Complications

Impact of increased visceral and cardiac fat on cardiometabolic risk and disease

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Short title: Visceral, epicardial and/or intrathoracic fat?
Abstract

Objective Previous studies have highlighted the associations between abdominal, cardiac or total fat accumulation and cardiovascular disease. The aim of this study was to investigate the impact of different ectopic fat depots on measurements of metabolic dysfunction and cardiovascular disease risk.

Methods Using magnetic resonance imaging in 113 subjects, we measured abdominal (visceral and subcutaneous) and cardiac (epicardial and extra-pericardial) fat depots and examined their association with overall (BMI) and abdominal obesity (waist circumference), dyslipidaemia (triglycerides, total and HDL cholesterol), glucose tolerance (by an oral glucose tolerance test) and insulin sensitivity, blood pressure and 10-year coronary heart disease risk by Framingham score.

Results Fat accumulation was proportional to the degree of obesity, with body fat ranging from 14 to 33 kg, visceral fat from 0.8 to 1.8 kg and cardiac fat from 134 to 236 g. Most cardiac fat (70% on average) was extra-pericardial, with a wide variability for both cardiac depots (epicardial: 172–2008 mm²; extra-pericardial: 100–5056 mm²). Only visceral and extra-pericardial fat, but not epicardial or subcutaneous fat, could discriminate between subjects with three or more factors of the metabolic syndrome or medium-to-high coronary heart disease risk score. Controlling for gender and BMI by multivariable analysis, the best marker of reduced insulin sensitivity was visceral fat (partial $r = –0.35$); extra-pericardial fat was the closest associate of increased blood pressure (partial $r = 0.26$) and both extra-pericardial and visceral fat clustered with hypertriglyceridaemia (partial $r = 0.29$ and 0.24; both $P < 0.02$).
**Conclusion** Increased epicardial fat does not necessarily translate into presence or prediction of disease. In contrast, increased deposition of visceral abdominal and extra-pericardial mediastinal fat are both associated with an enhanced cardiovascular disease risk profile.

**Keywords** epicardial, insulin resistance, intrathoracic fat, magnetic resonance imaging, metabolic syndrome, visceral fat

**Introduction**

Fat accumulates mainly in subcutaneous depots, but sizeable amounts of adipose tissue are also deposited in the abdomen (between and within organs), in the thorax (as epicardial, mediastinal and/or intramyocardial fat), in the pancreas and in skeletal muscle [1]. Although it is recognized that intracellular accumulation of fat is associated with organ dysfunction (i.e. lipotoxicity) [2], it is not feasible to measure it routinely as its measurement requires sophisticated techniques (i.e. high-field magnetic resonance spectroscopy or tissue biopsies). Other major sites of fat accumulation, such as visceral and cardiac depots, have been evaluated as markers of disease as their measurement is more practicable. Visceral fat has been related to both metabolic and cardiovascular dysfunction [3,4]. Cardiac fat is now recognized as a new cardiometabolic risk marker, as it is associated with increased insulin resistance, cardiovascular risk factors, visceral fat and, in general, with the metabolic syndrome [5,6]. In the supradiaphragmatic region, fat is deposited in the intrathoracic space (extra-pericardial adipose tissue or mediastinal fat), around the myocardium (epicardial adipose tissue) and as intramyocardial fat. Most of the research has focused on epicardial fat, which, given its location,
is supposed to have a metabolic role. Studies in animals [7] and in autoptic human hearts [8] have shown the importance of epicardial fat accumulation, but the interest in this fat depot has risen in recent years as new imaging techniques have become available. Epicardial fat constitutes approximately 30% of intrathoracic fat, the majority being present as extra-pericardial fat. However, it is not always simple to distinguish epicardial from extra-pericardial fat, especially in non-obese subjects, and the sum of epicardial and extra-pericardial fat has frequently been considered [6,9]. We and others have shown that extra-pericardial fat strongly correlates with obesity, increased visceral fat and insulin resistance similarly to visceral fat [6,10–12].

The question of whether these fat depots have similar clinical relevance as markers of metabolic dysfunction and cardiovascular disease risk has not been previously addressed. Therefore, in the present work, we set forth to assess the relationship between cardiac (both extra-pericardial and epicardial) fat and visceral fat accumulation and markers of coronary heart disease risk (lipid profile, blood pressure, insulin sensitivity and glucose tolerance) in a large group of subjects, including patients with Type 2 diabetes.

