International Journal of Obesity
https://doi.org/10.1038/s41366-020-00701-5

ARTICLE

Clinical Research

Neck adipose tissue accumulation is associated with higher overall and central adiposity, a higher cardiometabolic risk, and a pro-inflammatory profile in young adults

Maria Jose Arias-Tellez[1,2] · Francisco M. Acosta[1] · Yolanda Garcia-Rivero[3] · Jose Miguel Pascual-Gamarra[1] · Elisa Merchan-Ramirez[1] · Borja Martinez-Tellez[1,4] · Analiza M. Silva[5] · Julio Almansa Lopez[6,7] · Jose M. Llamas-Elvira[3] · Jonatan R. Ruiz[1]

Received: 4 April 2020 / Revised: 3 September 2020 / Accepted: 14 October 2020

Abstract

Objectives Neck adipose tissue (NAT) volume increases with general adiposity, with fat accumulating in different neck tissue compartments. In patients with certain malignant/benign tumours, the accumulation of NAT, and certain NAT distributions, have been associated with cardiometabolic risk (CMR). However, it is unknown whether the same relationships exist in healthy people, and whether NAT accumulation and distribution are related to the inflammatory status.

Methods In this cross-sectional study, 139 young healthy adults (68% women) underwent a computed tomography scan to quantify the volume of compartmental (i.e., subcutaneous, intermuscular and perivertebral) and total NAT at the height of vertebra C5. Anthropometric indicators were measured, and body composition determined using dual energy X-ray absorptiometry. Information on CMR factors (i.e., blood glycaemic and lipid markers, blood pressure and physical fitness) was also gathered, and a CMR score calculated. Several plasma cytokines and serum components of the innate immune system were measured to determine the inflammatory status.

Results Compartmental and total NAT volumes were directly related to body mass index (BMI), and lean, fat, and visceral adipose tissue (VAT) masses (all, $P \le 0.05$). Larger compartmental (especially intermuscular) and total NAT volumes were directly associated with the CMR score, several CMR factors (i.e., glycaemic and lipid markers and blood pressure), and the C3, C4 and leptin concentrations. They were, however, inversely correlated with the CMR factors high density lipoprotein-cholesterol (HDL-C) and physical fitness, and with the adiponectin concentration (all $P \le 0.05$). Several of these associations remained statistically significant ($P \le 0.05$) after adjustment for BMI, body fat percentage or VAT mass. Overall, results did not change after applying false discovery rate correction.

Conclusions NAT volume and its distribution among different tissue compartments is associated with the CMR and inflammatory profile of young healthy adults. Total NAT volume appears to be as valuable as VAT mass in terms of predicting CMR and inflammatory status.

Introduction

Obesity is a disorder of the energy homoeostasis system; in simple terms it is the result of energy intake being sustained above energy expenditure. Obesity is partly characterized by the limited expandability and dysfunction of adipocytes, an increased cardiometabolic risk (CMR), and a low-grade chronic pro-inflammatory status [1–3].

Traditional measures of obesity include the body mass index (BMI) and waist circumference [4] – factors with a bearing on cardiometabolic disease [5]. Several studies have proposed that fat accumulation in the neck (measured as neck circumference [NC]) provides an indicator

These authors contributed equally: Maria Jose Arias-Tellez and Francisco M. Acosta

Supplementary information The online version of this article (https://doi.org/10.1038/s41366-020-00701-5) contains supplementary material, which is available to authorized users.

✉ Francisco M. Acosta
acostaf@ugr.es

Extended author information available on the last page of the article

Published online: 02 November 2020

of upper body fatness, being NC associated with obesity and cardiovascular risk independent of BMI and visceral adipose tissue (VAT) mass [6, 7]. Accordingly, experimental evidence has shown that the splanchnic adipose tissue (including visceral fat) accounts for only a small percentage of systemic free fatty acid release during post absorptive and postprandial states, while non-splanchnic upper body adipose tissue contribute >50%, rendering it the largest contributor of all [8, 9]. All the evidence gathered to date supports the idea that non-splanchnic upper body fat, and particularly the NAT, might, at least partially, explain the obesity-related CMR not covered by the VAT [10–12].

Torriani et al. [10] showed that NAT increases with increasing adiposity, but that it follows a different pattern of accumulation across the neck subcutaneous, intermuscular and perivertebral compartments – a pattern that also differs between the sexes. Furthermore, they showed that the accumulation of NAT among these compartments correlated differently with CMR factors and the prevalence of metabolic syndrome. Similarly, Rosenquist et al. [11] observed that upper body subcutaneous fat, estimated by multidetector computed tomography imaging, was positively related to CMR factors and other measures of adiposity. Recently, Tal et al. [13] observed that a larger NAT volume relative to height, was directly associated with long-term mortality, independent of age and sex, as well as with the presence of type 2 diabetes mellitus. Current evidence would therefore seem to indicate that fat accumulation in the neck might play a role in the development of cardiometabolic abnormalities, or at least, that it could be a potential marker of CMR [10]. It should be noted, however, that all the above-mentioned studies involved cohorts of middle-aged (55–62 years old) patients who were retrospectively assessed for clinical purposes (i.e., malignant/benign tumours, suspected cardiovascular accidents, or vascular calcification) and included no estimate of physical fitness (a major CMR factor) [14]. It therefore remains to be seen whether these findings apply to young, healthy, sedentary adults, or whether a larger compartmental or total NAT accumulation are related to other CMR factors.

It is well known that inflammatory activity appears early in adipose tissue expansion, and exists during chronic obesity [15–17]. This can lead to maladaptive responses such as fibrosis, hypoxia and necrosis (among others) in adipose tissue, and negatively influence metabolic homoeostasis [18]. For instance, local changes in VAT deposits induced by adipocyte expansion are related to a low-grade systemic inflammation status characterized by elevated concentrations of circulating pro-inflammatory markers [17, 19–21]. Whether specific NAT compartments are associated with a more inflammatory profile is unknown. The aim of the present work was, therefore, to examine the relationship between compartmental/total NAT and overall/central adiposity, CMR, and inflammatory markers in young, healthy, sedentary adults.

Materials and methods

Study subjects and ethics statement

A total of 139 young, healthy adults (95 women), all belonging to the ACTIBATE study population (ClinicalTrials.gov, ID: NCT02365129) [22], took part in this cross-sectional study. All subjects had to be age 18–25 years old, have a sedentary lifestyle (i.e., undertaking <20 min moderate-vigorous physical activity <3 days/week at baseline), to be a non-smoker, take no medication, have had a stable body weight over the last 3 months (changes <3 kg), to have no cardiometabolic disease (e.g., hypertension or diabetes), and to have no first-degree relative history of cancer. The study was approved by the University of Granada Ethics Committee on Human Research (n° 924) and by that of the *Servicio Andaluz de Salud*. All work was performed in accordance with the Declaration of Helsinki (2013 revision); all subjects gave their written informed consent to be included. All assessments were made in Granada (Spain).

Procedures

^{18}F-FDG-PET/CT assays

All subjects underwent a ^{18}F-fluordeoxyglucose positron emission tomography combined with computed tomography (^{18}F-FDG-PET/CT), and the CT scan was used to quantify NAT volume and distribution (these analyses were completed over eight dates distributed between October and December of 2015 and 2016, i.e., four per year, with one test per subject). The subjects all confirmed they had met the requirements of: (i) arriving in a fasting state (at least 6 h), (ii) having slept as usual, (iii) having refrained from any moderate or vigorous physical activity (within 24 and 48 h respectively), (iv) having not consumed any alcoholic or stimulant beverages in the previous 6 h or taken any drugs that might affect the peripheral circulation in the last 24 h. The subjects were then invited to dress in standardized clothing and to void their bladders.

