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Cardiometabolic risk in overweight subjects with or without relative fat-free mass deficiency: the Strong Heart Study

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Abstract

Background—Sarcopenia is a condition mainly due to loss of fat-free mass (FFM) in elderly individuals. RFFMD, however, is also frequent in obese subjects due to abnormal body composition. Objective of this study was to evaluate the impact of relative fat-free mass deficiency (RFFMD) on cardiometabolic (CM) risk in obese normoglycemic individuals.

Methods—Overweight/obese American Indians from the Strong Heart Study population, without diabetes and with FBG ≤ 110 mg/dL and with GFR>60 mg/mL/1.73 m^2 were selected for this analysis (n=742). RFFMD was defined on the basis of a multivariable equation previously reported. Fasting glucose and 2hr -OGTT were measured together with urine albumin/creatinine excretion, laboratory and anthropometric parameters.

Results—In addition to lower FFM and greater adipose mass, participants with RFFMD had higher body mass index, waist circumference, C-reactive protein, fibrinogen, insulin resistance and urinary albumin/creatinine than participants with normal FFM (all $p<0.001$); they also had a greater prevalence of hypertension, impaired glucose tolerance (IGT) or OGTT-diabetes than participants with normal FFM (all $p<0.003$) and a near 2-fold greater probability of significant proteinuria ($p<0.01$). RFFMD was more frequent in women than in men: significant sex-RFFMD interactions were found for BMI and waist circumference (both $p<0.0001$).

Conclusions—RFFMD in overweight/obese normoglycemic individuals is associated with greater probability of hypertension, abnormalities of glucose tolerance and proteinuria. Assessment of RFFRMD might, therefore, help stratifying cardiometabolic risk among normoglycemic individuals with overweight/obesity.

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CONFLICT OF INTEREST:
No authors have conflict of interest to disclose.

Keywords

fat-free mass deficiency; cardiometabolic risk; overweight/obesity; normoglycemia; proteinuria

INTRODUCTION

Sarcopenia reflects a progressive decrease of anabolism and an increase of catabolism, along with reduced capability of muscle regeneration. Sarcopenia is also characterized by a disproportion between adipose body mass and fat-free mass (FFM) (1). The decline of FFM increases with age but is already detectable as early as in the third decade (2). Studies with computed tomography (3–5), MRI (6) or ultrasonography (7) suggest that loss of muscle mass is accompanied by infiltration with fat and connective tissue into the skeletal mass.

The consequent alteration of body composition is associated with macrophage-mediated release of pro-inflammatory cytokines (such as TNF-α, IL-6, IL-1) and adipokines (leptin, adiponectin and resistin) from adipocytes (8). Increasing evidence exists that chronic inflammation might be one of the factors promoting or worsening insulin resistance (9) and yielding metabolic syndrome (10). The loss of muscle mass aggravates insulin resistance, causing a vicious cycle, which results in further reduction of mobility and further loss of muscle mass. In a recent national survey performed in more than 13,500 US inhabitants within a wide range of BMI and a low-moderate prevalence of overweight/obesity, FFM deficiency relative to body height or body weight was associated with more severe insulin-resistance (11). To date limited information is available on the relationship between FFM deficiency and cardiometabolic (CM) risk.

The amount of fat mass and FFM can be estimated or directly measured by the assessment of body composition, using either bioelectric impedance analysis (BIA) or dual-energy X-ray absorptiometry (12). Debate exists about the best way to determine the relative deficiency of fat-free mass in the context of obesity, a condition in which fat-free mass is increased in absolute terms (13). We have recently developed a new method to estimate the amount of sex-specific FFM expected for a given BMI and fat distribution, based on the comparison between the amount of BIA-measured FFM and the value empirically predicted by a number of correlates in a reference normal population (14), to determine the “relative fat-free mass deficiency” (RFFMD) by offsetting the absolute increase in FFM often found in obesity.

The goal of the present analysis was to evaluate the impact of RFFMD on cardiometabolic risk and on early signs of end-organ damage of arteriosclerosis in a cohort of overweight/obese men and women with fasting glucose ≤ 110 mg/dL from the Strong Heart Study population.

