International Journal of Cardiology 162 (2013) 184–188

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Visceral abdominal adipose tissue and coronary atherosclerosis in asymptomatic diabetics☆,☆☆

Alla Khashper [b], Tamar Gaspar [b], Mali Azencot [a], Idit Dobrecky-Mery [a], Nathan Peled [b], Basil S. Lewis [a], David A. Halon [a,*]

[a] Department of Cardiovascular Medicine, Lady Davis Carmel Medical Center and the Ruth and Bruce Rappaport School of Medicine, Technion—Israel Institute of Technology, Haifa, Israel
[b] Department of Radiology, Lady Davis Carmel Medical Center and the Ruth and Bruce Rappaport School of Medicine, Technion—Israel Institute of Technology, Haifa, Israel

ARTICLE INFO

Article history:
Received 14 December 2010
Received in revised form 17 March 2011
Accepted 13 May 2011
Available online 8 June 2011

Keywords:
Visceral fat
Coronary atheroma
Coronary calcium
Computed tomography
Diabetes mellitus

ABSTRACT

Background: Visceral abdominal adipose tissue (VAT) may play an active role in the progression of coronary atherosclerosis. We examined the relation between VAT, non-alcoholic fatty liver disease and extent of coronary atheroma in patients with type 2 diabetes mellitus but no known coronary artery disease.
Methods: Coronary artery calcium and area, distribution and thickness of upper abdominal fat were measured in selected axial cross-sections from non-enhanced computed tomography (CT) scans of the chest. Coronary atheroma was assessed visually on a per vessel basis from 64 slice CT angiography using axial views and multi-format reconstructions. Fatty liver was diagnosed when liver density was <40 Hounsfield units (HU) or ≥ 10 HU below spleen density.
Results: The area of VAT was increased in patients with versus without multi-vessel coronary artery plaque (237.0 ± 101.4 vs 179.2 ± 79.4 mm^2, $p<0.001$). Waist circumference (101.6 ± 12.3 versus 95.3 ± 13.8 cm) and internal abdominal diameter (218.7 ± 33.0 vs 194.6 ± 25.7 mm) (both $p<0.001$) were increased in patients with multi-vessel plaque whereas subcutaneous fat was unrelated to coronary plaque. Presence of fatty liver (93/318 patients, 29.2%) did not correlate with presence or extent of coronary plaque. The correlation of VAT with multi-vessel plaque although nominally independent of the metabolic syndrome ($p = 0.04$) was not independent of waist circumference.
Conclusion: In asymptomatic subjects with DM and no history of CAD area of VAT correlated with the presence and extent of coronary atheroma but as a risk predictor added little independent information to that obtained by more readily obtainable measures of adiposity—waist circumference and internal abdominal diameter.

1. Introduction

Visceral abdominal adipose tissue (VAT) may play an active role in the progression of coronary atherosclerosis. Several studies have reported an association between VAT and the metabolic syndrome [1] and VAT and risk factors for coronary artery disease (CAD) [2,3] on the one hand and between VAT and specific aspects of CAD such as coronary artery calcium score [3], non-calcified plaque [4] and prevalent coronary arterial disease [1,5–7] on the other hand.

The possibility of an active metabolic role for VAT in the etiology of CAD [2,8], particularly in diabetic cohorts [6,9], has been suggested, whereas others have suggested that hepatic lipid deposits and VAT may represent a deficiency in the lower body fat reservoir [10].

In the Framingham Heart Study the extent of VAT was related to multiple metabolic risk factors including the metabolic syndrome [1]. This Framingham cohort however included less than 10% of diabetics. Since CAD is both highly prevalent and more rapidly progressive in diabetics it is of interest to ascertain if similar associations exist in a community based cohort of asymptomatic type 2 diabetics. Thus the aim of this study was to examine the relation of VAT to extent of CAD in an asymptomatic cohort of type 2 diabetics. Specifically we selected the presence of multi-vessel coronary artery plaque on computed tomographic (CT) coronary angiography as the primary measure of coronary plaque in this study. In addition to measurements of the area of VAT in a computed tomographic (CT) slice of the abdomen we also examined the predictive value of simple linear measurements of the abdominal diameters and of the thickness of the lipid deposits, directly available from any abdominal or chest CT scan. Since non-alcoholic fatty liver disease (NAFLD) is common in patients with the

☆ Presented in part at the annual meeting of the Radiological Society of North America, Chicago, November 30, 2009.
☆☆ Supported by a research grant from the European Foundation for the Study of Diabetes (EFSD/Pfizer grant).
* Corresponding author at: Department of Cardiovascular Medicine, Lady Davis Carmel Medical Center, 7 Michal Street, Haifa, 34362, Israel. Tel.: +972 4 8250588; fax: +972 4 8343755.
E-mail address: halondav@tx.technion.ac.il (D.A. Halon).