Since the original aim of the ACTIBATE study [22] was to detect the volume and activity of brown adipose tissue (BAT), participants were submitted to a personalized cooling protocol prior to the ^{18}F-FDG-PET/CT scan in order to stimulate BAT metabolic activity, as previously explained [23]. After 60 min of following this personalized

cooling protocol, a bolus of ^{18}F-FDG (180.6 ± 5.8 MBq ≈2.9 MBq/kg). was injected. One hour later, the subjects underwent PET/CT using a Siemens Biograph 16 PET/CT scanner (Siemens, Erlangen, Germany). After lying down on a flat table (supine position), with a thin pillow below their heads to make them feel more comfortable, a low dose CT scan (120 kV) was performed for attenuation correction and anatomic localization. Immediately thereafter, one static acquisition of 2 PET bed positions (6 min each) was performed from the atlas vertebra to the mid chest region.

Neck measurements

Quantification of neck adipose tissue As indicated above, for the main study purpose, only the CT component of the PET/CT was used. The CT scans were analysed using the Beth Israel plugin for FIJI software http://sourceforge.net/projects/bifijiplugins/ by the same researcher (JMPG). To determine the NAT volume and the distribution of fat across the different NAT compartments, several regions of interest (ROIs) were outlined at the level of C5 – the height at which NC measurement is usually performed (i.e., the level of laryngeal prominence [10])-, using a 3D-axial technique. NAT volumes were calculated for the chosen ROIs by determining the number of pixels within the radiodensity range of −300 to −10 Hounsfield Units (HU). An extended description of how the ROIs were drawn and analysed for each NAT specific compartment can be found in the Supporting Information (Appendix 1). Briefly, the three main NAT compartments were defined as:

i. subcutaneous NAT: adipose tissue in the posterior neck, between the skin and deep cervical fascia (see Fig. 1).
ii. intermuscular NAT: adipose tissue between the sternocleidomastoid, levator scapulae, semiespinalis and trapezius muscles, separated from the subcutaneous fat by the deep cervical fascia. No overlapping was allowed between the subcutaneous NAT and this compartment (see Fig. 1).
iii. perivertebral NAT: adipose tissue interspersed between the muscles surrounding vertebrae C5 (see Fig. 1).

In addition, using a 3-D sagittal view, another ROI was outlined at the height of C5 to determine the total NAT (i.e., with no compartmental differentiation) and lean tissue volume [24]. This ROI was drawn parallel to the body's sagittal axis, and included the entire neck length and width from the upper to the lower part of vertebra C5. Pixels were deemed to represent NAT when they fell within the same radiodensity range, while those within the range of −9 to 150 HU range were deemed to represent lean tissue

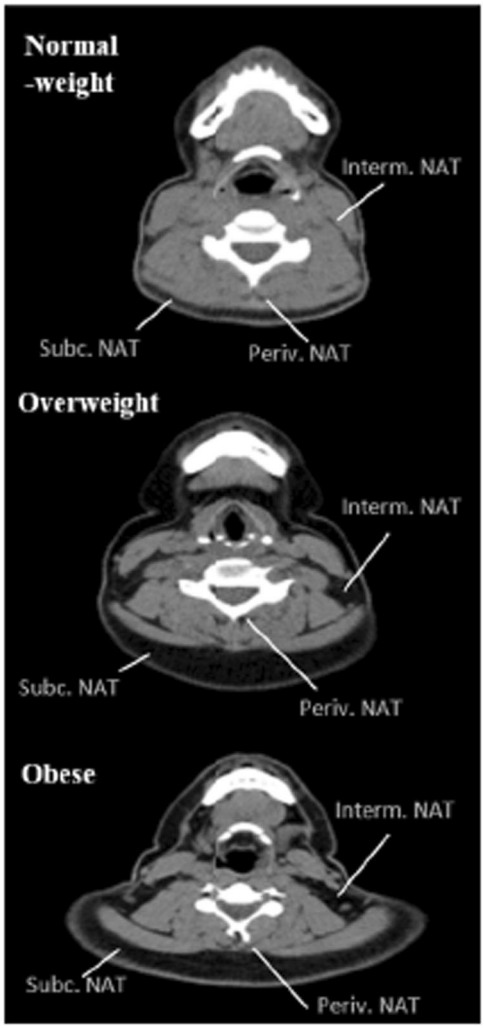

Fig. 1 Neck adipose tissue (NAT) accumulation based on the subject's nutritional status. This figure shows the NAT compartments (i.e., subcutaneous, intermuscular and perivertebral) in a typical normal-weight, overweight and obese subject.

(including skeletal muscle tissue, blood vessels and certain internal organs) [24].

Neck circumference NC was measured using an inextensible metallic tape over the thyroid cartilage, perpendicular to the longitudinal axis of the neck [25]. During this measurement subjects were in an anatomical position, standing or sitting with the head in the Frankfort plane and the shoulders relaxed.

Anthropometry and body composition

Subject weight and height were respectively measured using a model 769 calibrated digital scale and a portable model 213 stadiometer, both from SECA (Hamburg, Germany). BMI was determined as *body weight (kg)/height squared (m^2)*. On the same day, subjects underwent dual energy

x-ray absorptiometry using a Discovery Wi device (Hologic, Bedford, MA, USA) to determine fat mass, lean mass, and VAT mass. We additionally determined the lean and fat mass and percentage of the trunk and appendicular regions (i.e., arms and legs) for secondary analyses, given the fact that appendicular body composition represents a stronger predictor for physical fitness than whole body lean mass, in diseases such as heart failure [26].

Cardiometabolic and inflammatory profile

CMR and inflammation markers were normally assessed within 3 weeks of the ^{18}F-FDG-PET/CT assessment. Subjects came to our centre for the extraction of blood samples, and were asked to confirm having met the requirements of: (i) arriving in a fasting state (10–14 h), (ii) having slept as usual, (iii) having refrained from any kind of physical activity in the same morning when the blood extractions were performed (i.e., they had to come by means of motorized transport), (iv) having refrained from any moderate or vigorous physical activity (within 24 and 48 h respectively), and (v) having not consumed any stimulant beverage.

Glycaemic, lipids markers and HOMA index Serum glucose, total cholesterol, high density lipoprotein-cholesterol (HDL-C) and triglycerides were assessed following standard methods using an AU5832 automated analyzer (Beckman Coulter Inc., Brea CA, USA). Low density lipoprotein-cholesterol (LDL-C) was estimated as: [total cholesterol – HDL-C – (triglycerides/5)] (all in mg/dL) [27]. Serum insulin was measured using the Access Ultrasensitive Insulin Chemiluminescent Immunoassay Kit (Beckman Coulter Inc., Brea CA, USA). The homoeostasis model assessment of insulin resistance (HOMA) index was calculated as (insulin [μU/mL] × glucose [mmol/L]/22.5) [28].

Systolic and diastolic blood pressure An Omron M6 upper arm blood pressure monitor (Omron Healthcare Europe B. V. Hoofddorp, The Netherlands) was used to determine the systolic and diastolic blood pressure, with subjects seated and relaxed. Measurements were taken at three time points, and the mean determined for use in later analyses.

Physical fitness: muscular strength Handgrip strength was determined using an adjustable grip TKK 5101 Grip - D hand dynamometer (Takei, Tokyo Japan). Subjects were asked to squeeze gradually and continuously for a few seconds, and were encouraged to do their best when performing the tests. All tests were performed using the optimal grip-span [29]. Each subject performed two attempts with each hand, with the arm fully extended and maintaining the trunk erect. The maximum score for each hand was recorded in kilograms and the mean score of the left and right hand used in analyses. Muscular strength relative to body weight and lean body mass was also calculated.