METHODS

Study Population

The Strong Heart Study (SHS) is a population-based survey designed to estimate CV risk factors and disease in 4,549 American Indians, aged 45–74 yrs, from 13 communities in Arizona, Southwestern Oklahoma and South and North Dakota, which has been extensively described (15–17). For the purpose of the present analysis we analyzed participants of the 2nd exam, meeting the following inclusion criteria:

a. Presence of overweight or obesity, according to the NIH Clinical Guidelines (18)

b. ATP III-defined normal fasting glucose (< 110 mg/dL) and absence of antidiabetic therapy;

c. no prevalent CV disease (stroke, coronary heart disease, congestive heart failure), adjudicated by the SHS Mortality and Morbidity Committees (19);

d. no prevalent moderate-to-severe chronic renal disease, adjudicated by an estimated glomerular filtration rate (eGFR) ≥ 60 ml/min by the simplified MDRD formula (20);

e. fasting triglycerides <750 mg/dl;

Laboratory tests and definitions

Clinical examination and collection of blood samples after a 12-hour fast were performed in the morning at local Indian Health Service facilities by the study staff. All participants without known diabetes (fasting plasma glucose ≥126 mg/dL or ongoing antidiabetic treatment or history of diabetes indicated via questionnaire) underwent a standardized oral glucose tolerance test (OGTT). Homeostatic model assessment index was used to estimate insulin resistance (HOMA-IR) (21).

Waist circumference was used as a measure of central fat distribution: an anthropometric tape was applied at the level of the umbilicus (navel) with the patient supine and the participant was instructed to breathe quietly. The measurement was made and recorded to the nearest centimeter using the rounding method.

Hypertension was defined by JNC-7 criteria (blood pressure [BP] ≥140 and/or 90 mmHg or use of antihypertensive treatment). A random urine sample was obtained for measurement of creatinine and albumin. Urinary albumin/creatinine excretion ratio (UACR) was evaluated and proteinuria was diagnosed as UACR>30 μg/mg. C-reactive protein and fibrinogen were measured by standard methods. FFM and adipose body mass were estimated by using an RJL bioelectric impedance meter (model B14101; RJL Equipment Co.). Equations to estimate FFM in kg, based on total body water, using bioelectric resistance, had been previously validated in the American Indian population (22)

$$\mathrm{FFM_{men}\ (L)} = [e^{\{1.18\times\log[\mathrm{height\ (cm)}]\times 20.60\times\log[\mathrm{resistance}]\times 10.32\times\log[\mathrm{weight(kg)}]\}}]/0.732$$
$$\mathrm{FFM_{women}\ (L)} = [e^{\{1.20\times\log[\mathrm{height\ (cm)}]\times 20.55\times\log[\mathrm{resistance(V)}]\times 10.22\times\log[\mathrm{weight(kg)}]\}}]/0.732$$

The variability of FFM in relation to body mass index, waist-to-hip ratio and gender had been previously estimated in a reference normal-weight population (13). Estimated FFM (FFM_e) was therefore:

$$\mathrm{FFM_e} = 45.3 + [1.27\times \mathrm{BMI\ (kg/m^2)}] - [4.48\times \mathrm{WHR}] - 16.01\ [\mathrm{if\ woman}] - (1.81\ [\mathrm{if\ from}\times\mathrm{Arizona}] + 0.72\ [\mathrm{if\ from\ Oklahoma}])$$

This multivariable equation was used, thereafter, to estimate the predicted theoretical value of FFM in the SHS participants. The BIA-measured FFM was divided by FFM_e ($FFM_{o/p}$), to assess the relative deficency of FFM in obese participants as a percent of the predicted value.

Statistical analysis

Data were analyzed using SPSS 17.0 (SPSS, Chicago, IL). As previously reported (14), the 20th sex-specific normal percentile of $FFM_{o/p}$ was used to identify overweight or obese

subjects with RFFMD. Data are expressed as mean±SD, except for C-reactive Protein and urinary albumin/creatinine excretion, which were logarithmically transformed for parametric statistics and were expressed as median and interquartile range.