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doi:10.1016/j.ijcard.2011.05.059

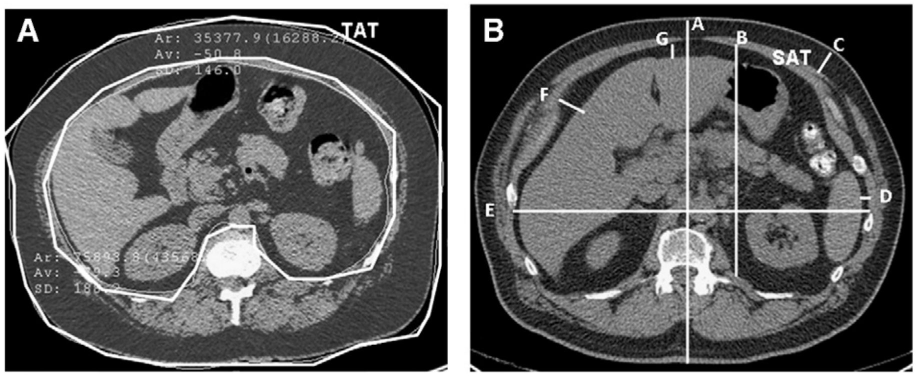

Fig. 1. A. Axial scan of the upper abdomen demonstrating areas of abdominal adipose tissue. A line drawn along the fascial plane of the abdominal muscles enclosed an area containing visceral adipose tissue. Subcutaneous adipose tissue was defined as the total intra-abdominal adipose tissue minus visceral adipose tissue. B. Axial section at upper abdominal level (D12) demonstrating sites of measurement. A—External diameter. B—AP internal diameter, C—Subcutaneous fat, D—Thickness of fat pad lateral to spleen, E—Internal transverse diameter, F—Fat pad lateral to liver and G—Fat pad anterior to liver.

metabolic syndrome and may correlate with extent of visceral and subcutaneous abdominal fat deposits we also examined the relation of NAFLD to coronary artery atheroma [7].

2. Methods

2.1. Patient cohort

Consecutive patients attending the diabetic clinic were screened for compliance with the study protocol and family practitioners informed of the study protocol screened type 2 diabetics for study participation. Patients were included in the study if they fulfilled the following criteria and had none of the exclusion criteria listed below: age 55–74 years, no history or symptoms of CAD or electrocardiographic (ECG) signs of previous myocardial infarction and had at least 1 of the following risk factors for cardiovascular events: age >60 years, history of systemic hypertension, current smoking (during last 3 months), family history of premature CAD in a first degree relative <55 years of age, cerebral, carotid or peripheral arterial disease, duration of DM from time of first diagnosis of at least 5 years, diabetic retinopathy or neuropathy or albuminuria (>30 mg/day) and provided informed consent for the study procedures. All subjects in the current study were also enrolled in an ongoing prospective study of cardiovascular outcomes in asymptomatic diabetics. Exclusion criteria were allergy to iodinated contrast media, serum creatinine >1.4 mg/dl, atrial fibrillation or daily intake of >20 ml of alcohol. From previous studies using CT coronary angiography in similar patient cohorts referred to our institution we assessed the expected prevalence of multi-vessel coronary artery plaque in this cohort to be 50%. On this basis, allowing for a sampling error of 6% (95% confidence limits) we estimated that a sample of 270 patients would be required to reveal a moderate association with the extent of abdominal fat. Metabolic syndrome was diagnosed from clinical characteristics according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria [5] when at least 2 of the following criteria were present in addition to DM: 1) increased waist circumference (>102 cm for men, >88 cm for women), 2) elevated triglycerides (≥150 mg/dl), 3) low HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women), 4) blood pressure (systolic ≥130 or diastolic ≥85 mm Hg). Blood pressure was measured at a study clinic visit in a sitting position using an automated sphygmomanometer following a resting period of at least 5 min. Patients with a technically inadequate CT angiogram were excluded from the study analysis. In keeping with the large majority of the local population all patients recruited were of Caucasian ethnicity.

