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Relative fat-free mass deficiency and left ventricular adaptation to obesity: The Strong Heart Study☆,☆☆

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ABSTRACT

Background: Relative fat-free mass (FFM) deficiency (RFFMD) can also occur in obesity, but the impact on left ventricular (LV) mass is unknown.
Methods: We assessed relations among reduced FFM, obesity and LV mass in a population with high prevalence of obesity. Echocardiograms were performed in 2625 participants (1694 women, 1199 non-obese) of the Strong Heart Study cohort, free of prevalent cardiovascular disease and kidney failure. FFM was estimated by bioelectric impedance and analyzed in the non-obese subpopulation in relation with sex, BMI and waist-to-hip ratio (WHR). RFFMD was estimated in the obese subpopulation as the percent of observed/predicted FFM<20th percentile of the non-obese distribution.
Results: RFFMD was more frequent in women than men. LV mass indices (by either height$^{2.7}$ or FFM) were greater in obese with than in those without RFFMD, even after adjusting for sex and diabetes (both $p<0.0001$). The greater LV mass index in obesity with RFFMD was related mostly to increased LV diastolic dimension paralleling increased stroke index and cardiac index, in the presence of normal ejection fraction. RFFMD remained associated with greater LV mass index ($p<0.0001$) even independently of older age, greater BMI, higher systolic and lower diastolic blood pressure (all $p<0.007$), with negligible effect of sex, waist/hip ratio and diabetes.
Conclusion: In obese SHS participants, RFFMD is associated with higher levels of LV mass, an effect related to adiposity more than central fat distribution and typical of female gender. Biological mechanisms of this association have to be better explored.

1. Introduction

Bone and muscle growth are influenced by gravity and physical activity stimulating mechanoreceptors regulating production of growth factors [1]. The word "sarcopenia" describes in general the process of age-related muscle loss and the associated frailty condition [2,3]. Definition of sarcopenia requires studying body composition and is still controversial [3].

A condition of relative loss of fat-free mass, however, has been recently recognized in the presence of obesity and called "sarcopenic obesity" [4]. The phenotype of sarcopenic obesity strongly depends on the adopted definition. Since obese individuals have larger amount of both fat and lean mass, they usually have a "*normal*" absolute quantity of muscle mass, and therefore they do not appear to be sarcopenic, though their muscle mass might be relatively inadequate for their size [5]. Thus, higher body mass index (BMI) can mask sarcopenia [3]. In general, excess energy intake, physical inactivity, low-grade inflammation, insulin resistance and changes in hormonal milieu are thought to be the main characteristics of sarcopenic obesity [6]. Because sarcopenia is generally considered a characteristic that might increase risk of morbidity in obesity [7], it is of interest to focus on phenotypic characteristics that might be associated with cardiovascular (CV) risk. Because left ventricular (LV) mass is substantially influenced by fat free mass [8], sarcopenia in the obese individual might be thought to be associated with reduced amount of LV mass, which might be protective, as LV hypertrophy is the most potent marker of cardiovascular risk [9]. Specifically, at present, there is little characterization of the CV phenotype of sarcopenia in obese populations. Accordingly, this study has been conceived to assess

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whether reduced fat-free mass is associated with the magnitude of LV mass, in a population of obese men and women.

2. Methods

2.1. Population

The Strong Heart Study (SHS) is a population-based cohort study of CV risk factors and disease in 4549 American Indians from 3 communities in Arizona, 7 in Southwestern Oklahoma and 3 in South and North Dakota, which has been extensively described [10–12]. For the purpose of the present analysis we analyzed participants to the 2nd exam, which included an echocardiogram (N = 3638, 89% of all living); we excluded participants who had history or signs of prevalent heart failure or coronary heart disease at the time of the 2nd SHS exam (ascertained MI or diagnosis of coronary heart disease by ECG evidence of the previous myocardial infarction – by Minnesota code –, coronary angiography, combination of typical symptoms with positive treadmill or imaging stress tests, or need for revascularization procedures). We also excluded participants with glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2, by the simplified MDRD formula. Prevalent CV disease was adjudicated by the Strong Heart Study Mortality and Morbidity Committees, as previously reported [13]. Thus 2625 participants (1694 women, 1426 obese) were available for the analysis.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Laboratory tests and definitions

