



Age-Related Different Relationships between Ectopic Adipose Tissues and Measures of Central Obesity in Sedentary Subjects

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Abstract

Accumulation of fat at ectopic sites has been gaining attention as pivotal contributor of insulin resistance, metabolic syndrome and related cardiovascular complications. Intermuscular adipose tissue (IMAT), located between skeletal muscle bundles and beneath muscle fascia, has been linked to physical inactivity, ageing and body mass index, but little is known about its relationship with the other AT compartments, in particular with increasing age. To address this issue, erector spinae IMAT, epicardial (EAT), intraabdominal (IAAT) and abdominal subcutaneous adipose tissue (SAT) were simultaneously measured by Magnetic Resonance Imaging (MRI) and related to waist circumference measurements and age in 32 sedentary subjects without cardiovascular disease (18 men; 14 women; mean age 48.5 ± 14 years). Fasting glucose, triglycerides and HDL-cholesterol were also assessed. We observed that, after dividing individuals according to age (\leq or >50 years), IMAT and EAT depots were significantly more expanded in older subjects (63.2 ± 8.3 years) than in the younger ones (38.4 ± 5.2 years) ($p < 0.001$). Overall, both IMAT and EAT showed stronger positive associations with increasing age ($\beta = 0.63$ and 0.67 , respectively, $p < 0.001$ for both) than with waist circumference ($\beta = 0.55$ and 0.49 , respectively, $p < 0.01$ for both) after adjusting for gender. In addition, the gender-adjusted associations of IMAT and EAT with waist circumference and IAAT were significant in individuals ≤ 50 years only ($p < 0.05$ for all) and not in the older ones. In contrast, no age-related differences were seen in the relationships of IAAT and SAT with waist circumference. Finally, serum triglycerides levels turned out not to be independently related with ectopic IMAT and EAT. In conclusion, the expansion of IMAT and EAT in sedentary subjects is more strongly related to age than waist circumference, and a positive association of these ectopic depots with waist circumference and IAAT amount can be postulated in younger individuals only.

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Introduction

The regional distribution of adipose tissue (AT) plays an important role in the development of metabolic and cardiovascular diseases [1]. Indeed, recent studies have suggested that the location [2] and inherent properties [3,4] of excess AT, rather than total body adiposity, influence the autocrine, paracrine and endocrine effects of AT.

Whereas AT stored in subcutaneous depots is able to buffer the energy excess and to protect against the development of the metabolic syndrome (MS), intraabdominal adipose tissue (IAAT) is part of a more complex phenotype including a dysfunctional subcutaneous adipose tissue (SAT) and triacylglycerol deposition at ectopic, undesirable sites such as liver [5], heart and skeletal muscle [6]. Excess IAAT accumulation and AT stored in ectopic locations are closely related to clustering cardiometabolic risk factors like chronic inflammation, liver insulin resistance,

hypertriglyceridemia and increased free fatty acid availability, presence of small, dense LDL particles, and reduced HDL cholesterol levels [3,7].

Thus, ectopic adipose depots resulting from this defect in energy partitioning, have been gaining attention as potential and "regional" contributors to insulin resistance and obesity comorbidities.

At present, epicardial adipose tissue (EAT), namely the ectopic fat located subepicardially around both ventricles and along the coronary arteries, is reported to correlate with BMI, waist circumference and IAAT [8,9], and to contribute independently to the development of coronary artery disease [10].

So far, few studies have focused on intermuscular adipose tissue (IMAT), which includes the visible storage of lipids in adipocytes located between the muscle fibers (also termed intramuscular fat) and between muscle bundles (literally intermuscular) [11,12,13].