Physical fitness: cardiorespiratory fitness Subjects' maximum oxygen consumption (VO_{2max}) was determined via a maximum exercise test using a Pulsar treadmill (H/P/Cosmos Sport & Medical GMBH, Nußdorf, Germany), based on the modified Balke protocol [30]. O_2 consumption and CO_2 production were measured by indirect calorimetry using a CPX Ultima CardiO_2 cart (Medical Graphics Corp, St Paul, USA) and a Model 7400 oronasal mask (Hans Rudolph Inc., Kansas City, MO, USA) equipped with a Prevent™ metabolic flow sensor (Medgraphics Corp., St. Paul, MN, USA). The criteria for achieving $VO_{2\,max}$ were: a respiratory exchange ratio of ≥1.1, a plateau in VO_2 (change of <100 mL/min in the last three consecutive 60 s stages), and a heart rate within 10 beats/min of the age-predicted maximum (208–0.7 × age) (Pallarés & Morán-Navarro, 2012). When no plateau in VO_2 was reached, $VO_{2\,peak}$ was obtained, and taken to represent cardiorespiratory fitness. The latter variable was also recorded relative to body weight and lean body mass.

Cardiometabolic risk score A CMR score based on variables included in the diagnostic of Metabolic Syndrome [31] was computed, including the subject's waist circumference, blood pressure, plasma glucose, and HDL-C and triglyceride concentrations. Each variable was standardized as follows: standardized value = (value − mean)/standard deviation. The HDL-C standardized values were multiplied by −1 to represent increasing values as directly proportional to the risk score. The final score was determined as the sum of the five standardized scores divided by five.

Pro and anti-inflammatory markers C-reactive protein, C3, C4, and β-microglobulin 2 concentrations were measured by immunoturbidimetric assay, employing the same AU5832 automated analyser as above. Interleukin (IL)-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-17a, interferon gamma (IFNɣ) and tumor necrosis factor alpha (TNF-α) were determined using a MILLIPLEX MAP Human High Sensitivity Cytokine Panel from the Luminex Corporation (Missouri, USA; Catalogue # HSCYTMAG-28SK). Leptin and adiponectin concentrations were measured using the MILLIPLEX MAG Human Adipokine Magnetic Bead Panel 2 (Catalogue # HADK2MAG-61K) and the MILLIPLEX MAP Human Adipokine Magnetic Bead Panel 1 (Catalogue # HADK1MAG-61K) respectively, both from the Luminex Corporation. Intra-assay CVs can be found in the Supporting Information [32].

Statistical analyses

Descriptive statistics for continuous and categorical variables were recorded for all subjects. All variables related to NAT, and the cardiometabolic (except muscular and cardiorespiratory fitness) and the inflammatory profile, were square root-transformed for correlational analyses to render their distributions closer to normal. All the analyses were performed separately for women and men given their important metabolic, phenotypic and NAT distribution differences, and given the influence of the interactions sex x body composition/CMR/inflammatory profile on NAT variables. The Kruskal–Wallis test was used to compare neck measurements across BMI categories. Pearson correlations were calculated to examine the relationship of compartmental and total NAT volume with NC, and to examine the relationship between neck measurements and body composition variables. Pearson correlation analysis was also conducted to examine the associations of neck measurements and VAT mass with CMR and the inflammatory profile. Adjustments for multiple comparisons were performed with the Benjamini-Hochberg procedure (False Discovery Rate-FDR- correction), to control the overall type I error rate [33]. This procedure was applied for the main analyses. Zou's confidence intervals [34] were obtained to compare the correlation coefficients of overlapping dependent significant correlations (as a preferred method to significance testing) using the web interface of the cocor package for R language (available at http://comparingcorrelations.org) [35]. All the other statistical analyses were performed using SPSS software version 21.0 (SPSS, Chicago, IL, USA). Significance was set at $P < 0.05$.

Results

In the present study, we initially included a total of 139 participants (see Flow Chart, Fig. S1) [32], all of whom underwent a ^{18}F-FDG-PET/CT scan in order to measure and quantify adipose tissue in the upper body region. Nevertheless, after checking and analysing all CT scans to measure and quantify NAT, several participants were excluded for each specific analysis (see Supporting Information for detailed information) [32]. The sample size varies for the different variables (e.g., NAT measures, body composition, cardiometabolic or inflammatory parameters). Therefore, in order to make the maximum use of the data, we performed the analyses with all valid data on the specified measures. The main characteristics of the whole study cohort are presented in Table S1.

NAT volume and distribution with increasing BMI

Figure 2 shows the pattern of NAT accumulation across BMI groups stratified as normal-weight, overweight and obese. The volumes of the subcutaneous, intermuscular and perivertebral and total NAT were larger in obese women and men compared to normal-weight women and men (all $P \le 0.05$; Fig. 2a–d respectively). The same pattern was seen for overweight women and men with respect to subcutaneous, intermuscular and total NAT (all $P \le 0.05$, a, b and d, respectively), but not for the perivertebral NAT ($P > 0.05$, c). Unlike the NAT, neck lean tissue volume did not vary across BMI categories ($P > 0.05$, Fig. S2). Furthermore, women who were overweight and obese, and men who were obese, returned larger NC values than their normal-weight counterparts (all $P \le 0.05$, Fig. 2e).

Associations of NAT volume and its distribution with anthropometric and body compositions parameters

The volume of subcutaneous, intermuscular, perivertebral and total NAT was directly associated with NC in both women and men (all $P \le 0.002$, Fig. S3), although these correlations were weaker in women than in men ($r = 0.43$–0.61 vs. 0.70–0.83, respectively).

The different compartmental and total NAT volumes were also directly associated with BMI, lean mass, fat mass, and VAT mass, in both sexes (all $P \le 0.05$, Fig. 3). The intermuscular and total NAT volumes showed the strongest correlations with BMI, fat mass and VAT mass, with $r > 0.69$ in women, and >0.8 in men. The NC also showed direct relationships with the same variables. These results remained similar when fat mass was substituted by percentage fat mas, although the strength of some associations was slightly less strong (see Fig. S4). Neck lean tissue volume was only associated with overall lean mass in women ($P \le 0.001$, Table S2). Table S3 shows the relationship of compartmental and total NAT with trunk and appendicular lean mass, and fat mass and percentage.

Association of NAT volume and its distribution with cardiometabolic risk and inflammatory profile

Larger NAT accumulations were associated with higher CMR scores in both women and men. The compartmental and (especially) total NAT volumes, and the NC, were directly associated with glycaemic and lipid markers and blood pressure (all CMR factors), and inversely with HDL-C and some physical fitness components (all $P \le 0.05$, see Table 1). These associations appeared to be stronger in the men than in the women. Total NAT volume and VAT mass seemed to be equally related to the CMR score (for both associations $r = 0.6$ and 0.8 for women and men, respectively). To statistically compare whether the correlation coefficients of the latter associations (and others) were similar, Zou's confidence intervals were determined. All correlation coefficients of total NAT volume and VAT mass

