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Original Article

Predictors of abdominal adipose tissue compartments: 18-year follow-up of young men with and without family history of diabetes☆

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ABSTRACT

Background: Abdominal adipose tissue (AAT) consists of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), which can be further divided into superficial and deep SAT. Despite being a key factor in the development of metabolic and cardiovascular diseases, what predicts future amount of AAT is largely unknown.
Objective: To determine long-term predictors of amount of AAT.
Methods: This was a mean 18-year follow-up study of a cohort of 94 healthy young Caucasian men, with and without a family history of diabetes (FHD). Cardiovascular risk markers were examined both at baseline and at follow-up. At follow-up, computed tomography (CT) of AAT was conducted to assess amount of superficial and deep SAT, and VAT.
Results: In multiple regression analyses, baseline body mass index (BMI) remained a positive predictor of future amount of superficial and deep SAT, while high-density lipoprotein (HDL) cholesterol was a negative predictor of all three sub-compartments. Baseline risk markers were generally stronger predictors among men with FHD, than among men without. In addition, FHD had greater impact on amount of deep SAT and VAT, than on amount of superficial SAT.
Conclusion: Our data suggest that the traditional cardiovascular risk markers BMI, HDL cholesterol and family history of diabetes are long-term predictors of the different abdominal adipose tissue compartments from young towards middle age in healthy men. In men with family history of diabetes, cardiovascular risk markers at a young age seem to be of greater importance to future amount of abdominal adipose tissue, than among men without.

1. Introduction

Abdominal obesity is an established risk factor for insulin resistance, type 2 diabetes and cardiovascular disease [1]. The negative impact from excess abdominal visceral adipose tissue (VAT) is well established [2]. However, there have been diverging reports on whether abdominal subcutaneous adipose tissue (SAT) has a protective or harmful influence [3]. Already 15–20 years ago, there were reports on the functional distinction between the deep and superficial SAT divided by a membranous layer [4,5]. The amount of deep SAT was found to be a cardiometabolic risk factor similar to VAT, while superficial SAT was much more beneficial [4,5]. Despite this, the majority of the ensuing studies have been conducted without considering the two substantially different sub-compartments of SAT. Consequently, most of the discrepancy regarding influence of SAT may be due to the lack of distinction between these two layers. Family history of diabetes (FHD) has been shown to be associated with adipose tissue dysfunction [6], and may also yield discrepant results if left unconsidered.

The relationship between sympathoadrenal activity and the accumulation of body fat is highly complex [7]. Although obesity is often associated with increased sympathetic nerve activity [8], several

Abbreviations: AAT, abdominal adipose tissue; BP, blood pressure; CT, computed tomography; FHD, family history of diabetes; GDR, glucose disposal rate; HT, hypertension; MST, mental stress test; SAT, subcutaneous adipose tissue; TGs, triglycerides; VAT, visceral adipose tissue.

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studies, including a cross-sectional study of the present population [9] and a prospective study of a similar cohort [10], have suggested negative associations between adrenaline release and obesity. Increased insulin resistance has also been shown to predict future VAT in middle-aged non-diabetics [11]. Still, what predicts future amount of AAT is largely unknown, since most studies are of a cross-sectional design. The aims of our study were to explore the predictive roles of cardiovascular risk markers on future amount of superficial and deep SAT, and VAT. Moreover, we investigated if FHD had any impact on the strength of these predictions.

2. Subjects and methods

The local and Regional Ethics Committees approved the study. Informed, written consent was obtained from all participants.

2.1. Participants

During 1991–2002, 158 men were included in five independent, but similar, studies at our research unit. These studies constitute the baseline examinations in the present study. Initially, the men were selected based on their screening blood pressure (BP) (below or above 140/90 mm Hg) from the military draft, 2–6 years prior to baseline. This selection was done to ensure a good BP range in the ensuing studies of the relation between BP and other cardiovascular risk markers. Amount of AAT was not significantly different between the high and normal screening BP-groups, and they were thus analyzed together. Both at baseline and at follow-up, they were examined for a broad range of cardiovascular risk markers. From January 2012 to November 2013 we re-examined 103 of these 158 men. We were unable to get in contact with 29 of them, and 19 did not respond, or declined the invitation. Of the 110 persons initially accepting to be included, seven were unable to participate for various reasons. Due to logistics, measurement of AAT was conducted on a different day than the main, whole-day examination. Eight of the men were then not able to attend. One participant had a 36% weight reduction between baseline and follow-up, and was therefore excluded. Thus, 94 participants underwent computed tomography (CT) assessment of AAT. Eleven participants used one or more of the following drugs at follow-up: thyroid hormone replacement drug ($n = 2$), antidepressants ($n = 3$), oral antidiabetic drug ($n = 1$), BP lowering medication ($n = 5$) and cholesterol lowering medication ($n = 3$).