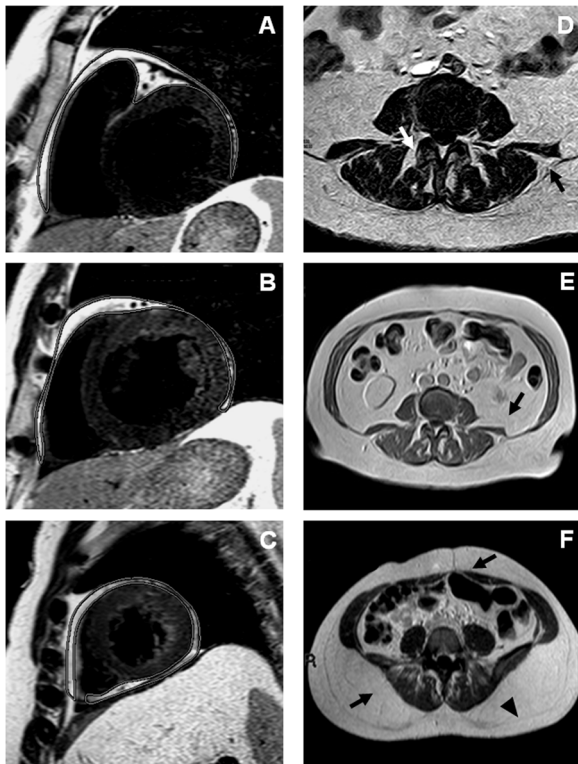


Figure 1. MRI measurements of adipose tissue depots. (A) Volumetric assessment of EAT. The contours of EAT were outlined in end-diastolic images of short-axis views covering the whole left and right ventricle. (B) IMAT of the erector spinae muscles at L3–L4 disk level. IMAT is visible between muscle groups (white arrow) and beneath the muscle fascia (black arrow). Abdominal L3–L4 (C) and L4–L5 (D) MRI scans with representation of IAAT and SAT respectively (black arrows). The black arrow head indicates the *fascia transversalis* dividing SAT into a deep and a superficial layer.
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IMAT is unambiguously linked with increase in body weight [14], physical inactivity or muscle disuse [15], and ageing [14,16]. Although recent studies suggest that IMAT accumulation may be primarily the result of inactivity or muscle impairments rather than ageing *per se* [17,18], therefore reflecting the importance of physical activity intervention even in the elderly, the potential relationship between central adiposity and IMAT accumulation, especially across different ages, is not fully understood.

Moreover, although IMAT accumulation has been shown to be significantly associated with insulin resistance [19,20] and increased risk of type 2 diabetes [21], it is still unclear whether or not IMAT can play an intermediary role in developing insulin resistance, beyond its mere significance as marker of metabolic abnormalities.

Comparative studies demonstrated that magnetic resonance imaging (MRI), which is a well-established, validated method for estimation of AT and identification of its compartments [22,23], has a higher sensitivity for identifying IMAT than computed tomography, because, not being density based, provides estimates not influenced by low density intra-myocellular lipids-enriched lean tissue [13].

According to this background, the primary aim of our study was to investigate the age-related association of erector spinae IMAT with adiposity measures and gender, in a sample of sedentary subjects. We additionally analyzed the relationships of MRI-

assessed IMAT with EAT, IAAT, abdominal SAT and with several common cardiometabolic risk parameters.

Materials and Methods

Study population

We enrolled 32 patients (18 men; 14 women) undergoing cardiovascular MRI for arrhythmias (frequent ectopic ventricular and supraventricular beats) in order to exclude genetic cardiomyopathy (hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy and dilated cardiomyopathy) or acquired cardiac disease (myocarditis, ischemic cardiac disease or inflammatory and autoimmune diseases). All subjects, before undergoing MRI, had been preliminarily evaluated by 12 leads electrocardiogram (EKG), 2D echocardiography, Holter EKG and stress test. Coronary artery disease was excluded by maximal negative stress test, or whenever indicated by coronary computed tomography angiography or coronary angiography. Inclusion criteria were: no pathological findings at the preliminary cardiologic evaluation and no pathological evidence revealed by cardiac MRI assessment; clinical history of normal fasting glucose; being non-smokers; having stable weight and dietary habits for ≥ 6 months prior to the study; having sedentary habits (based on self-report of no participation in vigorous routine or structured exercise). We excluded subjects affected by neoplasms, liver disease, renal insufficiency or any other severe systemic disease.