**Materials and methods**

**Subjects**

From our diabetes screening clinic, we recruited 113 individuals undergoing oral glucose tolerance testing who agreed to magnetic resonance imaging examination of body fat distribution and quantitation. The subjects (94 men and 19 women) had a mean age of 52 years and a BMI ranging from 18 to 40 kg/m$^2$. Twenty-one individuals had Type 2 diabetes (fasting plasma glucose $\geq 7.0$ mmol/l or a 2-h plasma glucose of $\geq 11.1$ mmol/l), 13 of whom were newly
diagnosed. The study protocol was approved by the local ethics committee and all subjects gave their informed consent to participate.

**Anthropometric measurements**

We measured weight (to the nearest 0.1 kg) and height (to the nearest 0.5 cm) and waist–hip ratio while the subjects were fasting and wearing only their undergarments. After a 30-min acclimation period, systolic, diastolic and mean blood pressure (calculated as diastolic blood pressure plus one third of the pulse pressure) were measured three times to the nearest 2 mmHg in the sitting position using a mercury sphygmomanometer and appropriately sized cuffs and then averaged. The 75-g oral glucose tolerance test was carried out in the morning (08.00 h) after a 10- to 12-h overnight fast and blood samples were collected every 30 min for 2 h for the measurement of plasma glucose and insulin concentrations. Eleven subjects without diabetes did not have an oral glucose tolerance test.

**Magnetic resonance imaging study**

Magnetic resonance imaging acquisition of the heart was carried out using a standardized protocol. Cardiac coil and electrocardiograph triggering were used for the sequences; during the acquisition time, patients were holding their breath (10–12 s). Cardiac adipose tissue scans were obtained by fast-spin echo T1-weighted sequences with oblique axial orientation, for a correct study of horizontal long axes of the heart [13] (echo time 42 ms; echo train length 23; bandwidth 62.50; slice thickness 8 mm; slice gap 0 mm; field of view 38 cm; matrix 288 × 224 ; phase field of view 0.75; number of excitations 1; trigger delay = minimum; 8-mm thick section with 0-mm intersection gap, field of view and a 256 × 256 matrix). Epicardial fat was defined as any adipose tissue located within the pericardial sac [11,12]. Extra-pericardial and epicardial fat areas were measured in a four-chamber view during the diastolic phase with the use of an in-house semi-automatic program to determine the margin of fat around the heart, identifying
region of interest and measuring the number of pixels, as previously described [12]. Two fat depots could be easily distinguished: (1) epicardial adipose tissue, the fat concentrated in the atrioventricular and interventricular grooves, along the major branches of the coronary arteries and, to a lesser extent, around the atria, over the free wall of the right ventricle and over the apex of the left ventricle; (2) extra-pericardial adipose tissue, the fat situated on the external surface of the parietal pericardium within the mediastinum, also termed intrathoracic fat.

To test whether fat area was a good indicator of cardiac fat mass, in a separate group of normal subjects (n = 20) we quantified cardiac fat by acquiring all images in the short axis view that covered the heart from the apex of the ventricula to the top of the atria. For each slice we quantified area and volume (calculated by multiplying each area by the thickness, i.e. 8 mm, with no gap between images). Weight of cardiac fat was then obtained by multiplying the volume (mm$^3$) by 0.92, which corresponds to cardiac fat density in g/kg [12]. Average fat area was 2656 mm$^2$; average fat volume was 22 586 mm$^3$, corresponding to a cardiac fat mass of 208 g. A strong linear relationship was found between cardiac fat mass and area measured in a four-chamber view ($r^2 = 0.87$, $P < 0.0001$), thus allowing the definition of a factor to calculate cardiac adipose tissue mass from area measurements (0.076 g/mm$^2$).

