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Differences Emerge in Visceral Adipose Tissue Accumulation After Selection for Innate Cardiovascular Fitness

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Abstract

Cardiorespiratory fitness (CRF) has been reported to be inversely associated with visceral adipose tissue (VAT) accumulation, independent of body weight. However, the confounding effect of physical activity on the association between CRF and VAT remains inadequately addressed. Based on $\text{VO}_{2\text{max}}$, 143 sedentary, overweight women were dichotomized into high-fit (HF) and low-fit (LF) groups. Body composition and VAT were measured using DEXA and CT, respectively, and activity-related energy expenditure (AEE) was calculated using the doubly-labeled water technique. No differences were observed between HF and LF for BMI (HF: 28.2 ± 1.3 ; LF: $28.3 \pm 1.31 \text{ kg/m}^2$), total body weight (HF: 77.5 ± 6.8 ; LF: $77.9 \pm 7.3 \text{ kg}$), total fat mass (HF: 33.5 ± 5.1 ; LF: $33.9 \pm 4.4 \text{ kg}$), or AEE (HF: 439.9 ± 375.4 ; LF: $517.9 \pm 298.7 \text{ kcal/day}$). Significant differences in visceral adiposity (HF: 68.5 ± 30.4 ; LF: $91.2 \pm 31.8 \text{ cm}^2$; $P < 0.001$) and insulin sensitivity (HF: 5.1 ± 1.8 ; LF: $3.1 \pm 2.4 \text{ S}_1 \times 10^{-4} \text{ min}^{-1} / \mu\text{IU/ml}$; $P < 0.01$) were observed between the high- and low-fitness groups, independent of age, race, and AEE. This study affirms previous findings that CRF is an important determinant of the accumulation of VAT, and this relationship is independent of physical activity.

Keywords

Weight Loss; Cardiovascular Fitness; Obesity; Metabolic Syndrome; Exercise

Introduction

Low cardiorespiratory fitness (CRF) is a well established risk factor in the pathogenesis of cardiovascular disease and type 2 diabetes (1–4). Genetic factors account for a significant

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proportion of the between-subject variability (~40–50% heritability) in CRF (5). These variations can produce vastly different phenotypes ranging from highly-gifted Olympic endurance athletes to functionally-limited individuals who are at greater risk of morbidity and mortality from cardiometabolic diseases. Recent investigations have sought to understand the underlying mechanisms of the observed association between CRF and cardiometabolic disease (6). Reported observations appear to indicate considerable impairments in glucose disposal, lipid oxidation, and mitochondrial function (6). Of particular interest is whether innate fitness without an exercise training stimulus is predictive of the development of increased cardiometabolic risk. Recent data indicate that rats artificially selected for innate treadmill running capacity (high vs. low) have substantially different cardiometabolic risk factor profiles (6). Specifically, untrained rats with a genetic predisposition for low endurance running capacity had a higher incidence of visceral adiposity, impaired glucose disposal, hyperlipidemia, and a decrease in mitochondrial proteins associated with CRF, when compared to untrained rats with a genetic predisposition for high endurance running capacity (6).

Arsenault et al (7), recently reported that visceral adipose tissue (VAT) accumulation, a well documented cardiometabolic disease risk factor, differs according to CRF status in humans. This observation was observed in individuals matched for BMI, which lends credence to the proposition that CRF may be an important determinant in the accrual of adipose tissue in a fat storage depot that has consistently been linked to cardiometabolic risk. Furthermore, we recently reported findings consistent with these observations in a sample of 187 overweight African- and European- American women (8). However, the confounding effect of physical activity on this relationship in humans has not been adequately addressed, and it remains to be demonstrated whether this association between CRF and VAT is independent of physical activity-related energy expenditure. Therefore the purpose of the present study was to determine if the association between CRF and VAT is independent of activity-related energy expenditure.

Methods

Subjects

participants were healthy, premenopausal women originally recruited as a part of a weight loss study (8). For study inclusion, women were required to be overweight (BMI 27–30 kg/m²), 20–41 years of age with a history of regular menstrual cycles, normoglycemic, and sedentary (<2 days/week of structured exercise). All women were nonsmokers and were not taking medications known to affect body composition or metabolism. Procedures followed were in accordance with the ethical standards of the institution committee on human experimentation. Each participant provided written informed consent to the protocol, which was approved by the Institutional Review Board and Human Services Regulation for Protection of Human Research Subjects. A detailed description of the study methodologies have been previously described (8).