Waist circumference was recorded as the average of two measurements while the patients were standing, at midpoint between the lowest rib and the iliac crest. Body mass index (BMI) was calculated by dividing the weight (in Kg) by the square of height (in meter). Blood pressure (BP) was measured in the sitting position, with a standard, appropriately sized sphygmomanometer cuff. Three measurements were averaged to calculate systolic and diastolic BP.

Blood samples were obtained after overnight fast and glucose, HDL-cholesterol, triglycerides were assessed by routine laboratory techniques. MS was diagnosed according to IDF criteria [24].

Written informed consent was obtained from each patient included in the study. The study was approved by the Ethical Committee of the Fondazione Policlinico Tor Vergata (Rome), and it conforms to the principles of the Declaration of Helsinki.

Magnetic Resonance Imaging

All patients underwent a standardized protocol including quantification of EAT volume during cardiac MRI and measurements of IMAT of rectus spinae, IAAT and SAT areas by two single slice detections at L3–L4 and L4–L5 level. MRI data were obtained with a Philips Intera 1.5 Tesla Achieva (Eindhoven, The Netherlands) scanner. Image analysis of EAT, IAAT and SAT was performed off-line using a stand-alone work station (Extended MR WorkSpace 2.6.3.4, 2012 Philips Medical System). SliceOmatic software (version 4.2; TomoVision, Montreal, Quebec, Canada) was used to analyze images of IMAT. To assess inter-observer reproducibility, a second independent observer repeated measurements in each dataset using the same conventions.

EAT volume. For the assessment of EAT, we used a black blood prepared T2-weighted multislice to obtain a transversal 4-chamber view and short-axis images. Images parameters were as follows: time of repetition [25] = 1600 ms, time to echo (TE) = 70 ms, slice thickness = 4 mm, interslice gap (GAP) = 2 mm and field of view (FOV) = 450 mm. EAT only included fat between the myocardial border and the internal visceral layer of the pericardium. Areas of EAT were traced manually on consecutive end-systolic short-axis images beginning at the mitral valve and ending at the last slice

containing cardiac tissue. The areas obtained for each slice were added together and multiplied by slice thickness to yield EAT volume (Fig. 1 A–C) [8].

IMAT area. A transverse section was obtained at L3–L4 disk level to measure IMAT of the erector spinae muscles (including the multifidus, longissimus, and iliocostalis). The erector spinae musculature was chosen for IMAT imaging analysis as unique skeletal muscle site for which the accuracy of MRI measurements of muscle tissue composition with corresponding histology *in vivo* was assessed [12]. The L3–L4 level was selected for the analysis because the muscle cross-sectional area has previously described as the largest overall at this level [26]. IMAT was defined as AT area visible between muscle groups and beneath the muscle fascia (Fig. 1 D).

A high-resolution T1-weighted TSE sequence was obtained and the scanning parameters were TR = 100 ms, TE = 8 ms, slice thickness = 3 mm, FOV = 256 mm. The gray-level intensity (threshold value) of the AT in the SAT region was determined and used as a reference [27]. This threshold value was reduced by 20% to identify the IMAT threshold (SliceOmatic software).

IAAT and SAT areas. IAAT is defined as intraabdominal fat bound by parietal peritoneum or transversalis fascia, excluding the vertebral column and the paraspinal muscles; SAT is fat superficial to the abdominal and back muscles. A breath-hold sequence was used to minimize the effects of respiratory motion on the images. A single image, located at L3–L4 level, obtained using a T1-weighted FFE pulse sequence (TR = 97 ms, TE = 4.6 ms, slice thickness = 5 mm, FOV = 445 mm), was chosen to assess IAAT area, previously validated as good predictor of total IAAT volume [28] (Fig. 1 E). The same sequence parameters except for FOV = 256 mm were used to measure SAT area at L4–L5 level [29] (Fig. 1 F).