Abdominal visceral and subcutaneous fat depots were measured using imaging procedures that have been published previously [12,14]. Briefly, images were acquired on a GE Signa Excite HD 1.5T scanner (slew rate: maximum 150 T m$^{-1}$ s$^{-1}$) that operates with a 50-mT/m gradient using a body coil. Thirty-two transverse, T1-weighted 256 × 256 images (repetition time = 135, echo time = 4.2, flip angle = 90°, field of view = 50 cm, pixel size 1.875 × 1.875 mm) centred through the space between L4 and L5 were acquired in breath hold with a slice thickness of 5 mm with no overlap. The subcutaneous fat area was analysed by automatic detection of the region of interest using an ad hoc developed software [14] and by
counting the number of pixels between the outer and inner margins of subcutaneous adipose tissue. The visceral (intra-abdominal) fat area was determined with the use of histograms specific to the visceral regions [14]. A factor of 0.92 was used to convert adipose tissue volume into adipose tissue mass [12].

Analytical determinations

Plasma glucose was measured by the glucose oxidase reaction (Beckman Glucose Analyzer; Beckman, Fullerton, CA, USA). Plasma insulin concentrations were measured by radioimmunoassay using specific kits (Linco Research, St Louis, MO, USA).

Calculations and statistical analysis

Cardiovascular risk factors were defined as a systolic blood pressure > 130 mmHg or a diastolic blood pressure > 85 mmHg, a waist circumference > 94 cm in men and > 80 cm in women, a serum triglyceride concentration > 1.7 mmol/l, an HDL cholesterol concentration < 1.0 mmol/l in men and < 1.3 mmol/l in women, and a fasting plasma glucose > 5.6 mmol/l [13]. An individual 10-year coronary heart disease risk was estimated using the Framingham Heart Study prediction score [15]. Insulin sensitivity was calculated as the oral glucose insulin sensitivity (OGIS) index, which equals the average metabolic clearance rate of glucose during the oral glucose tolerance test and has been validated against the euglycaemic insulin clamp technique [16].

Data are given as the mean ± SEM. Data with a skewed distribution (i.e. plasma triglyceride, cholesterol and insulin concentrations) are given as median and interquartile range and were log-transformed for use in statistical analysis. Differences between group mean values were evaluated using the t-test or Mann–Whitney U-test for normally and non-normally distributed variables, respectively. Correlations were calculated using Spearman coefficient. The independent association of visceral and cardiac fat accumulation with blood pressure,
triglyceride concentration and insulin sensitivity was evaluated by multiple and stepwise regression analysis adjusted for gender and BMI.

Results

Quantification of fat depots

All four fat depots, visceral, subcutaneous, epicardial and extra-pericardial fat, showed a wide variability (Table 1). On average, visceral fat made up ~30% of abdominal fat, while epicardial fat amounted to ~34% of intrathoracic fat. All fat depots were increased in proportion to degree of obesity (Fig. 1). Total body fat mass was associated with increased visceral fat ($r = 0.48$), subcutaneous fat ($r = 0.89$), epicardial fat ($r = 0.32$), and extra-pericardial fat ($r = 0.37$, all $P < 0.002$). Both epicardial and extra-pericardial fat also correlated significantly with BMI ($r = 0.34$ and $0.43$, $P < 0.0002$), waist circumference ($r = 0.41$ and $0.53$, $P < 0.0001$), visceral fat ($r = 0.34$ and $0.58$, $P < 0.0007$) and subcutaneous fat ($r = 0.34$ and $0.32$, $P < 0.002$).

Men had more extra-pericardial fat and visceral fat than women (extra-pericardial fat 1880 ± 96 vs. 1154 ± 153 mm², $P < 0.002$; visceral fat 1.44 ± 0.08 vs. 1.03 ± 0.19 kg, $P = 0.04$), but similar epicardial fat (818 ± 35 vs. 727 ± 93 mm², $P =$ not significant), for similar BMI and total fat mass.

Relation of fat depots to glucose tolerance and insulin resistance

No difference was found in epicardial, extra-pericardial, intrathoracic or abdominal subcutaneous fat between subjects with normal glucose tolerance ($n = 49$), impaired glucose tolerance ($n = 32$) and diabetes [$n = 21$ (of whom 13 had newly diagnosed diabetes)]. In contrast, visceral fat was higher in subjects with impaired glucose tolerance and Type 2 diabetes compared with those with normal glucose tolerance (normal glucose tolerance 1.16 ± 0.08,
impaired glucose tolerance 1.55 ± 0.13, Type 2 diabetes 1.76 ± 0.28 kg; \( P < 0.05 \) after correction for gender).