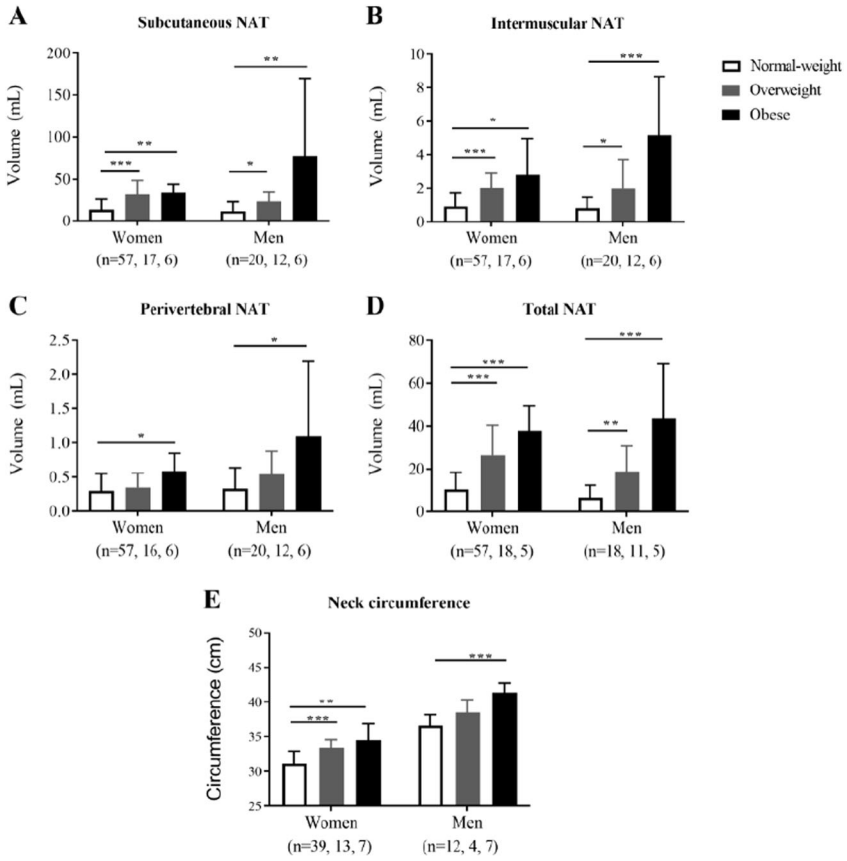

Fig. 2 Mean (and standard deviation) neck measurements with respect to BMI categories. The Kruskal–Wallis test was used to compare the compartmental (**a**–**c**) and total NAT volumes (**d**), and neck circumference (**e**), across BMI categories. NAT variables were square root-transformed before statistical analysis to render their distribution closer to normal. $*P \le 0.05$, $**P \le 0.01$, $***P \le 0.001$. Note that subjects who were underweight were pooled with the normal-weight subject. NAT neck adipose tissue.

with the CMR profile were found to be similar (data not shown) – except for the associations with high-density lipoprotein cholesterol and cardiorespiratory fitness relative to weight in men. Linear regressions showed that total NAT volume was deemed to explain 4.8 to 37.6%, and 11.9 to 66.2% of the variance for the significantly associated CMR variables in women and men, respectively (see Table 1, Supporting Information – Appendix 2). The highest explained variance was for the CMR score – being 37.6% in women, and 66.2% in men. Of note, when a stepwise linear regression was performed introducing total NAT volume and VAT mass as independent variables and the CMR score as the dependent variable, in men, VAT mass was excluded from the model, remaining only total NAT volume (the opposite was observed for women, data not shown).

Table 2 shows that, in women, the compartmental and total NAT volumes were directly associated with the concentrations of C3 and C4 (except for the perivertebral NAT), and leptin, and inversely associated with the adiponectin concentration (all $P \le 0.01$). In men, the compartmental and total NAT volumes were directly associated with the C3 and leptin concentrations (both $P \le 0.001$), and inversely associated with that of adiponectin ($P \le 0.05$, except the perivertebral NAT). Perivertebral NAT was the only NAT compartment volume associated with the C4 concentration ($P \le 0.01$). The NC was directly associated with the C4 and leptin concentrations in both women and men (all $P \le 0.01$). It is noteworthy that, overall, subcutaneous, intermuscular and total NAT volumes, and VAT mass, appeared to be similarly associated with the C3 ($r =$ 0.41–0.50 in women, $r = 0.59$–0.74 in men), C4 ($r =$ 0.32–0.39 in women), adiponectin ($r = -0.24$ to -0.31 in women; $r = -0.43$ to -0.56 in men) and leptin concentrations ($r = 0.38$–0.59 in women, $r = 0.57$–0.69 in men). Posterior analysis applying Zou's confidence interval confirmed that the correlation coefficients of the associations between total NAT volume and inflammatory profile vs. the associations between VAT mass and inflammatory profile, were similar (data not shown). Linear regressions showed that total NAT volume was deemed to explain 14 to 33%, and 36 to 46% of the variance for the significantly associated inflammatory-profile variables in women and men, respectively (see Table 2, Supporting Information – Appendix 2). In both sex, total NAT volume explained the largest explained variance for leptin.

After adjusting for multiple comparisons, most results related to the main analyses (Tables 1 and 2, and Fig. 2), remained similar. Of note, some of these relationships (for instance that of intermuscular and total NAT volume with the CMR score) remained significant ($P \le 0.05$) in women

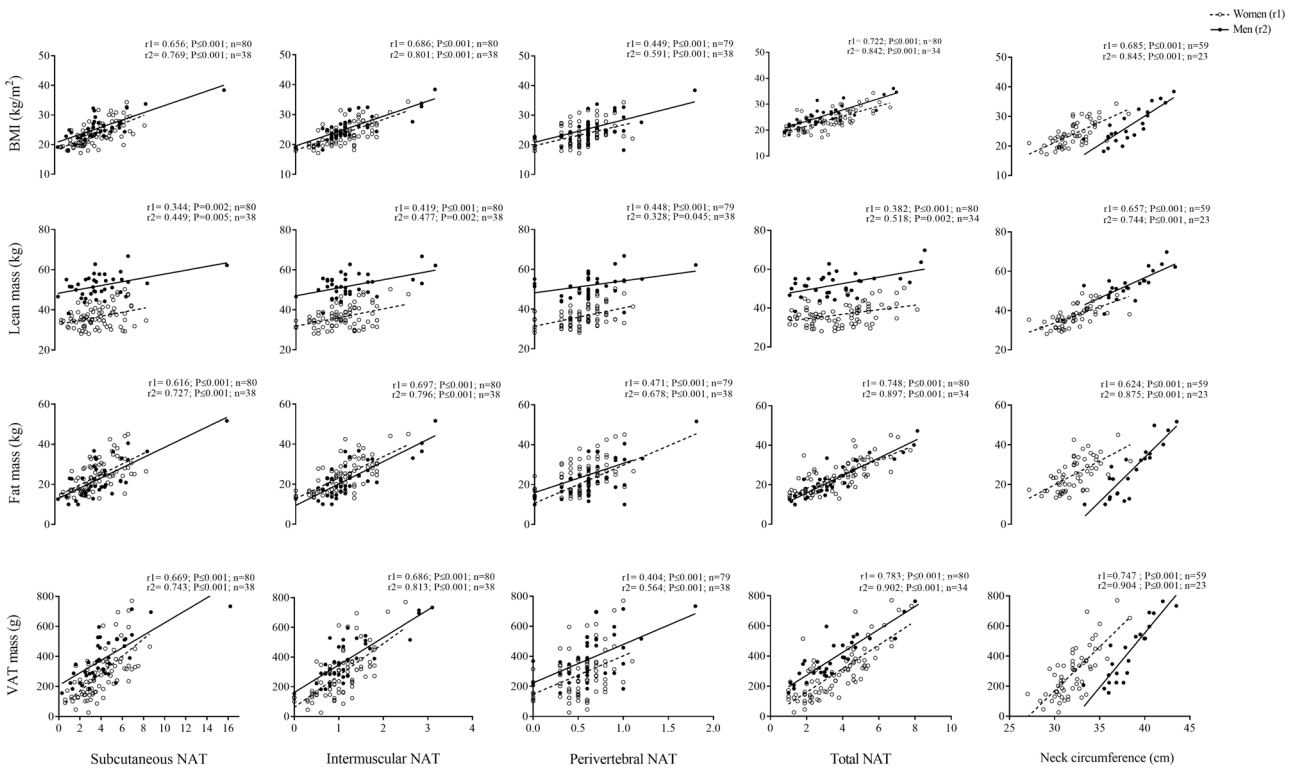

Fig. 3 Association between neck measurements and body composition in both sexes. Pearson correlation coefficients, *P* values and sample sizes are provided for both women and men. NAT variables were square root-transformed before analysis to render their distribution closer to normal. After applying False Discovery Rate (FDR, Benjamini-Hochberg) correction, all associations remained statistically significant ($P \leq 0.05$). BMI Body mass index, NAT Neck adipose tissue, VAT Visceral adipose tissue.

or/and men, independently of BMI, body fat percentage and VAT mass (see Table 1, Supporting Information – Appendix 3 for a detailed analysis) [32]. Furthermore, we found that when examining the relationship with cardiometabolic markers, total NAT volume and VAT mass outperformed BMI and other body composition parameters in most associations in men (see Table 2, Supporting Information – Appendix 3) [32]. Similarly, intermuscular and total NAT volumes, and neck circumference generally were more strongly associated with glycaemic and lipid markers than BMI and body composition parameters in women. Regarding the relationship with inflammatory markers in men (see Table 3, Supporting Information – Appendix 3) [32], intermuscular and total NAT volumes did not outperform BMI and body composition parameters. However, in women, intermuscular and total NAT volumes appeared to be more strongly associated with C-reactive protein, several components of the natural immune system and adiponectin than the rest of anthropometric and body composition parameters.