Indicator variables were included in all multivariate analyses for the three field centers. Descriptive statistics was obtained using analysis of variance and chi-square distribution for categories (with Monte Carlo method for computation of exact 2-tailed p value, when appropriate). Two-way analysis of co-variance was used to examine the combined effect of gender and the condition of RFFMD, adjusting for field center, using a full factorial model, including the interaction term and type III sum of squares. Binary logistic regression analysis was performed to investigate the independent influence of RFFMD on proteinuria, an early marker of end organ damage. Multicollinearity of the model was tested, by calculating the linear variance inflation factor and found to be sufficient to warranty good stability. The null hypothesis was rejected at 2-tailed $\alpha < 0.05$.

RESULTS

Study population included 742 participants (439 women or 59%); 494 of them had normal amount of FFM (252 men or 83% as compared to 242 women, or 55%). RFFMD was found in 51 men (17%) and in 197 women (45%). The odds of RFFMD was, therefore, 4-fold greater in women than in men (95% CI=2.8–5.7, p<0.0001).

Table 1 shows the characteristics of the two groups with or without RFFMD. In addition to lower fat-free mass and higher adipose mass, participants with RFMDD had higher body mass index (BMI), waist circumference (WC), C-reactive protein, fibrinogen, urinary albumin/creatinine and HOMA-IR, than participants with normal FFM (all p<0.001), but identical fasting glucose and HbA1c. Two-hour OGTT glucose was higher in participants with RFFMD than in those with normal FFM. Total cholesterol and triglycerides were similar in the two groups whilst HDL-cholesterol was higher in RFFMD due to the higher prevalence of females.

Categorical analysis showed that participants of both genders with RFFMD had a higher prevalence of cardiometabolic risk factors. The prevalence of hypertension was 38.3% and 29.8% in RFFMD+ and RFFMD−, respectively (OR= 1.47; 95% CI: 1.1–2.02; p< 0.02); in the hypertensive subgroup only 59.2% (54.7 vs.62.6% in RFFMD+ and RFFMD− group, respectively; p= n.s.) of participants was on regular antihypertensive treatment. Abnormalities of glucose tolerance were detected in 101 participants with RFFMD (41%) and in 147 participants with normal FFM (30%). In particular, IGT was detected in 124 participants with normal FFM (25%) and in 77 with RFFMD (31%), whereas OGTT-diabetes was detected in 23 (5%) and 24 participants (10%), respectively (p<0.003). Thus, the probability of diabetes or IGT was more than 50% greater in RFFMD participants than in those with normal FFM (OR=1.62, 95% CI=1.18–1.23, p<0.003). Proteinuria was detected in 42 participants (9%) without and in 38 with RFFMD (15%; OR= 1.94; 95% CI= 1.22–3.11; p<0.01) (Fig. 1).

Based on exploratory statistics showing association between RFFMD and proteinuria, binary logistic regression analysis was run to determine whether the association was confirmed independent of age, sex, presence of diabetes diagnosed at the 2-h OGTT, hypertension, antihypertensive therapy and inflammation markers. Proteinuria was independently associated with impaired glucose tolerance (OR= 1.96; CI= 1.19–3.23, p< 0.01), and higher systolic BP (OR= 1.20; CI= 1.16–4.16, p<0.02), but not with RFFMD (p=0.20), fibrinogen and CRP and antihypertensive treatment (Table 2).

The same analysis was also run in the sub-population with IFG<100 mg/dL and these results were fully confirmed (not shown)

Gender differences

Since RFFMD was more frequent in women, we performed two-way analysis of variance to evaluate sex-RFFMD interaction. Table 3 shows that a significant difference existed in body composition between genders: women with RFFMD exhibited larger waist circumference than men with or without RFFMD and women with normal FFM. Table 2 also shows that, despite fasting glucose was not different in relation to RFFMD, 2-h OGTT was higher in RFFDM than in participants with normal FFM and that markers of inflammation (fibrinogen and CRP) were increased in the presence of RFFDM, an alteration that tended to be more evident in women than in men (fibrinogen: $p< 0.01$; CRP: $p= 0.08$). RFFMD was also associated with increased urinary albumin/creatinine excretion.