Fasting plasma glucose was measured by standard methods. Diabetes (fasting glucose ≥ 126 mg/dL or ongoing antidiabetic treatment) was diagnosed by the 1997 American Diabetes Association recommendations. Obesity was classified by the 1998 NIH guidelines (BMI ≥ 30 kg/m^2). Waist-to-hip ratio (WHR) was used as a measure of central fat distribution. Hypertension was defined by the JNC-7 criteria (blood pressure [BP] ≥ 140/90 mm Hg or use of antihypertensive treatment). Insulin resistance was estimated using HOMA-resistance index [14]. C-reactive protein and fibrinogen were measured by standard methods. Fat-free mass and adipose body mass were estimated by using an RJL bioelectric impedance meter (model B14101; RJL Equipment Co.). Equations to estimate fat-free mass (FFM) in kilogram, based on total body water, using bioelectric resistance, had been previously validated in the American Indian population [15]:

$$FFM_{men} = \left[e^{\{1.18\times\log[\text{height (cm)}]\times 20.60\times\log[\text{resistance}]\times 10.32\times\log[\text{weight(kg)}]\}}\right]/0.732$$

$$FFM_{women} = \left[e^{\{1.20\times\log[\text{height (cm)}]\times 20.55\times\log[\text{resistance(V)}]\times 10.22\times\log[\text{weight(kg)}]\}}\right]/0.732.$$

The variability of FFM in relation to body mass index, waist-to-hip ratio and gender was preliminarily estimated in non-obese SHS participants. The multivariable equation was used thereafter to estimate the predicted theoretical value of FFM in the 1426 obese participants, based on their BMI, waist-to-hip ratio and sex. Thus, observed FFM was divided by the predicted value ($FFM_{o/p}$), to assess the relative deficit of FFM in obese participants.

2.3. Echocardiography

During the 2nd SHS exam, echocardiograms were performed using phased-array commercial echocardiographs with M-mode, 2-dimensional and Doppler capabilities, as previously reported [12]. LV dimensions and septal and posterior LV wall thickness were measured by the American Society of Echocardiography recommendations [16,17]. LV mass was obtained by an anatomically validated formula and normalized for body surface area or body height in $m^{2.7}$ or FFM [18]. Clear-cut LV hypertrophy was identified as LV mass index > 47.24 g/$m^{2.7}$, the population specific cut-point [19] for both men and women, shown to maximize the population attributable risk in the SHS cohort. LV volumes were estimated from linear dimensions by the z-derived method [20] and used to derive stroke volume. Stroke volume and cardiac output were also normalized (stroke index and cardiac index) by height in meters raised to the specific allometric power [21]. Standard methods were used to calculate relative wall thickness, as a measure of LV geometry, and ejection fraction, as a measure of LV systolic function.

2.4. Statistical analysis

Data were analyzed using the SPSS 17.0 (SPSS, Chicago, IL). Multiple linear regression analysis was used to analyze the variance of FFM and to extract the relative coefficients of regression of BMI, WHR and sex in the non-obese population. Indicator variables were included in all multivariate analyses for the three field centers, Arizona, South/North Dakota, and Oklahoma. Multicollinearity was assessed by computing variance inflation factor with a conservative pre-specified limit of 3 to accept the stability of the model. The distribution of the ratio of observed-to-predicted FFM was analyzed in the non-obese population and the 20th percentile was arbitrarily assumed as the partition for definition of RFFMD. The multivariate equation was used to generate a predicted value of FFM in the obese population and the 20th normal percentile of the observed/predicted ratio was used to identify obese subjects with RFFMD. They were compared to obese individuals with normal fat-free mass (i.e. > 20th percentile).

Descriptive statistics was obtained, using the chi-square distribution for categories (with Monte Carlo method for computation of exact 2-tailed p value, when appropriate) and analysis of variance. Analysis of co-variance was used to adjust for relevant confounders. Least square linear regression was used to assess univariate relation between LV mass index and $FFM_{o/p}$. Multiple linear regression analysis was used to analyze whether RFFMD maintained an independent relation with LV mass index, after adjusting for all demographic, anthropometric and hemodynamic factors that potentially influence the magnitude of LV mass index.

The null hypothesis was rejected at 2-tailed $\alpha < 0.05$.

3. Results

In the group of 1199 non-obese participants, 688 were women (57%), 437 hypertensive (37%) and 435 diabetic (36%). The average BMI was 26.09 ± 2.75 kg/m^2, WHR was 0.94 ± 0.06 and FFM was 48.89 ± 9.63 kg. Table 1 displays the equation describing the variability of FFM and the multicollinearity diagnostic. The equation could explain 79% of the variance of FFM with a standard error of the estimate that was < 10% of the mean. Variance inflation factor was < 1.3 for all variables, demonstrating an optimal stability of the model.

As expected, the observed FFM was on average 100% of predicted (standard deviation was 8.8%). $FFM_{o/p}$ was normally distributed and the 20th percentile was 93.47%, a value that was used as partition for arbitrary definition of relative fat-free mass deficiency (RFFMD) in the obese sub-population.