Sensitivity analyses are provided in the Supporting Information [32]. Coefficients of variation (CVs) of NAT measures (indicating the consistency of our data), and Bland-Altman plots comparing inter-evaluator estimate differences in NAT assessment, are also provided in the Supporting Information [32].

Discussion

The present results show NAT accumulation to be greater in those subjects with higher adiposity values, and that the compartmental and total NAT volumes are associated with overall and central adiposity. The compartmental (especially intermuscular) and total NAT volumes were also directly associated with CMR and inflammatory status. Several of these associations remained statistically significant independently of BMI, body fat percentage and VAT mass, such as is the case for the relationship between total NAT volume and the CMR score. These findings suggest that total NAT volume might be as valuable as VAT mass in terms of predicting CMR and inflammatory status, and that NC might be a useful clinical variable for estimating CMR, especially in men.

Torriani et al. [10] recently reported that the NAT increases with increasing adiposity, and that it seems to follow different accumulation patterns across the subcutaneous, intermuscular and perivertebral compartments,

Table 1 Association between neck measurements/visceral adipose tissue (VAT) and cardiometabolic risk (CMR) factors in women and men.

	Subcutaneous NAT				Intermuscular NAT				Perivertebral NAT				Total NAT				Neck circumference (cm)				VAT mass (g)			
	Women		Men		Women		Men		Women		Men		Women		Men		Women		Men		Women		Men	
	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n
Glucose	0.18	(78)	0.29	(38)		(78)	**0.30**	(38)	0.22	(77)	0.21	(38)	**0.25***	(78)	**0.63*****	(34)	**0.32***	(58)	**0.63*****	(23)	**0.26***	(93)	**0.60*****	(44)
Insulin	**0.44*****	(78)	**0.50*****	(38)	**0.41*****	(78)	**0.63*****	(38)	**0.28***	(77)	**0.49****	(38)	**0.59*****	(78)	**0.68*****	(34)	**0.54*****	(58)	**0.61****	(23)	**0.49*****	(93)	**0.72*****	(44)
HOMA	**0.43*****	(78)	**0.52*****	(38)	**0.41*****	(78)	**0.65*****	(38)	**0.29***	(77)	**0.49****	(38)	**0.57*****	(78)	**0.69*****	(34)	**0.55*****	(58)	**0.62****	(23)	**0.49*****	(93)	**0.73*****	(44)
Total cholesterol	−0.07	(78)	0.19	(38)	0.02	(78)	0.34*	(38)	0.07	(77)	0.18	(38)	−0.13	(78)	**0.46****	(34)	0.12	(58)	**0.51***	(23)	−0.02	(93)	**0.54*****	(44)
LDL-C	−0.01	(78)	0.23	(38)	0.13	(78)	**0.37***	(38)	0.20	(77)	0.22	(38)	−0.04	(78)	**0.48****	(34)	0.21	(58)	**0.55****	(23)	0.06	(93)	**0.53*****	(44)
HDL-C	**−0.30****	(78)	−0.16	(38)	**−0.37*****	(78)	−0.35*	(38)	**−0.31****	(77)	−0.18	(38)	**−0.39*****	(78)	**−0.53*****	(34)	−0.20	(58)	**−0.26**	(23)	**−0.33*****	(93)	−0.32*	(44)
TC/HDL-C	0.24*	(78)	0.27	(38)	**0.39*****	(78)	**0.53****	(38)	**0.36*****	(77)	0.27	(38)	**0.27***	(78)	**0.73*****	(34)	**0.32***	(58)	**0.56****	(23)	**0.33*****	(93)	**0.63*****	(44)
LDL-C/HDL-C	0.19	(78)	0.28	(38)	**0.34****	(78)	**0.50****	(38)	**0.35****	(77)	0.27	(38)	0.21	(78)	**0.68*****	(34)	**0.32***	(58)	**0.57****	(23)	**0.28****	(93)	**0.60*****	(44)
Triglycerides	**0.25***	(78)	0.14	(38)	**0.37*****	(78)	**0.39***	(38)	0.18	(77)	0.23	(38)	**0.27***	(78)	**0.63*****	(34)	0.23	(58)	0.44**	(23)	**0.33*****	(93)	**0.60*****	(44)
SBP	**0.31****	(79)	0	(37)	**0.38*****	(79)	0.07	(37)	**0.37*****	(78)	−0.13	(37)	**0.33****	(79)	0.28	(33)	**0.47*****	(58)	0.21	(22)	**0.42*****	(94)	**0.39****	(43)
DBP	0.24*	(79)	0.10	(37)	0.22*	(79)	0.23	(37)	0.12	(78)	0.04	(37)	**0.29****	(79)	**0.38***	(33)	0.14	(58)	0.32	(22)	**0.27****	(94)	**0.51*****	(43)
Muscular strength/weight	**−0.53 *****	(72)	**−0.52****	(31)	**−0.62*****	(72)	**−0.68*****	(31)	**−0.38*****	(71)	−0.35	(31)	**−0.59*****	(73)	**−0.65*****	(28)	**−0.39****	(59)	**−0.61****	(23)	**−0.67*****	(85)	**−0.65*****	(37)
Muscular strength$_{LM}$	**−0.33****	(72)	−0.28	(31)	**−0.41*****	(72)	**−0.45***	(31)	**−0.28***	(71)	−0.07	(31)	**−0.36****	(73)	**−0.31**	(28)	−0.26*	(59)	−0.12	(23)	**−0.41*****	(85)	**−0.26**	(37)
CRF/weight	**−0.41*****	(79)	**−0.45****	(34)	**−0.36*****	(79)	**−0.55*****	(34)	−0.07	(78)	**−0.56*****	(34)	**−0.57*****	(79)	**−0.43***	(29)	**−0.41*****	(59)	**−0.55***	(19)	**−0.55*****	(94)	**−0.62*****	(39)
CRF$_{LM}$	−0.08	(79)	−0.18	(34)	−0.002	(79)	−0.23	(34)	0.11	(78)	−0.28	(34)	−0.18	(79)	0.03	(29)	−0.22	(59)	−0.14	(19)	−0.13	(94)	−0.28	(39)
CMR score	**0.55*****	(76)	**0.49****	(37)	**0.66*****	(76)	**0.64*****	(37)	**0.45*****	(75)	**0.37***	(37)	**0.62*****	(75)	**0.82*****	(33)	**0.61*****	(57)	**0.69*****	(22)	**0.68*****	(90)	**0.81*****	(43)

Pearson correlation coefficients were determined to examine the association of neck adipose tissue (NAT) and circumference, and VAT mass, with the glycaemic and lipid markers, blood pressure and physical fitness. *$P \le 0.05$, **$P \le 0.01$, ***$P \le 0.001$. Values that remained statistically significant ($P \le 0.05$) after applying False Discovery Rate correction (Benjamini-Hochberg) are shown in bold. Of note, we followed a conservative approach, pooling all comparisons together, by sex. All NAT and cardiometabolic profile variables (except for muscular and cardiorespiratory fitness) were square root-transformed to bring their distributions closer to normal. *CRF* cardiorespiratory fitness, *CRF* cardiorespiratory fitness relative to lean body mass, *DBP* diastolic blood pressure, *HDL* high-density lipoprotein-cholesterol, *HOMA* homoeostatic model assessment of insulin resistance, *LDL-C* low-density lipoprotein-cholesterol, *LDL-C/HDL-C* low-density lipoprotein cholesterol (LDL-C)/HDL-C ratio, *TC/HDL-C* total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) ratio, *SBP* systolic blood pressure, *VAT* visceral adipose tissue.