DISCUSSION

In overweight/obese participants with normal fasting glucose and relatively normal kidney function from the SHS population, we could demonstrate for the first time that 1) participants with RFFMD, are more likely to exhibit abnormalities of glucose tolerance (or even type 2 DM after OGTT) than those with normal FFM; 2) RFFMD is associated with hypertension and early renal damage in the absence of moderate-to-severe kidney failure; 3) RFFMD is significantly more frequent in women than in men and shows different characteristics in the two genders: increased central adipose mass in women and a reduction in FFM in men.

A previous investigation in a large unselected population suggested that sarcopenia exacerbates insulin resistance and further deteriorates blood glucose levels in obese subjects (23), but no attempt was made to verify whether these effects are also present in normoglycemic individuals. In addition, while sarcopenia in elderly people is characterized by weight loss, substantial loss of FFM, and frailty (24), overweight/obese individuals often exhibit absolute increase in FFM (14); thus, in this case it is critical to evaluate the balance between FFM and adipose mass (12).

The equivalent of sarcopenia in obesity is a condition of pathological modification of body composition, rather than an absolute loss of lean body mass. On this basis, we have labeled this type of sarcopenia as “relative fat-free mass deficiency”, based on an approach that takes into account body mass index and fat distribution (14). On this background, in our study we excluded individuals with normal body weight and/or impaired fasting glucose.

In this population with imbalance between lean and adipose body mass, we observed increased prevalence of hypertension, abnormalities of glucose metabolism as well as higher levels of inflammatory markers. Thus, the evidence of normal fasting glucose cannot exclude an impairment of glucose metabolism when RFFMD is present. Our finding has important clinical implications since elevation of 2-hr plasma glucose is associated with increased risk of left ventricular mass, as shown in non diabetic participants of the SHS cohort with both IFG and/or IGT (25).

RFFMD-related differences were not only confined to biochemical parameters but also involved clinical aspects of early end-organ damage. Overweight/obese participants with RFFMD had, in fact, a significantly higher prevalence of proteinuria. This association was fully attributable to systolic BP and 2-hr post-load plasma glucose.

Detection of proteinuria is consistent with our previous observations that, RFFMD is unexpectedly associated with increased left ventricular mass, independently of other risk factors, with a 40% higher probability of clear-cut left ventricular hypertrophy in an unselected SHS population (14). Both left ventricular hypertrophy and proteinuria are potent markers of preclinical cardiovascular disease and are prognostic factors of cardiovascular events (26). Thus, in obese individuals with RFFMD, particular attention should be paid to detect early signs of target organ damage.

Another interesting finding is that RFFMD was more frequent and severe among women than in men and possibly implies a more unfavorable cardiovascular risk profile in the female gender. A possible explanation is related to the different body composition between genders since females with RFFMD had a definitely greater central adipose mass with similar muscle mass than RFFMD− females, whereas males with RFFMD showed a remarkable loss of the FFM compared to RFFMD− males. This is in line with the finding of less FFM in females, both in physiological and trained conditions (27–28) and with some resistance of females to increase their lean body mass under GH replacement therapy, compared with males (29). Being RFFMD in overweight/obesity a condition of altered body composition, it is reasonable that, due to the different hormonal milieu, this relative sarcopenia can occur more frequently in women, who in fact exhibit greater BMI and waist girth, reflecting a severe degree of central obesity. In contrast, RFFMD in men is associated with lower BMI and waist circumference, indicating a real absolute reduction of FFM.