3.1. Characteristics of obese participants with normal and reduced FFM

Obese participants with RFFMD exhibited the same prevalences of diabetes (54%) and hypertension (48%) as participants with normal FFM (55% and 47%). Table 2 shows that reduced FFM was a characteristic of obese women (59% vs 16% among men, p < 0.0001). Participants with RFFMD had slightly lower mean diastolic BP, greater BMI and waist girth, but lower WHR (reflecting the greater proportion of women). They also exhibited higher fibrinogen and CRP (all p < 0.0001).

3.2. LV geometry and function

LV mass was smaller in obese participants with, than in those without RFFMD (due to the different proportion of women), a difference that was offset when LV mass was normalized for body surface area and reverted when LV mass was normalized by either $height^{2.7}$ or FFM (Table 3, both p < 0.0001). These latter differences were also confirmed after adjusting for sex and the presence of diabetes. The greater LV mass index in obesity associated with RFFMD was related mostly to increased LV diastolic dimension and also to some degree of wall thickening (Table 3). Relative wall thickness was in fact statistically higher in participants with RFFMD, but this difference was blunted when adjusting for covariates. Stroke index and cardiac index were consistently higher in the individuals with RFFMD, paralleling the difference in LV chamber dimension, with similar ejection fraction.

In the whole obese population, LV mass indexed for $height^{2.7}$ was negatively related to FFM as a percent of predicted (r = −0.23,

Table 1
Variables associated with FFM in the non-obese SHS population.

	B	p ≤	Variance inflation
(Constant)	50.92		
Arizona center	−1.70	0.0001	1.25
Oklahoma center	0.87	0.004	1.29
BMI (kg/m^2)	1.23	0.0001	1.16
Waist/hip ratio	−2.72	0.24	1.28
Age (years)	−0.11	0.0001	1.03
Female gender	−15.84	0.0001	1.11

Multiple R = 0.89, SEE = 4.40 kg.

Table 2
General characteristics of obese SHS participants without or with relative FFM deficiency

	Normal FFM (n = 774)	RFFMD (n = 652)
Age (years)	58.7 ± 7.6	58.6 ± 7.3
Sex (% women)‡	54	90
Systolic BP (mm Hg)	130.4 ± 18.5	130.3 ± 17.9
Diastolic BP (mm Hg)*	76.7 ± 9.9	75.5 ± 9.1
History of hypertension (n[%])	372 (48%)	313 (48%)
Heart rate (bpm)	72.0 ± 10.6	72.8 ± 10.8
BMI (kg(m^2)‡	34.1 ± 3.6	36.9 ± 5.4
Waist girth (cm)‡	113.3 ± 9.5	117.9 ± 12.8
WHR‡	0.98 ± 0.06	0.96 ± 0.05
Fat-free mass (kg)‡	60.5 ± 12.0	48.8 ± 6.8
GFR_{MDRD} (mL/min/1.73 m^2)	84.1 ± 27.1	85.2 ± 31.7
Fibrinogen (mg/dL)‡	351.4 ± 78.4	381.2 ± 76.9
CRP (mg/dL)‡	1.36 ± 0.87	1.76 ± 0.93

Abbreviations: RFFMD = relative fat-free mass deficiency; BP = blood pressure; BMI = body mass index; WHR = waist/hip ratio; GFR = Glomerular filtration.
* p<0.02.
‡ p<0.0001.

p<0.0001), a relation that remained independent of other significant variables, including older age, marginally greater association with female gender, greater BMI, history of hypertension, higher systolic BP, and lower diastolic BP (Table 4), without significant multicollinearity.

This multiple regression model was also run separately in men and women (Table 5). The two models were substantially similar with small differences largely attributable to the different statistical power. In both genders, magnitude of LV mass index was independently associated with higher systolic and lower diastolic BP, higher BMI and higher FFM as a percent of predicted (all 0.06<p<0.0001), with similar regression coefficients. Older age and history of hypertension were more related to LV mass index in women than in men.

4. Discussion

This is the first observational study evaluating LV adaptation to obesity in relation with relative FFM deficiency, in a large population-based cohort with high prevalence of obesity. Our attention has been especially focused on LV mass, which is considered the most potent (and correctible) marker of cardiovascular risk [9,22,23], recently shown to be a bioassay also for other harmful cardiovascular CV characteristics, including LV geometry and function [24].