Table 2 Association between neck measurements/visceral adipose tissue (VAT) mass and inflammatory markers in women and men.

	Subcutaneous NAT				Intermuscular NAT				Perivertebral NAT				Total NAT				Neck circumference (cm)				VAT mass (g)			
	Women		Men		Women		Men		Women		Men		Women		Men		Women		Men		Women		Men	
	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n
C-reactive protein	**0.29***	(78)	0.21	(38)	**0.377*****	(78)	0.20	(38)	0.17	(78)	**0.52*****	(38)	**0.39*****	(78)	0.19	(34)	0.12	(58)	0.26	(23)	**0.32****	(93)	0.25	(44)
IL-2	−0.19	(64)	0.13	(34)	−0.17	(64)	−0.11	(34)	−0.05	(64)	−0.13	(34)	−0.06	(63)	−0.09	(30)	0.08	(42)	−0.13	(18)	−0.09	(76)	0.02	(38)
IL-4	−0.14	(64)	0.24	(34)	−0.12	(64)	−0.01	(34)	0.02	(64)	−0.17	(34)	−0.06	(63)	−0.05	(30)	0.13	(42)	−0.18	(18)	−0.01	(76)	0.06	(38)
IL-6	−0.13	(64)	0.20	(34)	−0.06	(64)	0.00	(34)	0.03	(64)	0.01	(34)	0.05	(63)	−0.05	(30)	0.17	(42)	−0.09	(18)	0.02	(76)	0.07	(38)
IL-7	**−0.32****	(64)	0.28	(34)	−0.29*	(64)	0.04	(34)	−0.08	(64)	−0.26	(34)	−0.23	(63)	−0.04	(30)	−0.15	(42)	−0.16	(18)	−0.20	(76)	0.11	(38)
IL-8	−0.07	(64)	0.32	(34)	0.02	(64)	0.10	(34)	−0.003	(64)	0.05	(34)	0.07	(63)	0.17	(30)	0.02	(42)	0.31	(18)	0.05	(76)	0.17	(38)
IL-10	−0.04	(64)	0.003	(34)	0.02	(64)	−0.43	(34)	0.08	(64)	−0.40*	(34)	−0.03	(63)	0.10	(30)	0.04	(42)	−0.03	(18)	−0.02	(76)	0.14	(38)
IL-17a	−0.05	(64)	0.19	(34)	0.06	(64)	0.05	(34)	0.03	(64)	−0.19	(34)	−0.09	(63)	0.12	(30)	−0.01	(42)	0.03	(18)	−0.09	(76)	0.09	(38)
IFNγ	0.07	(64)	−0.13	(34)	0.11	(64)	−0.15	(34)	−0.06	(64)	−0.18	(34)	0.02	(63)	−0.01	(30)	−0.03	(42)	−0.02	(18)	−0.06	(76)	0.003	(38)
TNFα	0.04	(64)	0.03	(34)	0.14	(64)	−0.07	(34)	−0.11	(64)	−0.13	(34)	0.08	(63)	0.05	(30)	0.19	(42)	0.04	(18)	0.03	(76)	0.15	(38)
Complement 3	**0.41*****	(78)	**0.59*****	(38)	**0.48*****	(78)	**0.60*****	(38)	0.21	(78)	**0.58*****	(38)	**0.46*****	(78)	**0.62*****	(34)	**0.40****	(58)	**0.74*****	(23)	**0.50*****	(93)	**0.67*****	(44)
Complement 4	**0.32****	(78)	0.18	(38)	**0.32****	(78)	0.28	(38)	0.14	(78)	**0.43****	(38)	**0.39*****	(78)	0.31	(34)	0.21	(58)	0.25	(23)	**0.39*****	(93)	0.30*	(44)
β-microglobulin 2	0.18	(78)	−0.31	(38)	**0.28***	(78)	−0.36*	(38)	0.13	(78)	−0.12	(38)	0.19	(78)	0.01	(34)	−0.27*	(58)	−0.10	(23)	−0.02	(93)	−0.24	(44)
Adiponectin	**−0.31****	(75)	**−0.43****	(37)	**−0.31****	(75)	**−0.52*****	(37)	**−0.33****	(75)	−0.32	(37)	**−0.31****	(74)	**−0.56*****	(33)	−0.15	(54)	−0.36	(22)	−0.24*	(89)	**−0.43****	(43)
Leptin	**0.38*****	(76)	**0.57*****	(37)	**0.46*****	(76)	**0.67*****	(37)	**0.37*****	(76)	**0.63*****	(37)	**0.59*****	(76)	**0.69*****	(33)	**0.37****	(54)	**0.69*****	(22)	**0.59*****	(91)	**0.69*****	(43)

Pearson correlation coefficients were determined to examine the association between neck measurements and inflammatory markers. *$P \le 0.05$, **$P \le 0.01$, ***$P \le 0.001$. Values that remained statistically significant ($P \le 0.05$) after applying False Discovery Rate correction (Benjamini-Hochberg) are shown in bold. Of note, we followed a conservative approach, pooling all comparisons together, by sex. All NAT and inflammatory profile variables were square root-transformed to bring their distributions closer to normal.

IL interleukin, *IFNγ* interferon gamma, *TNFα* tumour necrosis factor-alpha, *VAT* visceral adipose tissue.

with each differently related to CMR, in patients with successfully treated malignant/benign tumours. The present results are in line with these findings, although the perivertebral NAT seemed to be less affected by increasing adiposity. Indeed, the compartmental NAT volumes were similarly related to total and central body composition variables, but the perivertebral NAT volume returned the weakest associations. Also in agreement with the above authors, the intermuscular and total NAT volumes showed the strongest association with the CMR factors examined, and total NAT seemed to be as predictive as VAT mass with respect to overall CMR. Interestingly, potential differences between the sexes were seen in the relationship between the NAT variables and body composition and CMR, which were stronger in men. It is known that women are more likely to accumulate fat in the lower body (i.e., the gluteofemoral zone) than are men, who tend to accumulate more visceral fat [36], and that this body fat distribution is differently related to CMR [37]. Thus, it might be speculated that NAT accumulation is also different in women and men and might also be differently related to CMR. Torriani et al. [10] previously showed that women were more likely to accumulate neck fat in the subcutaneous NAT compartment, and men in the intermuscular and perivertebral NAT compartments. This finding, together with the present results, reinforces the hypothesis that NAT accumulation in specific compartments is gender-dependent, and that it might be differently related to CMR (more so in men). However, this might be partially driven by the fact that men had a higher average BMI in the present cohort. Together, these findings underline the relationship between NAT accumulation and cardiometabolic disease, and shed some light on traditionally non-explored adipose fat deposits that might provide therapeutic targets.

To better understand the pathophysiology of NAT (and its specific distribution), studies are required that examine whether NAT accumulation is related to the low grade pro-inflammatory status commonly associated with obesity [38]. The present work therefore examined whether the compartmental and total NAT volumes were associated with the systemic anti- and pro-inflammatory factors previously shown to be associated with VAT [21]. Overall, the present results show the intermuscular and total NAT volumes and the VAT mass to be similarly related, in terms of direction and strength, to the C3, C4, adiponectin and leptin concentrations. The lack of studies in this area precludes comparisons being made, although some [39, 40] have compared inflammation signalling in gluteal and abdominal subcutaneous white adipose tissue, and report the expression of inflammatory or cytokine genes in the former region in persons with obesity comorbidities (e.g., hyperlipidaemia and insulin resistance) to be considerably weaker than that seen in the latter. This suggests that the accumulation of fat – including the NAT – across specific adipose tissue deposits, might contribute differently to the low-grade chronic pro-inflammatory state. This idea warrants further research. It also arises the possibility that the intermuscular and total NAT volume may be valuable markers for VAT mass in studies where CT of the neck region is available, but not CT or DXA for body VAT composition.