2.2. Examinations at baseline

The protocols at baseline are described elsewhere [12–16]. Briefly, all participants were Caucasian, previously healthy, and not on any medication. They were thoroughly examined for cardiovascular risk markers, including insulin sensitivity measured by the hyperinsulinemic isoglycemic glucose clamp, which was an absolute inclusion criterion. The hyperinsulinemic isoglycemic glucose clamp was conducted for 90 min in 37 participants [13,15], and for 120 min in the remaining 57. Body weight, to the nearest kilogram, and height, to the nearest centimeter, were measured with the subjects standing in underwear only. BMI was calculated as weight divided by height (in meters) squared. Fasting lipid concentrations were measured. To assess sympathetic and adrenal medullary activity, venous plasma catecholamines were measured by a radioenzymatic technique at rest and during an arithmetic mental stress test (MST) in 83%, as previously described [9].

2.3. Examinations at follow-up

All men were instructed to fast and abstain from tobacco from midnight, and abstain from alcohol and excessive physical activity 24 h preceding examinations, which commenced at 7.30–08.00 a.m. The same doctor, blinded to any previous results, examined all participants. Insulin sensitivity was assessed with a 120-minute hyperinsulinemic isoglycemic glucose clamp, using a modification of the method described by DeFronzo et al. [17], as previously described [18] and validated [19,20]. A higher glucose disposal rate (GDR) implies better insulin sensitivity. Office BP was measured in a highly standardized way using Dinamap CARESCAPE V100 (GE Medical, Milwaukee, WI, USA), as recently described in detail [21]. Heart rate was calculated as mean of values measured at 0, 60, 90 and 120 min during the glucose clamp, like at baseline. Two independent examiners measured waist circumference, and mean values were used. The participants were weighed wearing light indoor clothing, and 1 kg was subtracted. BMI was calculated like at baseline. According to the World Health Organization (WHO) guidelines [22], 17.0% ($n = 16$) were obese (BMI ≥ 30 kg/m^2), 42.6% ($n = 40$) were overweight (BMI between 25.0–29.9 kg/m^2) and 40.4% ($n = 38$) had normal weight (BMI between 18.5–24.9 kg/m^2) at follow-up. Blood samples were taken using an adapter (BD Vacutainer Luer-Lok Access Device, Plymouth, UK). Serum glucose, cholesterols and triglycerides (TGs) were measured using Cobas 8000 (Roche, Mannheim, Germany). A questionnaire regarding i.e. exercise and family history of diabetes and hypertension (HT) was answered on the day of examination. For validation, 33 participants answered the same questionnaire a second time after two weeks. Forty-four participants reported HT in at least one first-degree relative, no one reported type 1 diabetes, and 19 men reported type 2 diabetes (8 maternal, 10 paternal, and 1 in both parents) among first-degree relatives. Thirteen participants had family history of both diabetes and HT.

CT was performed on a different day than the whole-day examination. To assess any significant weight change, the participants were weighed in the same way as on the whole-day examination. CT was performed using a Somatom Sensation 64 CT Scanner (Siemens, Erlangen, Germany) with the patient examined in a supine position, arms extended above the head. One single axial scan was performed without intravenous contrast medium through the mid-abdomen, at the level of $L_{3/4}$. CT parameters were 120 kV, 200 mAs, and slice thickness 5 mm. The dicom images were analyzed using Osirix v 5.8.2, 32 bit (Pixmeo, Geneva, Switzerland). The circumferences were tracked for superficial and deep SAT compartments, divided by a membranous layer, and the muscle compartment including the spine (Fig. 1). The VAT compartment was measured by tracking the inner abdominal circumference, and calculated by highlighting the pixels containing fat (−30 to −190 Hounsfield units). The doctor reading the CT scans was blinded to the other study results.

2.4. Statistical methods

PASW Statistics for Windows, versions 20–22 (IBM SPSS, Chicago, IL, USA) were used for analyses. Data are presented as mean ± standard deviation or median (interquartile range), unless otherwise stated. Parametric tests were applied for normally distributed data, and non-

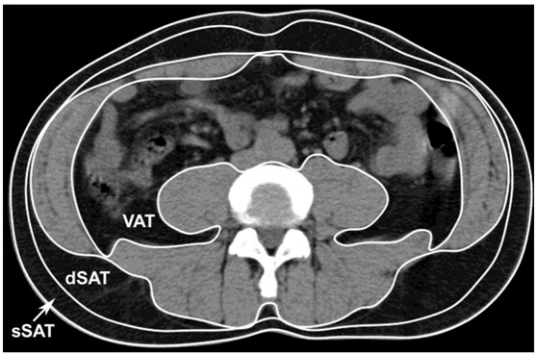

Fig. 1. Axial CT scan at level $L_{3/4}$ showing VAT (visceral adipose tissue), dSAT (deep subcutaneous adipose tissue) and sSAT (superficial subcutaneous adipose tissue).