Statistical analysis

Statistical analysis was performed with the SPSS 19.0 software (SPSS, Chicago). Descriptive statistics were given by means \pm SD. The Kolmogorov-Smirnov test was used to verify quantitative variables for normality distribution and non-normal distributed parameters were logarithmically transformed before being used in the subsequent parametric procedures. Comparisons between groups were made using Student's unpaired *t*-test. Relationships between continuous variables were evaluated using Pearson partial correlations including gender, waist circumference and IAAT as potential confounders and resulting β coefficients were provided to evaluate the strengths of the associations. For all these analysis a *p*-value <0.05 based on two-sided test was considered statistically significant.

Results

The study population was constituted by 18 men and 14 women, aged 48.5 ± 14 years, with mean BMI of 25.6 ± 3.9 Kg/m² and waist circumference of 103.5 ± 14.8 cm. Whereas no gender-related differences were seen in EAT and IAAT depots, IMAT was significantly more represented in women than in men (W: 925.4 ± 491.3 mm²; M: 501.1 ± 337 mm²; $p < 0.05$).

All fat depots were positively correlated with both age and waist circumference (Table 1), but the correlation's coefficients revealed distinct patterns. Indeed, IMAT and EAT were more strongly associated with age than waist circumference, whereas SAT followed an opposite trend, and IAAT resulted similarly associated with both. The same distinct patterns were observed when looking at the correlations of fat depots with BMI (IMAT: $\beta = 0.47$, $p < 0.01$; EAT: $\beta = 0.46$, $p < 0.01$; IAAT: $\beta = 0.63$, $p < 0.0001$; SAT: $\beta = 0.77$, $p < 0.0001$) instead of waist circumference.

We therefore divided our sample according to age (≤ 50 and > 50 years), resulting in two subgroups significantly different for age ($p < 0.001$) and anthropometric measures, so that the older ones had concomitantly higher waist circumference ($p < 0.01$) and BMI ($p < 0.001$) than the younger ones (Table 2). Similarly, IMAT, EAT, IAAT and SAT amounts were significantly more represented in older subjects compared to the younger ones (Fig. 2 A–D).

Even though the older subjects enrolled in our sample study were characterized by an overall greater amount of fat mass compared to the younger ones, as reflected by differences in MRI assessments and anthropometric parameters, the subsequent regression analysis showed that IMAT and EAT quantitative amounts were positively gender-adjusted associated with waist circumference, but in younger subjects only ($p < 0.05$ for both) (Fig. 3 A,B). On the other hand, SAT and IAAT quantitative depots showed great linear relationship with waist circumference in both younger and older subjects (Fig. 3 C,D), even though the strength of these associations was unexpectedly non significant for IAAT in the older ones ($p = 0.09$).

In accordance to what observed with waist circumference measures, both IMAT and EAT depots turned out to be gender-adjusted associated with IAAT in younger (IMAT: $\beta = 0.57$, $p < 0.05$; EAT: $\beta = 0.6$, $p < 0.01$), but not in subjects > 50 years. Interestingly, IMAT and EAT were not associated with SAT.

Of interest, the quantitative amounts of IMAT and EAT were significantly correlated with each other, but once again in younger subjects only ($\beta = 0.6$, $p < 0.01$) (Fig. 4), whereas the same pattern of relationship was not observed in the older.

Finally, we observed that IMAT ($\beta = 0.46$, $p < 0.01$) and IAAT ($\beta = 0.56$, $p < 0.001$), but not EAT and SAT, were positively correlated with serum triglycerides, after adjusting for hypolipidemic therapies. However, after adjusting for either waist circumference or IAAT, the correlation between IMAT and triglycerides

Table 1. Gender-adjusted correlations of fat depots with age and waist circumference.