From a clinical point of view, the volumetric quantification of NAT might not be viable given the high cost, technical difficulties and exposure to radiation involved in CT imaging. However, the NC showed correlation coefficients with CMR factors (Table 1) similar to those of the compartmental and total NAT volumes. In addition, the NC showed strong and moderate-to-strong associations with the NAT volumes in both men and women. These findings are in line with those of large cohort studies showing NC to be directly associated with a large battery of CMR markers [7, 41, 42], and moderately associated with upper body subcutaneous fat volume [38]. Although NC did not show such a strong relationship with systemic inflammatory markers as did the intermuscular and total NAT volumes, it would seem to be a good marker of CMR in young, healthy, sedentary adults, and might provide a practical screening tool for determining the latter.

These results should be interpreted with caution. They may not be generalizable to people with excess upper body fat due to the difficulties of accurately outlining the ROIs for distinguishing specific NAT compartments. A multidetector-based analysis of a neck area beyond that studied in the present work, as described elsewhere [11], may help better characterize the NAT. Furthermore, since a thin pillow was placed below the head, which was therefore slightly inclined, ROIs for estimating the NAT volumes could only be drawn for the posterior part of the neck around the level of C5. In addition, the subjects underwent a personalized cold exposure prior to their PET/CT scan, which might have had a very small effect (cold exposure only induces a mean change of only ~3 HU) [43] on the radiodensity readings, leading to a small number of voxels that should have been classified as NAT. Of note, CMR and inflammation parameters were normally assessed within 3 weeks of the ^{18}F-FDG-PET/CT assessment. Further work should examine the molecular signatures of the neck region to try to reveal the underlying mechanisms (e.g., lipid metabolism and regulation) by which NAT accumulation contributes to a higher CMR and a more pro-inflammatory status.

In conclusion, an increase in NAT volume is associated with a higher CMR and a more pro-inflammatory state in young, healthy, sedentary adults. Some of the relationships of NAT measures with CMR and inflammatory markers were independent of BMI, body fat percentage and/or VAT mass. Our findings suggest that total NAT volume might be as valuable as VAT mass in terms of predicting CMR and

inflammatory status, and suggest that NC might be a useful clinical variable for estimating CMR, especially in men. Further research is warranted to understand the mechanisms giving rise to these associations.

Funding This study was funded by the Spanish Ministry of Economy and Competitiveness via the Fondo de Investigación Sanitaria del Instituto de Salud Carlos III (PI13/01393) and PTA 12264-I, Retos de la Sociedad (DEP2016-79512-R) and European Regional Development Funds(ERDF), the Spanish Ministry of Education (FPU 13/03410), the Fundación Iberoamericana de Nutrición (FINUT), the Redes Temáticas de Investigación Cooperativa RETIC (Red SAMID RD16/0022), the AstraZeneca HealthCare Foundation, the University of Granada Plan Propio de Investigación 2016 – Excellence actions: Unit of Excellence on Exercise and Health (UCEES) – and Plan Propio de Investigación 2018: Programa Contratos-Puente, the Junta de Andalucía, Consejería de Conocimiento, Investigación y Universidades (ERDF, SOMM17/6107/UGR) - and the Fundación Carolina (C.2016-574961). This study is part of a PhD thesis conducted with the framework of the Biomedicine Doctoral Studies Programme of the University of Granada, Spain.

Author contributions MJAT, FAM, JMPG, BMT, JMLL, JRR designed the study; MJAT, FAM, YGR, JMPG, EMR, and BMT conducted the research; JMLL and JRR provided essential reagents and materials; MJAT, FAM, JMPG, and EMR analysed the data and performed the statistical analysis; MJAT and FAM wrote the manuscript; MJAT, FAM, YGR, JMPG, EMR, BMT, AMS, JAL, JMLL, and JRR reviewed the manuscript and provided scientific assistance; JRR had primary responsibility for the paper's final content.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Lafontan M. Historical perspectives in fat cell biology: the fat cell as a model for the investigation of hormonal and metabolic pathways. Am J Physiol Cell Physiol. 2012;302:C327–59. https://doi.org/10.1152/ajpcell.00168.2011.
2. Halade GV, Kain V. Obesity and cardiometabolic defects in heart failure pathology. Compr Physiol.2017;7:1463–77. https://doi.org/10.1002/cphy.c170011.
3. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome-a new worldwide definition. Lancet. 2005;366:1059–62. https://doi.org/10.1016/s0140-6736(05)67402-8.
4. Cornier MA, Despres JP, Davis N, Grossniklaus DA, Klein S, Lamarche B, et al. Assessing adiposity: a scientific statement from the American Heart Association. Circulation. 2011;124:1996–2019. https://doi.org/10.1161/CIR.0b013e318233bc6a.
5. Amirabdollahian F, Haghighatdoost F. Anthropometric Indicators of Adiposity Related to Body Weight and Body Shape as Cardiometabolic Risk Predictors in British Young Adults: Superiority of Waist-to-Height Ratio. 2018;2018:8370304. https://doi.org/10.1155/2018/8370304.
6. Alzeidan R, Fayed A Performance of neck circumference to predict obesity and metabolic syndrome among adult Saudis: a cross-sectional study. 2019;6:13. https://doi.org/10.1186/s40608-019-0235-7.
7. Preis S, Massaro J, Hoffmann U, D'Agostino RB Sr, Levy D, Robins SJ, et al. Neck circumference as a novel measure of cardiometabolic risk: the Framingham Heart study. J Clin Endocrinol Metab. 2010;95:3701–10. https://doi.org/10.1210/jc.2009-1779.
8. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. J Clin Investig. 2004;113:1582–8. https://doi.org/10.1172/jci21047.
9. Guo Z, Hensrud DD, Johnson CM, Jensen MD. Regional postprandial fatty acid metabolism in different obesity phenotypes. Diabetes. 1999;48:1586–92. https://doi.org/10.2337/diabetes.48.8.1586.
10. Torriani M, Gill CM, Daley S, Oliveira AL, Azevedo DC, Bredella MA. Compartmental neck fat accumulation and its relation to cardiovascular risk and metabolic syndrome. Am J Clin NutR. 2014;100:1244–51. https://doi.org/10.3945/ajcn.114.088450.
11. Rosenquist K, Therkelsen K, Massaro J, Hoffmann U, Fox C. Development and reproducibility of a computed tomography-based measurement for upper body subcutaneous neck fat. J Am Heart Assoc. 2014;3:e000979. https://doi.org/10.1161/jaha.114.000979.
12. Pandzic JV, Grizelj D, Livun A, Boscic D, Ajduk M, Kusec R, et al. Neck adipose tissue - tying ties in metabolic disorders. Horm Mol Biol Clin Investig. 2018;33. https://doi.org/10.1515/hmbci-2017-0075.
13. Tal S, Litovchik I The association between neck adiposity and long-term outcome. 2019;14:e0215538. https://doi.org/10.1371/journal.pone.0215538.
14. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA. 2009;301:2024–35. https://doi.org/10.1001/jama.2009.681.
15. Carobbio S, Pellegrinelli V, Vidal-Puig A. Adipose tissue function and expandability as determinants of lipotoxicity and the metabolic syndrome. Adv Exp Med Biol. 2017;960:161–96. https://doi.org/10.1007/978-3-319-48382-5_7.
16. Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome-an allostatic perspective. Biochimica et biophysica acta. 2010;1801:338–49. https://doi.org/10.1016/j.bbalip.2009.12.006.
17. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Investig. 2017;127:1–4. https://doi.org/10.1172/jci92035.
18. Sam S Differential effect of subcutaneous abdominal and visceral adipose tissue on cardiometabolic risk. Horm Mol Biol Clin Investig. 2018;33. https://doi.org/10.1515/hmbci-2018-0014.
19. Bruun JM, Lihn AS, Pedersen SB, Richelsen B. Monocyte chemoattractant protein-1 release is higher in visceral than subcutaneous human adipose tissue (AT): implication of macrophages resident in the AT. J Clin Endocrinol Metabol. 2005;90:2282–9. https://doi.org/10.1210/jc.2004-1696.
20. Kranendonk ME, van Herwaarden JA, Stupkova T, de Jager W, Vink A, Moll FL, et al. Inflammatory characteristics of distinct abdominal adipose tissue depots relate differently to metabolic risk factors for cardiovascular disease: distinct fat depots and vascular risk factors. Atherosclerosis. 2015;239:419–27. https://doi.org/10.1016/j.atherosclerosis.2015.01.035.
21. Pou KM, Massaro JM, Hoffmann U, Vasan RS, Maurovich-Horvat P, Larson MG, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. Circulation. 2007;116:1234–41. https://doi.org/10.1161/circulationaha.107.710509.
22. Sanchez-Delgado G, Martinez-Tellez B, Olza J, Aguilera CM, Labayen I, Ortega FB, et al. Activating brown adipose tissue through exercise (ACTIBATE) in young adults: rationale, design