Much debate is still ongoing concerning definition of sarcopenic obesity [3,5,6]. Similar to what is reported for elderly people, obesity is often associated with reduced physical activity and energy expenditure, which favor further accumulation of abdominal fat [25], worsening insulin resistance and enhancing the inflammatory response associated with visceral fat [26]. Inflammatory markers have been reported to be negatively associated with the amount of muscle mass [27,28] and both interleukin-6 and C-reactive protein are predictors of loss of lean mass in middle-age men and women [29]. Other inflammatory cytokines produced in the visceral fat participate to the loss of lean mass, such as tumor necrosis factor-α and leptin [5]. Our findings are very consistent with this scenario, as C-reactive protein was substantially increased in SHS participants with RFFMD.

Thus, in obesity the loss of fat-free mass is constantly associated with further accumulation of fat. The method that we used to quantify relative FFM deficiency in the context of an unselected population with high prevalence of obesity allowed to account at least in part for the known increase in FFM occurring with obesity and making unrealistic the evaluation of sarcopenia based on the raw assessment of FFM. Our method is consistent with the predominant trend to consider FFM in relation to adipose mass [6] and has the advantage of being targeted on the specific studied population. It is suggested that, in the context of obesity, sarcopenia be considered as a condition of abnormal body composition, altering a normal balance between fat and fat-free mass [3,5]. Accordingly, sarcopenia in obesity might be better defined as a "relative FFM deficiency". A novelty of our approach is the consideration of the amount of fat-free mass as related not only to the measure of obesity (BMI) but also to central fat distribution (WHR), sex and age, all factors that have been related to sarcopenia. The predictive equation developed in the non-obese population of the SHS was applied in the obese SHS sub-population and gave surprising results.

In the SHS population, a relative FFM deficiency in the context of obesity is revealed to be mostly a feminine characteristic. Only 16% of male participants were classified as sarcopenic, compared to 58% of women. There is no mechanistic explanation of this difference, which cannot be provided by the present cross-sectional analysis, but this finding is in line with both the evidence of less fat-free mass in women in both

Table 3
Raw and adjusted differences in LV geometry, function and performance between participants without or with relative FFM deficiency.

	Normal FFM (n = 774)	RFFMD (n = 652)	p≤	*Adjusted p≤
LV dimension index (cm/m)	3.04 ± 0.26	3.13 ± 0.27	0.0001	0.0001
LV mass (g)	170.1 ± 39.0	155.3 ± 31.3	0.0001	0.004
LV mass index (g/$m^{2.7}$)	42.2 ± 9.7	45.7 ± 9.8	0.0001	0.0001
LV mass/FFM (g/kg)	2.86 ± 0.67	3.22 ± 0.69	0.0001	0.0001
LV mass/BSA (g/m^2)	83.06 ± 17.80	81.41 ± 16.21	0.07	0.76
Relative wall thickness	0.348 ± 0.043	0.354 ± 0.043	0.009	0.455
Ejection fraction (%)	64.5 ± 5.9	65.4 ± 5.5	0.003	0.496
Stroke index (mL/$m^{2.04}$)	26.4 ± 4.3	28.3 ± 4.4	0.0001	0.0001
Cardiac index (L/min/$m^{1.83}$)	1.97 ± 0.39	2.11 ± 0.41	0.0001	0.0001

Abbreviations: FFM = fat-free mass.
* Adjusted for field center, sex and presence of diabetes.

Table 4
Independent association of relative FFM deficiency with LV mass index in obese SHS participants.

	B	Beta	p<	VIF
Age (years)	0.21	0.16	0.0001	1.33
Female gender	1.23	0.06	0.07	1.63
Systolic BP (mm Hg)	0.12	0.22	0.0001	2.04
Diastolic BP (mm Hg)	−0.10	−0.09	0.002	1.72
History of hypertension	1.18	0.06	0.05	1.56
BMI (kg/m^2)	0.48	0.23	0.0001	1.15
Waist/hip ratio	4.87	0.03	0.33	1.39
Diabetes	−0.11	−0.01	0.82	1.09
GFR_{MDRD} (mL/min/1.73 m^2)	0.00	0.00	0.96	1.08
Observed/predicted FFM	1.85	0.09	0.0006	1.29

Table 5
Independent association of relative deficiency of FFM with LV mass index in obese men and women of the SHS cohort.