	Age		Waist circumference	
	β	<i>p</i> value	β	<i>p</i> value
IMAT area	0.63	0.0001	0.55	0.001
EAT volume	0.67	0.0001	0.49	0.004
IAAT area	0.68	0.0001	0.66	0.0001
SAT area	0.40	0.02	0.84	0.0001

EAT epicardial adipose tissue, IMAT intermuscular adipose tissue, IAAT intraabdominal adipose tissue, SAT subcutaneous adipose tissue.

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Table 2. Study population characteristics according to age.

Clinical Features	≤50 yrs	>50 yrs	<i>p</i>
N	19	13	
Gender (F/M)	7/12	7/6	
Age (yrs)	38.4±5.2	63.2±8.3	<0.0001
Waist circumference (cm)	97.1±13	112.9±12.3	<0.01
BMI (Kg/m ²)	23.8±3.4	28.2±3	<0.001
Systolic BP (mmHg)	121.8±11.2	133±11	<0.01
Diastolic BP (mmHg)	76±7.5	81.9±7.7	<0.05
Glucose (mg/dl)	92.5±9	107.9±31.8	<i>ns</i>
Triglycerides (mg/dl)	93.1±46.4	127.7±47.1	<i>ns</i>
HDL-Chol (mg/dl)	48.1±12.1	55.9±20.2	<i>ns</i>
IFG/T2D	2/0	2/2	
MS	3	8	
Hypolipidemic TH	0	5	

BMI body mass index, BP blood pressure, EAT epicardial adipose tissue, IFG impaired fasting glucose, IMAT intermuscular adipose tissue, IAAT intraabdominal adipose tissue, MS metabolic syndrome, SAT subcutaneous adipose tissue, T2D type 2 diabetes, TH therapies.

*significantly different ($p < 0.05$). Data are expressed as mean ± SD.

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was no more significant (waist; $\beta = 0.23$, $p = 0.2$; IAAT: $\beta = 0.19$, $p = 0.3$). Accordingly, patients with MS, who had greater IAAT (MS: 101.3 ± 17.5 cm²; no-MS: 57 ± 9.2 cm²; $p < 0.05$), SAT (MS: 290.4 ± 31.3 mg/dl; no-MS: 199.1 ± 24.3 mg/dl; $p < 0.05$), fasting glucose (MS: 110.2 ± 9.6 mg/dl; no-MS: 92 ± 2.2 mg/dl; $p < 0.05$) and triglycerides levels (MS: 141.4 ± 12.2 mg/dl; no-MS: 88.6 ± 10.2 mg/dl; $p < 0.01$), showed a similar, but not significant, trend for IMAT (MS: 848.3 ± 128 mm²; no-MS: 609.8 ± 100 mm²; $p = ns$) and no difference in EAT (MS: 47.1 ± 5.7 ml; no-MS:

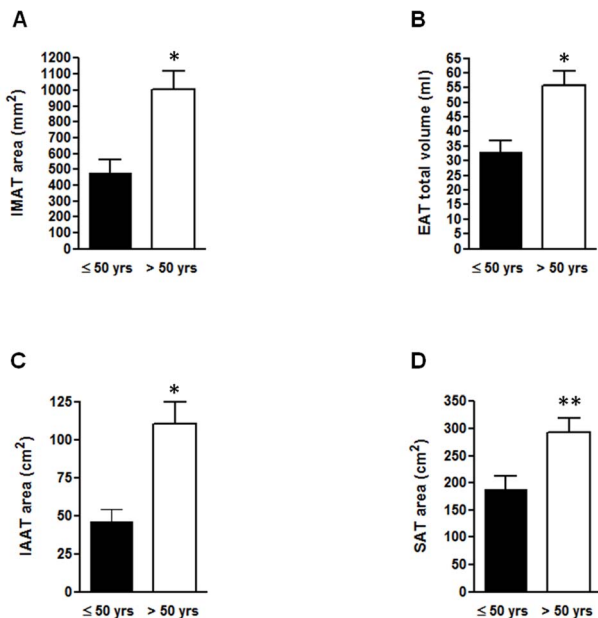


Figure 2. Adipose tissue depots amounts according to age. Erector spinae IMAT area (A), EAT total volume (B), IAAT (C) and SAT (D) areas in subjects ≤50 years and >50 years. * $p < 0.001$, ** $p < 0.05$. doi:10.1371/journal.pone.0103381.g002

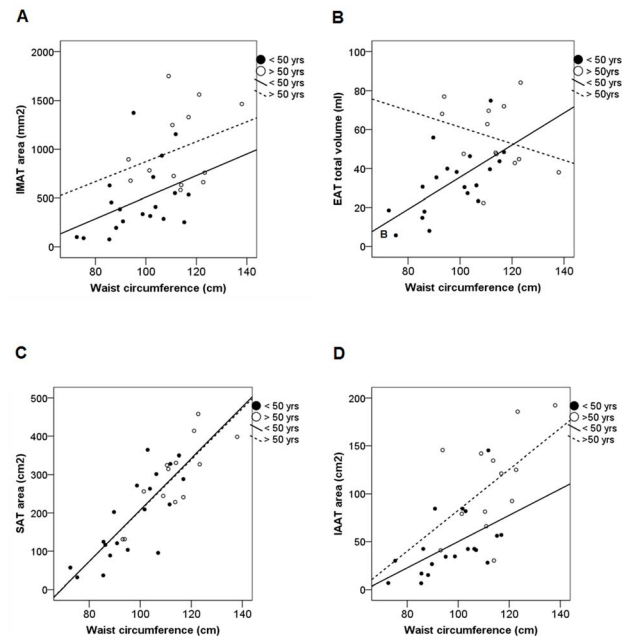


Figure 3. Correlations of adipose tissue depots with waist circumference according to age. Correlations of IMAT area (A), EAT total volume (B), SAT (C) and IAAT (D) areas with waist circumference. Solid lines represent correlations in younger subjects (≤50 years): IMAT: $\beta = 0.46$, $p = 0.03$; EAT: $\beta = 0.63$, $p = 0.005$; SAT: $\beta = 0.81$, $p = 0.0001$; IAAT: $\beta = 0.51$, $p = 0.02$ (gender-adjusted correlation coefficients). Dashed lines represent correlations in older subjects (>50 years): IMAT: $\beta = 0.14$, $p = ns$; EAT: $\beta = -0.13$, $p = ns$; IAAT: $\beta = 0.54$, $p = 0.09$; SAT: $\beta = 0.76$, $p = 0.002$. doi:10.1371/journal.pone.0103381.g003

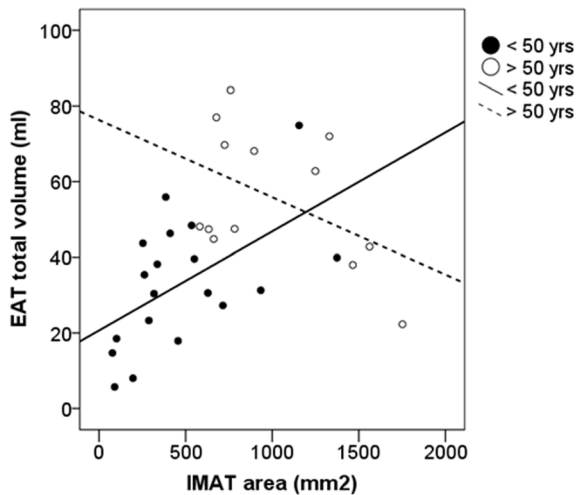


Figure 4. Correlation of IMAT with EAT according to age. Correlations between IMAT area with EAT total volume. Solid lines represent the correlation in younger subjects (≤ 50 years) ($\beta=0.6$, $p=0.007$). Dashed lines represent the non significant correlation in older subjects (> 50 years) ($\beta=-0.3$, $p=ns$). doi:10.1371/journal.pone.0103381.g004

$39.8 \pm 4.6 \text{ mm}^2$; $p=ns$) amounts compared to subjects without MS.