2.2. Multi-detector computed tomography imaging protocol

CT scans were performed using a 64 slice scanner (Brilliance 64, Philips Healthcare, Cleveland, Ohio) with retrospective ECG gating. Oral or intravenous beta blocking drugs were used to lower heart rate when above 70 bpm and isosorbide dinitrate spray (2.5 mg) was administered routinely. Average heart rate during the scan was 58 per minute.

A non-enhanced thoracic CT scan was performed followed by a contrast enhanced scan. The non-enhanced scan was used for measurement of the coronary artery calcium score (Agatston units), and for detection of NAFLD and quantitation and distribution of VAT. Agatston score was measured with semiautomatic software installed in the CT workstation and upper abdominal fat distribution was assessed from an axial cross-section at the level of D12-L1 as detailed below.

2.3. Fatty liver and abdominal fat assessment

An assessment of hepatic and splenic attenuation was made from three different axial cuts from the non-enhanced scan using a region of interest avoiding the large vessels and any focal lesions. Values were recorded in Hounsfield Units (HU) from the axial slice in which the differentiation between hepatic and spleen attenuation was greatest. NAFLD was diagnosed on a non-enhanced CT scan when liver density was <40 HU or ≥10 HU less than that of the spleen [11]. Total, visceral and subcutaneous adipose tissue areas were determined from an axial CT image taken at the level of D12-L1 using semi-automatic software for fat tissue detection included in the CT workstation. Within the region of interest fat was defined as pixels with an attenuation of −200 to −30 HU [12].

Total pixels identified as fat inside the external abdominal contour constituted the total area of adipose tissue. VAT was defined as the area of intra-abdominal fat bound by parietal peritoneum excluding the vertebral column and the paraspinal muscles. Subcutaneous fat was calculated by subtraction of VAT from total abdominal fat (Fig. 1A). Measurements of subcutaneous fat, transverse, antero-posterior, internal and external diameters of the abdomen, thickness of fat pad lateral to the liver and spleen and pre-hepatic fat pad were made on an axial cut of the upper abdomen at the level of D12-L1 (Fig. 1B).

2.4. Contrast enhanced scans

Contrast enhanced scans were performed at 120 kV with a bolus of 70–100 ml intravenous contrast (mean 86 ± 14 ml) at a flow rate of 5–7 ml/s followed by a 50 ml saline chaser bolus. Images were constructed at 75% of the R–R interval and additional reconstructions were made if required. Presence of coronary arterial plaque was identified in axial and longitudinal curved multiplanar reformatted reconstructions in multiple projections and the grade of coronary luminal stenosis was assessed visually in relation to the immediately proximal plaque free segment. Coronary arteries were reported on a per vessel basis as normal (no atheroma), containing non-obstructive atheromatous plaque, or with stenosis (≥1 coronary lesion obstructing ≥50% of the lumen).

2.5. Statistical analysis

Statistical analysis was performed using PASW statistics (V.17, Chicago, Illinois, USA). Baseline characteristics in men and women and continuous measurements of abdominal lipid in relation to coronary arterial plaque were examined using Student's t-test for independent samples. Coronary artery calcium score was normalized by logarithmic transformation prior to analysis. Univariate and multivariate linear and logistic regression analyses were used as appropriate to examine correlations and predictors of coronary plaque. A 2 sided p-value of ≤0.05 was considered statistically significant.

All subjects provided written informed consent and the study protocol was approved by the institutional review board. The ongoing clinical outcome study is registered at ClinicalTrials.gov as NCT00321542.

3. Results

The study included 318 patients (age 63.2 ± 5.5 years) of whom 152 (47.8%) were men. Clinical characteristics and abdominal fat findings are presented in Tables 1 and 2. Intra-abdominal diameters (see Fig. 1 for definitions) were greater in men than in women (all $p < 0.001$). The average attenuation of liver was 39.7 ± 13.3 HU and liver/spleen ratio was 1.0 ± 0.3. Coronary plaque (any degree) was present in 133 (87.5%) men and 114 (68.7%) women ($p < 0.001$). Multi-vessel coronary plaque was found in 116 (76.3%) men and 67