterial stiffness, is a pre-clinical measure. However, stiffness of mainly elastic arteries is predictive of incident cardiovascular disease and mortality. A recent meta-analysis estimated a 14-15% increased cardiovascular disease and mortality risk per 1m/s increase in cfPWV. On the basis of these data, our estimates may translate to comparable or even greater increases or decreases in risk per 10 kg increase in trunk fat mass or decreases in peripheral fat mass in young adults over the course of 6 years, respectively. All together, our data support the view that adiposity-related increases in central stiffness may explain, at least in part, the increased cardiovascular disease and mortality attributed to a central patterning of fat distribution.