Limitations and clinical applicability of the study

The study was performed in a highly selected population with a high prevalence of metabolic abnormalities. The question of whether use of RFFMD will ultimately be of utility in clinical practice to refine assessment of CV risk in this population and in others of different ethnicity remains uncertain. However, our previous study and others on this topic seem to support this possibility. Moreover there is a possible clinical implication of the present findings since quantification of RFFMD might prompt an early starting of pharmacological treatment.

In conclusion, the present study demonstrates that in overweight/obese individuals with fasting glucose below 110 mg/dL, RFFMD is associated with unfavorable cardiometabolic risk profile, particularly in women. Estimation of body composition and assessment of RFFMD might, therefore, help stratifying cardiometabolic risk among individuals with overweight/obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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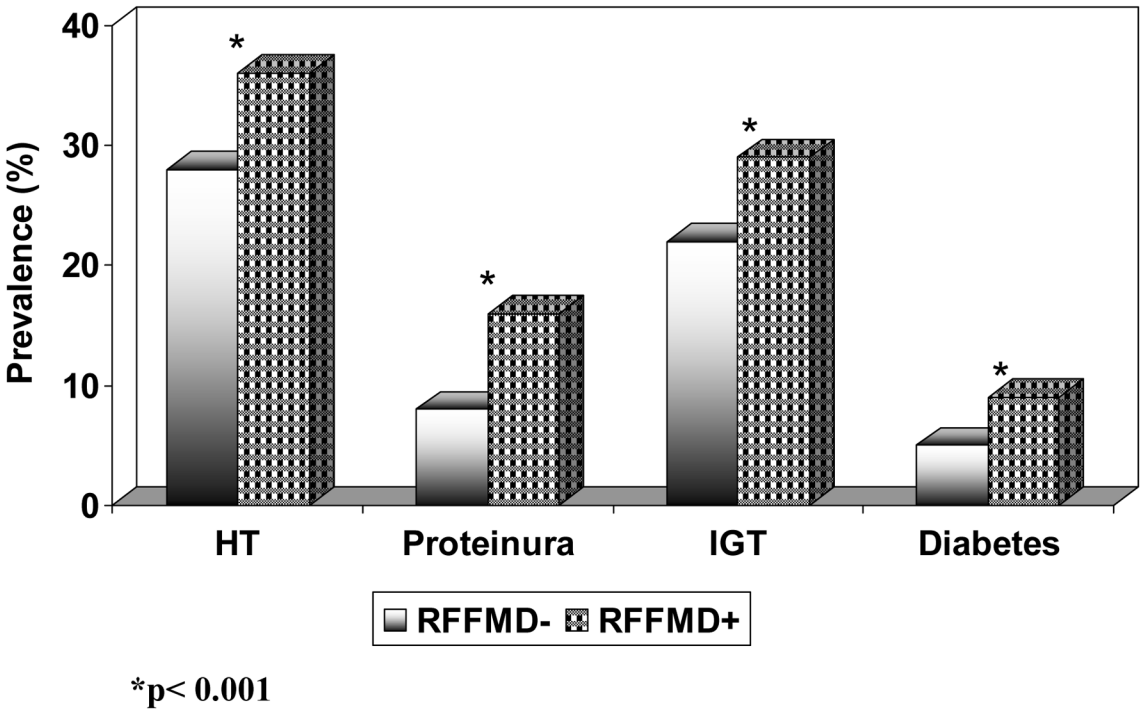

Fig. 1.

Prevalence of hypertension, proteinuria, impaired glucose tolerance and diabetes in 742 participants with normal fasting glucose, divided into two groups (with and without fat-free mass deficiency)

Table 1

Characteristics of the population sample based on relative fat free mass deficiency.