Discussion

In the present study we observed that IMAT, as well as EAT, quantitative amounts are more strongly related with age than waist circumference in sedentary individuals, and that in younger subjects only (≤ 50 yrs in our study population) a positive association of IMAT depots with waist circumference measures and IAAT amount can be postulated. In addition, no significant and independent relationships were observed between ectopic quantitative depots (IMAT and EAT) and circulating triglycerides levels. Even though in our study population IMAT depots were shown to be more represented in women than in men ($p < 0.05$), the associations reported above turned out to be not influenced by gender. We hypothesize that such a gender-difference in IMAT amount could have been driven by chance, since mid-calf and total body IMAT have been previously reported to be equally distributed among genders [20,30] and, in addition, no significant gender-related differences in EAT, IAAT and SAT amounts were detected in our sample study.

Even though IMAT could be conceivably more expanded with increasing age, some previous studies have reported conflicting results for this association [16]. Plausible explanations for such a discrepancy might rely on the fact that most studies in the field have failed to account for activity levels and disease conditions or, alternatively, have investigated on subjects in an extremely narrow range of age. Consequently, as ectopic AT depots are known to be strongly influenced by exercise, so that high physical activity is proven to reduce IMAT amount both in younger and older master athletes [18], we decided to apply no age restriction among enrollment criteria of our study population, as well as to focus on well established sedentary subjects in order to avoid this above reported potential confounder on our analysis.

Interestingly, IMAT and EAT depots appeared to be more strongly associated with age than waist circumference or BMI, whereas similar trends were not reported for either IAAT or SAT (Table 1).

The reasons for these findings are not completely understood, but it can be postulated that the distinct origin of ectopic fat, which consists in the dysdifferentiation of muscle mesenchymal progenitors, or the close anatomic contact of AT with muscular fibers, which favors paracrine effects of myokines (IL-6, myostatin, follistatin) and metabolites on the biology of the surrounding AT, could account for distinct behaviors of intermuscular and epicardial adipocytes comparing with those constituting IAAT and SAT [11].

Our observations are in line with the notion that, with increasing age, body fat becomes centralized and is redistributed from subcutaneous to visceral compartments, even in healthy people [31,32], suggesting that this redistribution could additionally involve ectopic sites such as IMAT and EAT depots and therefore lead to their greater expansion. Accordingly, ageing-associated changes in AT distribution are a well-established phenomenon irrespective of gender or race, accompanied by an increased risk of MS, AT chronic inflammation and decreased proliferation and differentiation of preadipocytes [33]. In addition, as older adults are often weaker than predicted by sarcopenia alone [34] and high levels of leg IMAT are associated with decreased muscle strength as well as muscle quality [16], the increase of fat within skeletal muscle is likely to contribute further to physical impairment and disability in the elderly. Similarly to EAT, where the lack of interposed fascia allows pro-inflammatory [35], cardiodepressant [36] and pro-fibrotic [37] factors to affect myocardial structure and function, IMAT may promote myosteatosis, myofibrosis [38] and functional impairment, by secreting paracrine mediators and enhancing lipolysis rates within skeletal muscle. Accordingly, both IMAT and Tumor Necrosis Factor- α mRNA levels are increased in paretic limbs of stroke survivors [39].

Noteworthy, we also observed that IMAT and EAT amounts positively correlated with waist circumference and reciprocally irrespective of gender, but in younger individuals (≤ 50 yrs) only, in contrast with what noted for SAT and IAAT which tended to correlate similarly with waist circumference in both age groups (≤ 50 yrs and > 50 yrs).