The insulin sensitivity index was inversely associated with visceral fat \( (r = -0.62, \ P < 0.0001) \), subcutaneous fat \( (r = -0.46, \ P < 0.0001) \) and extra-pericardial fat \( (r = -0.46, \ P < 0.0001) \), but not with epicardial fat.

**Relation of fat depots to cardiovascular disease risk**

When subjects were grouped according to the presence of factors of the metabolic syndrome [none \( (n = 13) \); one \( (n = 26) \); two \( (n = 26) \); three or more \( (n = 48) \)], visceral, extra-pericardial and intrathoracic fat, but not subcutaneous or epicardial fat, were significantly associated with \( \geq 3 \) factors (Fig. 2). In subjects with increased blood pressure (systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg), fat was increased as visceral fat (1.3 ± 0.1 vs. 1.6 ± 0.1 kg, \( P = 0.04 \)) and extra-pericardial fat (1579 ± 88 vs. 2178 ± 204 mm\(^2\), \( P = 0.002 \)), but no significant difference was observed in subcutaneous fat (3.1 ± 0.2 vs. 3.3 ± 0.2 kg, \( P = 0.40 \)) or epicardial fat (800 ± 39 vs. 814 ± 64 mm\(^2\), \( P = 0.86 \)). Ten-year risk for coronary heart disease was calculated using the Framingham score. In univariate analysis, visceral, extra-pericardial and total intrathoracic fat were each significantly associated with a high 10-year coronary heart disease risk, while no association was found for epicardial or subcutaneous fat (Fig. 3). The same relationships were obtained when only male subjects were considered.

**Cardiac and visceral fat as marker of cardiometabolic risk**

In a stepwise multiple regression model adjusting for gender and BMI, we evaluated the impact of fat accumulation (i.e. visceral, subcutaneous, epicardial and extra-pericardial fat) on blood pressure, plasma triglycerides and insulin resistance. Blood pressure (both systolic and diastolic) was significantly associated only with extra-pericardial fat (partial \( r = 0.26, \ P < 0.02 \)). Triglyceride concentration was best associated with both visceral fat (partial \( r = 0.24, \ P < 0.02 \)
and extra-pericardial fat (partial $r = 0.29$, $P < 0.007$), but not epicardial fat. Insulin sensitivity was associated only by visceral fat (partial $r = -0.35$, $P = 0.002$). Ten-year coronary heart disease risk was significantly associated only with visceral fat (partial $r = 0.38$, $P < 0.0003$).

**Discussion**

General obesity, and in particular ectopic fat accumulation, is associated with an increased incidence of cardiovascular disease, mainly because of the release of adipokines that impair insulin signalling and promote endothelial dysfunction, adhesion of monocytes and formation of foam cells in the arterial wall [17]. As expected, we found that ectopic fat accumulates in proportion to the degree of obesity, mainly as visceral fat (0.8–1.8 kg for a total body fat of 14–33 kg), but also, to a lesser extent, as cardiac fat (134–236 g). Moreover, there was a sizeable effect of gender, with men accumulating more extra-pericardial and visceral fat than women despite similar BMI and total fat mass. When examining which ectopic fat depot was clinically relevant as a marker of metabolic dysfunction and coronary heart disease risk, we found that elevated triglyceride concentrations were associated with increased visceral and extra-pericardial fat, but not with epicardial or subcutaneous fat, while glucose intolerance (either impaired glucose tolerance or Type 2 diabetes) was associated with increased visceral fat. Only visceral and extra-pericardial fat were significantly elevated in subjects with increased blood pressure and/or high 10-year coronary heart disease risk (calculated using the Framingham score).

By accounting for gender and overall adiposity (as BMI) in a multivariable analysis, we found that visceral fat was the best marker of reduced insulin sensitivity, extra-pericardial fat was the closest associate of increased blood pressure and both extra-pericardial and visceral fat clustered with hypertriglyceridemia. Only visceral, total intrathoracic and extra-pericardial fat, but not epicardial or subcutaneous fat, could discriminate subjects with more than three factors
of the metabolic syndrome or those with a medium to high coronary heart disease risk score (Figs 1 and 2).