	RFFMD −(n= 494)	RFFMD +(n= 248)
Age (yrs)	57.8±7.5	58.4±7.4
Sex (M/F) (n)	252/242	51/197*
Heart Rate (bpm)	69.6±10.4	71.1±10.8
BMI (kg/m^2)	29.9±3.6	33.1±5.7*
Waist Circumference (cm)	103.0±10.1	109.0±13.8*
Fat-Free Mass (kg)	56.7±11.1	46.7±7.0*
Adipose Mass (kg)	28.5±8.0	36.4±11.4*
C-reactive Protein (mg/dL) §	1.06(0.98–1.14)	1.38(1.32–1.55)*
Fibrinogen (mg/dL)	326±61	352±62*
Fasting Glucose (mg/dL)	98±7	98±7
2hr- OGTT (mg/dL)	127±42	142±46*
HbA1c (%)	5.3±1.0	5.2±0.8
HOMA	3.6±2.7	4.4±3.3*
Cholesterol (mg/dL)	193±36	189±36
Triglycerides (mg/dL)	140±79	130±62
HDL-cholesterol (mg/dL)	41±13	46±13*
Glomerular Filtration rate (mg/mL/1.73 m^2)	90±53	89±27
Urinary albumin/creatinine (μg/mg)§	6.7(0.86–0.94)	9.2(1.00–1.13)*

M±SD;

§Median(IQ)

*p< 0.001

Table 2

Multivariate logistic regression for proteinuria as dependent variable

	B	Sig.	Exp(B)	95% C.I. for Exp(B) - LowerUpper
Age	0.03	.07	1.03	1.00–1.06
Sex (M/F)	−0.05	.86	0.95	0.55–1.66
RFFMD (n/y)	0.35	.20	1.42	0.84–2.40
2hr OGTT diabetes (n/y)	0.67	.01	1.96	1.19–3.23
Hypertension (n/y)	0.79	.02	2.20	1.16–4.16
Antihypertensive treatment (n/y)	−0.39	.30	0.68	0.32–1.42
C Reactive Protein	0.21	.17	1.24	0.91–1.69
Fibrinogen	0.001	.46	1.00	0.99–1.00
Constant	−3.16			

Table 3

Analysis of characteristics of men and women with or without RFFMD. The interaction between gender and RFFMD is reported.

	Men (n= 303)		Women (n= 439)			
	RFFMD −(n= 252)	**RFFMD +(n= 51)**	**RFFMD −(n= 242)**	**RFFMD +(n= 197)**	**Effect of RFFMD: p≤**	**Sex × RFFMD interaction: p≤**
Age (yrs)	57.5±7.5	57.8±7.6	58.1±7.6	58.6±7.3	0.80	0.90
Heart Rate (bpm)	69.1±11.1	67.5±10.5	70.1±9.6	72.0±10.6	0.69	0.07
BMI (kg/m2)	29.9±3.7	29.3±4.3	29.8±3.5	34.1±5.8	0.0001	0.0001
Waist Circumference (cm)	103.5±9.4	101.8±7.5	102.5±10.7	110.9±14.4	0.03	0.0001
Fat-Free Mass (kg)	65.8±7.3	55.0±5.6	47.2±4.3	44.6±5.6	0.0001	0.0001
Adipose Mass (kg)	25.7±7.0	27.3±6.5	31.5±8.0	38.8±11.2	0.0001	0.0001
Fasting Glucose (mg/dL)	99.0±6.4	98.5±7.2	97.7±7.3	98.3±7.7	0.42	0.30
2hr-glucose (mg/dL)	119.2±38.9	133.0±41.6	135.8±43.1	144.7±46.9	0.02	0.68
HOMA-IR	3.5±3.0	4.1±2.4	3.6±2.5	4.4±3.5	0.06	0.59
Fibrinogen (mg/dL)	325.6±62.0	330.6±43.9	326.4±60.2	358.1±64.4	0.006	0.01
C-reactive Protein (mg/dL) §	0.85(0.34–1.46)	0.92(0.52–1.44)	1.31(0.61–1.82)	1.53(0.99–2.23)	0.02	0.08
Glomerular Filtration rate (mg/mL/1.73 m^2)	92.6±69.2	96.2±27.2	87.4±26.2	86.7±26.6	0.07	0.66
Urinary albumin/creatinine (μg/mg) §	5.8(4.0–11.5)	7.4(5.5–21.8)	7.3(4.7–13.4)	9.4(5.4–19.5)	0.02	0.78

M±SD;

§Median(IQ)