and methodology. Contemp Clin Trials. 2015;45:416–25. https://doi.org/10.1016/j.cct.2015.11.004.
23. Martinez-Tellez B, Sanchez-Delgado G, Garcia-Rivero Y, Alcantara JMA, Martinez-Avila WD, Munoz-Hernandez MV, et al. A new personalized cooling protocol to activate brown adipose tissue in young adults. Front Physiol. 2017;8:863. https://doi.org/10.3389/fphys.2017.00863.
24. Chung H, Cobzas D, Birdsell L, Lieffers J, Baracos V Automated segmentation of muscle and adipose tissue on CT images for human body composition analysis. Paper presented at: Medical Imaging 2009: Visualization, Image-Guided Procedures, and Modeling 2009.
25. Stewart A, Marfell-Jones M, Olds T, Ridder dH. International Society for Advancement of Kinanthropometry. International standards for anthropometric assessment. Lower Hutt, New Zealand: International Society for the Advancement of Kinanthropometry. 2011:50–3.
26. Carbone S, Billingsley HE, Rodriguez-Miguelez P, Kirkman DL, Garten R, Franco RL, et al. Lean mass abnormalities in heart failure: the role of sarcopenia, sarcopenic obesity, and cachexia. Curr Probl Cardiol. 2019:100417. https://doi.org/10.1016/j.cpcardiol.2019.03.006.
27. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499–502.
28. Matthews D, Hosker J, Rudenski A, Naylor B, Treacher D, Turner R. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412–9.
29. Ruiz-Ruiz J, Mesa JL, Gutiérrez A, Castillo MJ. Hand size influences optimal grip span in women but not in men. J Hand Surg. 2002;27:897–901.
30. Balke B, Ware RW The present status of physical fitness in the Air Force. SCHOOL OF AVIATION MEDICINE RANDOLPH AFB TX;1959.
31. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640–5. https://doi.org/10.1161/circulationaha.109.192644.
32. Arias Tellez MJ, Acosta FM, Garcia-Rivero Y, Pascual-Gamarra JM, Merchan-Ramirez E, Martinez-Tellez B, et al. Neck adipose tissue accumulation is related to a higher overall and central adiposity, cardiometabolic risk, and a pro-inflammatory profile in adults. figshare. Online resource. 2020. https://doi.org/10.6084/m9.figshare.12037233.v1.
33. Dmitrienko A, D'Agostino RB Sr, Huque MF. Key multiplicity issues in clinical drug development. Stat Med. 2013;32:1079–111. https://doi.org/10.1002/sim.5642.
34. Tate RL, Perdices M, Rosenkoetter U, Shadish W, Vohra S, Barlow DH, et al. The Single-Case Reporting Guideline In BEhavioural Interventions (SCRIBE) 2016 Statement. Phys Ther. 2016;96:e1–10. https://doi.org/10.2522/ptj.2016.96.7.e1.
35. Diedenhofen B, Musch J. cocor: a comprehensive solution for the statistical comparison of correlations. PLoS ONE. 2015;10:e0121945. https://doi.org/10.1371/journal.pone.0121945.
36. Williams CM. Lipid metabolism in women. Proc Nutr Soc. 2004;63:153–60.
37. Karpe F, Pinnick KE. Biology of upper-body and lower-body adipose tissue-link to whole-body phenotypes. Nat Rev Endocrinol. 2015;11:90–100. https://doi.org/10.1038/nrendo.2014.185.
38. Lee JJ, Pedley A, Therkelsen KE, Hoffmann U, Massaro JM, Levy D, et al. Upper body subcutaneous fat is associated with cardiometabolic risk factors. Am J Med. 2017;130:958–66.e951. https://doi.org/10.1016/j.amjmed.2017.01.044.
39. Malisova L, Rossmeislova L, Kovacova Z, Kracmerova J, Tencerova M, Langin D, et al. Expression of inflammation-related genes in gluteal and abdominal subcutaneous adipose tissue during weight-reducing dietary intervention in obese women. Physiol Res. 2014;63:73–82.
40. Pinnick KE, Nicholson G, Manolopoulos KN, McQuaid SE, Valet P, Frayn KN, et al. Distinct developmental profile of lower-body adipose tissue defines resistance against obesity-associated metabolic complications. Diabetes. 2014;63:3785–97. https://doi.org/10.2337/db14-0385.
41. Vallianou NG, Evangelopoulos AA, Bountziouka V, Vogiatzakis ED, Bonou MS, Barbetseas J, et al. Neck circumference is correlated with triglycerides and inversely related with HDL cholesterol beyond BMI and waist circumference. Diabetes/metabolism Res Rev. 2013;29:90–7. https://doi.org/10.1002/dmrr.2369.
42. Preis SR, Pencina MJ, D'Agostino RB Sr, Meigs JB, Vasan RS, Fox CS. Neck circumference and the development of cardiovascular disease risk factors in the Framingham Heart Study. Diabetes Care. 2013;36:e3. https://doi.org/10.2337/dc12-0738.
43. UD M, Raiko J, Saari T, Saunavaara V, Kudomi N, Solin O, et al. Human brown fat radiodensity indicates underlying tissue composition and systemic metabolic health. J Clin Endocrinol Metab. 2017;102:2258–67. https://doi.org/10.1210/jc.2016-2698.

Affiliations

Maria Jose Arias-Tellez[1,2] · Francisco M. Acosta[1] · Yolanda Garcia-Rivero[3] · Jose Miguel Pascual-Gamarra[1] · Elisa Merchan-Ramirez[1] · Borja Martinez-Tellez[1,4] · Analiza M. Silva[5] · Julio Almansa Lopez[6,7] · Jose M. Llamas-Elvira[3] · Jonatan R. Ruiz[1]

[1] PROFITH "PRO-moting FITness and Health Through Physical Activity" Research Group, Department of Physical and Sports Education, Sport and Health University Research Institute (iMUDS), Faculty of Sports Science, University of Granada, Granada, Spain

[2] Department of Nutrition, Faculty of Medicine, University of Chile, Independence, 1027 Santiago, Chile

[3] Servicio de Medicina Nuclear, Hospital Universitario Virgen de las Nieves, Granada, Spain; Instituto de Investigación Biosanitaria (ibs. GRANADA), Servicio de Medicina Nuclear, Granada, Spain

[4] Department of Medicine, Division of Endocrinology, and Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, the Netherlands

[5] Exercise and Health Laboratory, CIPER, Faculdade Motricidade Humana, Universidade de Lisboa, Estrada da Costa, 1495-688 Cruz Quebrada, Portugal

[6] U.G.C. Física y Protección Radiológica, Hospital Universitario Virgen de las Nieves, Granada, Spain

[7] Instituto de Investigación Biosanitaria (ibs. GRANADA), U.G.C. Física y Protección Radiológica, Granada, Spain