Cardiorespiratory Fitness Testing

following an overnight fast, VO_{2max} was determined using indirect calorimetry with a modified Bruce graded treadmill protocol (hunter). Standard criteria for heart rate (> 90% of age predicted max), respiratory quotient (> 1.15), and VO₂ plateauing were used to ensure achievement of VO_{2max}. All participants achieved at least two criteria for VO₂ max.

Insulin sensitivity (S_I)

following an overnight fast, a frequently sampled, intravenous glucose tolerance test and mathematical modeling (9,10) were used to assess insulin sensitivity.

Body composition and fat distribution

total fat mass was measured via dual-energy X-ray absorptiometry using a GE Lunar Prodigy densitometer (GE LUNAR Radiation, Madison WI). Visceral adipose tissue (VAT) was assessed by computed tomography with a HiLight/Advantage Scanner (General Electric, Milwaukee, WI).

Measurement of energy expenditure

free-living TEE was measured over 14 days of controlled diet and energy-balance conditions using the doubly-labeled water technique. Samples were analyzed in triplicate for H_2^{18}O and $^2\text{H}_2\text{O}$ by isotope ratio mass spectrometry at the University of Alabama at Birmingham. When all samples for deuterium and oxygen-18 were reanalyzed in seven subjects, values of TEE were in close agreement (coefficient of variation = 4.3%). CO_2 production rates were determined using a fixed assumption for the dilution space ratio (1.0427) using Equation R2 of Speakman *et al* (11), and energy expenditure was calculated using equation 12 of de Weir (12) using a mean value for the dietary food quotient of 0.88 obtained from the foods provided. REE was measured immediately after awakening between 6 and 7AM on three consecutive mornings. After resting for 15 min, REE was measured for 30 min with a computerized, open-circuit, indirect calorimetry system with a ventilated canopy (Delta Trac II; Sensor Medics, Yorba Linda, CA). The last 20 min of measurement was used for analysis. Oxygen uptake (VO_2) and carbon dioxide production (CO_2) were measured continuously and values were averaged at 1-minute intervals. Coefficient of variation for the repeat REE was <4%. The average REE for the three consecutive mornings was considered more reflective of the subjects' normal REE and is thus the value reported. AEE was estimated by subtracting REE from TEE after reducing TEE by 10% to account for the thermic response to meals.

Statistical Analyses

participants were dichotomized into high-fit and low-fit groups based on the results of the $\text{VO}_{2\text{max}}$ test. In order to achieve distinct groups based on CRF, the groups were distributed by calculating the mean $\text{VO}_{2\text{max}}$ value for the entire sample and then distributing participants who were one standard deviation below (LF) or above (HF) the mean into their respective groups. A 7-day physical activity recall was used as an additional means to ascertain the type and intensity of self-reported physical activity (13). Descriptive statistics (mean $\pm$ SD) for all variables of interest at baseline were analyzed using Student's t-tests, and ANOVA was used to compare the dependent variable of interest while controlling for selected independent variables that were identified from Pearson correlation analyses. Statistical analyses were performed using the SAS software package (version 9.1; SAS Institute, Cary, NC), and alpha was set at 0.05 for all tests.

Results

Table 1 presents the results of these analyses by CRF group. Seventy-three African-American and 70 European-American women were included in the analysis (age: 34.3 ± 6.5 y; BMI: 28.3 ± 1.3 kg/m²; body weight 77.7 ± 7.1 kg; total fat mass: 33.8 ± 4.7 kg; VAT: 80.8 ± 33.1 cm²; $\text{VO}_{2\text{max}}$: 28.4 ± 4.6 ml/kg/min; S_1 : $0.40 + 0.23 \times 10^{-4} \text{min}^{-1} \mu\text{IU/ml}$). No differences were observed between CRF groups for BMI, body weight, total fat mass, body fat percentage, TEE, SEE, or AEE. After adjusting for age, race, AEE, and moderate-to-vigorous self-reported physical activity, the low-fit group presented with significantly greater cardiorespiratory fitness (whether expressed in relation to fat-free mass, total mass, or an absolute values) visceral fat accumulation and was less insulin sensitive. Furthermore, the addition of BMI to the model did not change the findings (LF: 91.0 ± 31.8 cm²; HF: 68.7 ± 30.4 cm²; $P < 0.001$).