	Men (n = 67)				Women (n = 585)			
	B	Beta	p<	VIF	B	Beta	p<	VIF
Age (years)	0.14	0.11	0.03	1.22	0.24	0.18	0.0001	1.37
Systolic BP (mm Hg)	0.13	0.27	0.0001	1.87	0.11	0.20	0.0001	2.16
Diastolic BP (mm Hg)	−0.10	−0.12	0.05	1.78	−0.09	−0.07	0.04	1.58
History of hypertension	0.16	0.01	0.87	1.46	1.58	0.08	0.04	1.62
BMI (kg/m^2)	0.54	0.24	0.0001	1.14	0.47	0.23	0.0001	1.17
Waist/hip ratio	2.56	0.02	0.76	1.25	5.93	0.03	0.35	1.09
Diabetes	−0.48	−0.03	0.57	1.13	0.02	0.00	0.97	1.09
GFR_{MDRD} (mL/min/1.73 m^2)	0.01	0.05	0.32	1.10	−0.01	−0.02	0.55	1.06
Observed/predicted FFM	2.08	0.09	0.06	1.06	1.82	0.09	0.004	1.14

physiological and trained conditions [30–32] and with some resistance of females to increase their lean body mass under growth hormone replacement therapy, compared with males [33].

Obese participants with relative FFM deficiency in the present study exhibited anthropometric measures consistent with the large proportion of women, with lower WHR, but greater waist girth, reflecting both gynoid fat accumulation and central fat distribution. As a consequence of the relative FFM deficiency identified in 46% of the SHS obese participants, decreased LV mass and LV mass indices could be expected. Unindexed LV mass was in fact lower in these individuals, but this was entirely due to the greater proportion of women. This difference was expectedly offset by normalization with body surface area, which is known to severely underestimate the impact of obesity on LV geometry [19,34]. In contrast, when normalized for either height$^{2.7}$ or fat free-mass, LV mass index was substantially greater in the subgroup with RFFMD than in the group of obese subjects with normal body composition. This finding provides a further potential explanation for our previous analysis, demonstrating that in the SHS cohort, obese women exhibit values of LV mass index greater than obese men [31], a difference that the model of regression shown in Table 4 indicates might be substantially related to the greater relative FFM deficiency, which obscures the gender effect previously detected. Myocardial composition is different in men and women and this difference increases with aging, because myocardial fat metaplasia occurs in women [35]. This finding is consistent also with the evidence that, though the independent association of LV mass index with FFM as a percent of predicted is of similar magnitude in men and women (with statistical significance difference due to the different cell size), older age is substantially more important in women than in men, confirming also the data from the Framingham Heart Study [36].

In the analysis previously performed [31], central adiposity emerged as a leading correlate of greater LV mass, whereas, in the present analysis, including the relative deficit of fat-free mass, central fat distribution (evaluated by WHR) did not show independent association with LV mass index, suggesting that the deficiency of fat-free mass might be at the basis of the previously detected relation between LV mass index and central fat distribution [37].

Because LV mass ratiometrically normalized for fat-free mass (as well as for the allometric measure of body height) is increased in the presence of relative FFM deficiency, it is unlikely, though not impossible, that this increase be due to a disproportionate growth of cardiomyocytes. Other myocardial tissue components are likely to be involved, namely fat. Fat might contribute together with the other cell components of myocardium to determine the magnitude of LV mass when obesity is associated with significant loss of FFM. This possibility is supported by the previous evidence.

Fat infiltration in the heart of obese subjects, especially those with visceral adiposity, has been demonstrated in obese individuals, characterized by a disarray of myocardial composition (Virchow's "fatty atrophy" of the heart), with fat accumulation and relative reduction of active muscle mass [38–40].

Our results also confirm that adipose mass is directly related to LV hypertrophy and, at the cardiac level, masks the loss of FFM that occurs in a high proportion of obese individuals. Because the difference in FFM between men and women is confirmed also in the SHS population [31], the paradox effect of relative FFM deficiency on LV geometry in the context of obesity might be especially important in women to explain their increased magnitude of LV mass, a finding that is supported by the previous evidence [41,42], but also requires more investigation.

4.1. Study limitations

Two potential limitations should be considered. While the condition of "sarcopenia" is well described in elderly population, as it implies loss of muscle mass and frailty [3], it is not yet certain in the context of obesity, and many different approach have been attempted [2–4,43]. We have generated a method that accounts for major correlates in normal conditions and implicitly adjusts for them in non-physiological conditions. While we may not have the best method, this approach accounts in part also for the second potential limitation of the study, its conduct in a single ethnic population. Even considering that our findings may not necessarily be extrapolated to other ethnic groups, the method to assess relative FFM deficiency does not refer to partition values extracted from other reference populations, whereas, rather, the deficiency is measured based on individual variables. This approach is very similar to what has been done previously to evaluate the compensatory or not compensatory nature of LV mass in Caucasian populations [44].

4.2. Conclusion

Obesity with relative FFM deficiency is associated with higher levels of LV mass, an effect related to general adiposity more than central fat distribution and typical of female gender. Mechanisms of this association have to be explored.

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