Nutrition, Metabolism & Cardiovascular Diseases (2014) **24**, 271–276

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

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

L.A. Ferrara [a,*], B. Capaldo [a], C. Mancusi [b], E.T. Lee [c], B.V. Howard [d], R.B. Devereux [e], G. de Simone [b,e]

[a] Department of Clinical Medicine and Surgery, Federico II University Hospital, Via S. Pansini 5, 80131 Naples, Italy
[b] Department of Translational Medical Sciences, Federico II University, Naples, Italy
[c] Center for American Indian Health Research, University of Oklahoma, Oklahoma City, OK, USA
[d] Medstar Research Institute, Washington, D.C., USA
[e] Department of Medicine, Weill Cornell Medical College, New York, NY, USA

Received 27 March 2013; received in revised form 25 June 2013; accepted 6 August 2013
Available online 9 October 2013

KEYWORDS
Fat-free mass deficiency;
Cardiometabolic risk;
Overweight/obesity;
Normoglycemia;
Proteinuria

Abstract *Background and aim:* 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 and results: 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 2 h-OGTT were measured together with urine albumin/creatinine excretion, laboratory and anthropometric parameters. 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.

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

* Corresponding author. Tel./fax: +39 (0)817462302.
E-mail address: ferrara@unina.it (L.A. Ferrara).

0939-4753/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.numecd.2013.08.009

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 $\leq$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 4549 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) $\geq$60 ml/min by the simplified MDRD formula [20];
e) fasting triglycerides < 750 mg/dl;

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[b]
Heart Rate (bpm)	69.6 ± 10.4	71.1 ± 10.8
BMI (kg/m^2)	29.9 ± 3.6	33.1 ± 5.7[b]
Waist circumference (cm)	103.0 ± 10.1	109.0 ± 13.8[b]
Fat-free mass (kg)	56.7 ± 11.1	46.7 ± 7.0[b]
Adipose mass (kg)	28.5 ± 8.0	36.4 ± 11.4[b]
C-reactive protein (mg/dL)[a]	1.06(0.98–1.14)	1.38(1.32–1.55)[b]
Fibrinogen (mg/dL)	326 ± 61	352 ± 62[b]
Fasting glucose (mg/dL)	98 ± 7	98 ± 7
2 h-OGTT (mg/dL)	127 ± 42	142 ± 46[b]
HbA1c (%)	5.3 ± 1.0	5.2 ± 0.8
HOMA	3.6 ± 2.7	4.4 ± 3.3[b]
Cholesterol (mg/dL)	193 ± 36	189 ± 36
Triglycerides (mg/dL)	140 ± 79	130 ± 62
HDL-cholesterol (mg/dL)	41 ± 13	46 ± 13[b]
Glomerular filtration rate (mg/mL/1.73 m^2)	90 ± 53	89 ± 27
Urinary albumin/creatinine (μg/mg)[a]	6.7(0.86–0.94)	9.2(1.00–1.13)[b]

M ± SD.
[a] Median (IQ).
[b] $p < 0.001$.

Laboratory tests and definitions

Clinical examination and collection of blood samples after a 12-h fast were performed in the morning at local Indian Health Service facilities by the study staff. All participants without known diabetes (fasting plasma glucose $\geq$ 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

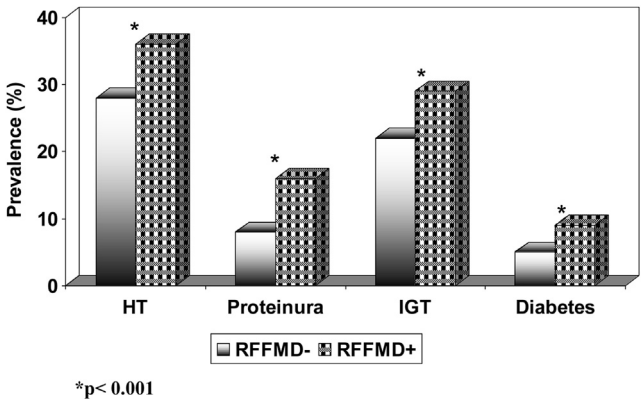

Figure 1 Prevalence of hypertension, proteinuria, impaired glucose tolerance and diabetes in 742 participants with normal fasting glucose, divided into two groups (with and without fat-free mass deficiency).