Discussion

The results of the present study are consistent with the widely accepted theory that cardiorespiratory fitness is an important factor in determining cardiometabolic risk. To our knowledge this is the first report that differences emerge in VAT and insulin sensitivity solely based on selection for CRF in sedentary overweight women, and this association is independent of age, race, AEE, and self-reported exercise. Furthermore there were no significant differences between groups for BMI, total body weight, total fat mass, or body fat percentage, which adds considerable strength to the argument that CRF, independent of overall body weight or fat mass, may be an underlying causal factor in the accumulation of fat in ectopic fat depots, which are known to convey considerable metabolic disease risk.

Although the exact mechanisms by which CRF determines VAT accumulation remain unclear, the CRF-related elevation in insulin sensitivity is likely mediated in part by the reduced accumulation of VAT, a well accepted mediator of whole-body insulin sensitivity (14). In addition, HF participants may have a higher proportion of slow-twitch, oxidative, type I muscle fibers with inherently greater ability for glucose and fatty acid oxidation (FAO) (17–20). Specifically, impairments in FAO have been hypothesized to induce skeletal muscle insulin-resistance due to an accumulation of lipotoxic fatty acid intermediates (e.g., ceramides, DAGs, ect) (17), and it appears plausible that impairments in mitochondrial FAO may be an underlying mechanism by which CRF partly determines both VAT accumulation and insulin sensitivity. Considerable deficiencies for several key mitochondrial proteins (PPAR- γ , PGC-1 α , COXI, UCP2, F₁-ATP synthase) that influence mitochondrial oxidative capacity and the progression of metabolic disease have been reported in rats selected for low innate running capacity (6).

In conclusion, this study affirms previous findings that CRF is an important determinant of the accumulation of VAT, and this relationship is independent of physical activity. Future investigations are warranted to examine the underlying mechanism by which CRF regulates VAT accumulation independent of total energy expenditure.

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Table 1

Results based on selection for high or low cardiorespiratory fitness. Group values are adjusted for age and race, unless otherwise noted (N = 143).

Variable	High-Fit (n = 65)	Low-Fit (n = 78)	P Value
Age (y)	32.3 (6.9)	35.9 (5.7)	0.001
BMI (kg/m ²)	28.2 (1.2)	28.3 (1.3)	0.64
Weight (kg)	77.5 (6.8)	77.9 (7.3)	0.51
Fat Mass (kg)	33.5 (5.0)	34.0 (4.4)	0.35
Body Fat (%)	43.1 (4.1)	43.5 (3.1)	0.36
VO _{2max} (ml/kg/min)	33.3 (2.9)	25.0 (1.9)	< 0.001
VO _{2max} (ml/kg of lean mass/min)	57.9 (3.8)	43.6 (2.2)	< 0.001
VO _{2max} (L/min)	2.5 (0.3)	1.9 (0.2)	< 0.001
TEE (kcal/day)	2029 (422)	2098 (368)	0.45
REE (Kcal/day)	1382 (117)	1359 (131)	0.46
AEE (Kcal/day)	439 (375)	517 (298)	0.27
Moderate/Vigorous Physical Activity (min/day)	6.4 (5.6)	3.8 (5.7)	0.06
Visceral Adipose Tissue (cm ²)	68.5 (30.4)	91.2 (31.8)	< 0.001
Adjusted for Age, Race, AEE, Mod-Vig PA	77.4 (32.2)	86.5 (32.4)	0.01
S _I (×10 ⁻⁴ min ⁻¹ /μIU/ml)	4.4 (2.3)*	3.7 (2.5) [†]	0.03
Adjusted for Age, Race, AEE, Mod-Vig PA	5.1 (1.8)*	3.1 (2.4) [†]	0.009

TEE: total energy expenditure; REE: resting energy expenditure; AEE: activity-related energy expenditure. Data are presented as mean (SD).

* n = 42

[†] = 39.