Even though all recruited subjects did not practice structured or routine exercise, some evidence suggests that even changing the way a muscle is used may play an important role in the level of fatty infiltration seen with ageing: for instance, brisk walking, which is less likely to be practiced by the olders, can decrease IMAT amount [17]. Besides, the higher loss percentage of IAAT compared to IMAT and EAT after exercise-induced weight loss may reflect distinct lipolytic properties [40,41], and allows to speculate that ectopic compartments also respond differently to inactivity.

We could additionally postulate that these age-related different patterns could be consequent to modifications in sex hormones levels, chronic stress-induced mild hypercortisolemia and prolonged sympathetic nervous system activation, or even to nutritional factors, across the ages [3]. With regard to the latter, fructose-sweetened beverages consumption may have a potential effect on body fat distribution independent of its impact on overall AT accretion, namely stimulating deposition of triglycerides in ectopic sites by depot-specific modulation of lipogenic enzymes [42].

Due to its association with age [15], physical inactivity [18], adiposity [43], muscle function impairment [16] and type 2 diabetes, IMAT has been suggested to be a risk factor for obesity-related diseases along with IAAT. The association with insulin resistance and glucose metabolism has been previously reported for erector spinae, thigh and total body IMAT [20,38,40,44,45]

irrespective of race, weight, height, and total skeletal muscle volume [19]. Furthermore, thigh IMAT was significantly associated with increased systemic levels of inflammatory cytokines and C-Reactive Protein, which have been linked to insulin resistance, type 2 diabetes and age-related sarcopenia [46,47].

Nevertheless, it is currently unknown whether IMAT can play a modifying role in the pathogenesis of insulin resistance or it is to be alternatively considered a marker of metabolic dysfunction only. The finding that IMAT amounts were positively correlated with serum triglycerides, even though no causal relationship can be affirmed, could suggest a contribution of IMAT in determining obesity- and age-related metabolic diseases.

In accordance, IMAT is assumed to modulate blood flow to the muscle, impair insulin diffusion capacity [20,48], and increase local inflammation and lipolysis rates within the muscle. However, after controlling for waist circumference or IAAT, the correlation between IMAT and triglycerides was no more significant, highlighting the greater relevance of IAAT in directly influencing the metabolism, putatively through its greater extent and unique anatomic location, which allow the release of free fatty acids into the portal system to the liver and pancreas.

Finally, we acknowledge some study limitations, mainly related to the cross-sectional design which does not allow to assess cause-effect relationships, and to the small sample size which precludes to address other potential confounders using covariate analysis, e.g. the interaction between age and waist circumference in their relationships with IMAT or EAT. The study is also adversely affected by the lack of any direct measure of insulin resistance, which would have been useful to better characterize our study

population from a metabolic perspective, although the presence of MS diagnosed according to IDF criteria can provide indirect information about insulin resistance status [49]. On the other hand, we believe that major strengths of our study derive from the use of MRI, namely the gold standard technique to assess AT quantitative distribution and from the opportunity to include individuals with known sedentary habits and in a wide distribution of age.

In summary, herein we report that in sedentary subjects without cardiovascular disease IMAT as well as EAT depots are related with increasing age to a greater extent than observed with waist circumference, and that the positive association of IMAT amount with waist circumference and IAAT is likely to be significant for younger individuals only. Further research is needed to better clarify these issues and, more generally, to better characterize the role of ectopic AT depots in the pathophysiology of cardiometabolic diseases.

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Author Contributions

Conceived and designed the experiments: VG. Performed the experiments: VG LM. Analyzed the data: VG LM M. Di Roma AB. Contributed reagents/materials/analysis tools: CL PP. Contributed to the writing of the manuscript: VG LM M. D'Admao MF DL AB PS.

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