Despite its small amount, cardiac fat, in particular epicardial fat, has been proposed as an important cardiovascular risk factor because of its location [5,11]. The clinical significance of epicardial fat is posited by the fact that this tissue has an increased expression of inflammatory genes [6,18–21] and is perfused by the coronary vasculature [8]. However, a cause–effect relationship has not been proven [22]. Moreover, most of the studies linking epicardial fat with risk have been conducted in subjects with severe cardiac disease—often those undergoing cardiac surgery—as recently pointed out by Sacks [22]. This could explain why the association between epicardial fat and cardiovascular disease risk factors did not emerge in the present series.

The impact of increased extra-pericardial fat (also named mediastinal or intrathoracic fat) is less known. Even in studies where extra-pericardial fat was quantified, it was not considered as important as epicardial fat. Only few studies have quantified extra-pericardial fat by magnetic resonance imaging or computed tomography. Studies using ultrasound measured only epicardial thickness, probably because the acoustic window does not allow measurements as accurate and reproducible as those obtained by magnetic resonance imaging or computed tomography [23]. However, despite the fact that extra-pericardial fat is not in local anatomical contact with the coronary arteries, it constitutes the majority of cardiac fat accumulation (~70% on average), making it unlikely that it is just an inert compartment. In fact, recent studies from the Framingham cohort have found epicardial fat to be associated with coronary artery calcification, whereas extra-pericardial fat was associated with abdominal aortic calcification [11] and was better correlated with metabolic risk factors than epicardial fat, equalling visceral fat in predictive power. Moreover, the correlation between cardiac fat and measures of left ventricular
structure and function was stronger for extra-pericardial than epicardial fat in women (but was lost when adjusting for body weight or visceral fat), while in men only intrathoracic fat remained correlated with left ventricular end diastolic volume [24]. In our subjects, extra-pericardial, but not epicardial, fat was associated with insulin resistance, increased blood pressure and 10-year coronary heart disease risk. Extra-pericardial fat also correlated with visceral fat, confirming previous results [6,11,12]. This is in line with previous studies using computed tomography and magnetic resonance imaging, which measured both epicardial and extra-pericardial fat, and showed an association between cardiac fat, insulin resistance and blood pressure [12,25].

In conclusion, fat accumulates everywhere as body weight increases; the largest ectopic depots are visceral fat in the abdominal area and extra-pericardial fat in the intrathoracic area. Our results reconsider the role of epicardial fat as an important marker of cardiometabolic risk. Visceral fat was the best marker of altered cardiovascular disease risk profile and increased extra-pericardial fat was associated with coronary heart disease risk. In this cohort, epicardial fat did not show an independent association with measurements of metabolic dysfunction or coronary heart disease risk, indicating that increased epicardial fat alone does not necessarily translate into presence or prediction of disease.

**Competing interests**

Nothing to declare.

**Acknowledgments**

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References


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**Figure 1** Cardiac (epicardial, extra-pericardial and intrathoracic fat area) and abdominal (visceral and subcutaneous mass) fat distribution by degree of obesity (*P < 0.05 vs. lean in each group). NS, not significant.

**Figure 2** Cardiac (epicardial, extra-pericardial and intrathoracic fat area) and abdominal (visceral and subcutaneous mass) fat distribution in relation to the number of factors associated with the metabolic syndrome (*P < 0.05 vs. zero factors in each subgroup).

**Figure 3** Cardiac (epicardial, extra-pericardial and intrathoracic) fat area in relation to 10-year coronary heart disease (CHD) risk calculated from the Framingham score (*P < 0.05 vs. low risk).
Figure 1

Cardiac fat area (mm²)

- Epicardial
- Extra-pericardial
- Total cardiac fat

Abdominal fat mass (kg)

- Visceral
- Subcutaneous

Degree of Obesity

L = lean
OW = overweight
Ob = obese
**Figure 2**

Cardiac fat area (mm²)
- Epicardial
- Extra-pericardial
- Total cardiac fat

Abdominal fat mass (kg)
- Visceral
- Subcutaneous

Metabolic Syndrome Factors:
0   1 2  >3    0   1  2   >3

Metabolic Syndrome Factors:
0   1 2  >3    0   1  2   >3

Note: * indicates statistical significance.
Figure 3