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Association Between Insulin Resistance and Lean Mass Loss and Fat Mass Gain in Older Men without Diabetes Mellitus

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Abstract

OBJECTIVES—To examine the associations between insulin resistance and changes in body composition in older men without diabetes mellitus.

DESIGN—Longitudinal cohort study of older men participating in the Osteoporotic Fractures in Men (MrOS) study.

SETTING—Six U.S. clinical centers.

PARTICIPANTS—Three thousand one hundred thirty-two ambulatory men aged 65 and older at baseline.

MEASUREMENTS—Baseline insulin resistance was calculated for men without diabetes mellitus using the homeostasis model assessment of insulin resistance (HOMA-IR). Total lean,

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Author Contributions: Lee: study concept, data analysis, interpretation of data, and preparation of manuscript. Boyko, Lewis, Hoffman, and Everson-Rose: interpretation of data and critical review of the manuscript. Strotmeyer and Cawthon: acquisition of data, interpretation of data, and critical review of the manuscript. Barrett-Connor and Orwoll: acquisition of data and subjects, interpretation of data and critical review of the manuscript.

appendicular lean, total fat, and truncal fat mass were measured using dual energy X-ray absorptiometry scans at baseline and 4.6 ± 0.3 years later in 3,132 men with HOMA-IR measurements.

RESULTS—There was greater loss of weight, total lean mass, and appendicular lean mass and less gain in total fat mass and truncal fat mass with increasing quartiles of HOMA-IR ($P < .001$ for trend). Insulin-resistant men in the highest quartile had higher odds of 5% or more loss of weight (odds ratio (OR) = 1.88, 95% confidence interval (CI) = 1.46–2.43), total lean mass (OR = 2.09, 95% CI = 1.60–2.73) and appendicular lean mass (OR = 1.57, 95% CI = 1.27–1.95) and lower odds of 5% or more gain in total fat mass (OR = 0.56, 95% CI = 0.45–0.68) and truncal fat mass (OR = 0.52, 95% CI = 0.42–0.64) than those in the lowest quartile. These findings remained significant after accounting for age, site, baseline weight, physical activity, and change in physical activity. These associations were also independent of other metabolic syndrome features and medications.

CONCLUSION—Greater lean mass loss and lower fat mass gain occurred in insulin-resistant men without diabetes mellitus than in insulin-sensitive men. Insulin resistance may accelerate age-related sarcopenia.

Keywords

older men; lean mass; fat mass; insulin resistance; body composition

Insulin resistance is a condition that is related to older age and excess adiposity.^{1,2} Approximately 29% of U.S. adults aged 60 and older have diabetes mellitus, the majority of which is type 2 diabetes mellitus, and more than 37% of adults without diabetes mellitus in this age category have some degree of insulin resistance, evidenced by impaired fasting glucose or impaired glucose tolerance.³ Given the high prevalence of insulin resistance in older adults, understanding the effects of insulin resistance on body composition, physical function, and health in older adults is of critical importance. Insulin is a potent anabolic hormone. It stimulates peripheral glucose uptake; downregulates hepatic glucose production; and plays an important role in inhibiting muscle proteolysis, stimulating muscle protein synthesis, and inhibiting adipose tissue lipolysis.⁴ In the presence of insulin resistance, one would anticipate impaired insulin action on muscle and fat resulting in lean and fat mass loss.

It has been hypothesized that insulin resistance plays a role in age-related muscle loss, and indirect evidence supports this process.^{5–7} Older adults with diabetes mellitus have a higher rate of muscle mass loss than those without.⁸ This may partially explain the finding that older adults with metabolic syndrome or diabetes mellitus also have a greater decline in physical function.^{9,10} Although the pathophysiology of declining muscle mass may be related to insulin resistance, it cannot be concluded from epidemiological studies in people with diabetes mellitus without accounting for coexisting metabolic abnormalities or the effect of treatments for diabetes mellitus. To examine this association further, changes in lean mass associated with varying degrees of insulin resistance were evaluated in older men without diabetes mellitus.

There are few studies examining the association between insulin resistance and changes in fat mass. In contrast to the hypothesized inverse relationship between insulin resistance and fat mass change, there was a greater accumulation of visceral fat with insulin resistance in Japanese-American men.¹¹ If insulin resistance predisposes to fat mass gain and muscle mass loss, the combined effects may explain the attenuation in overall weight gain for insulin-resistant, young adults.^{12,13} These findings may differ in an older population with the propensity to lose weight and to experience a greater proportion of fat than lean mass

loss with weight loss.^{14,15} Insulin resistance in older adults is associated with weight loss.¹⁶ Therefore, the associations between insulin resistance and changes in fat mass were also evaluated in older men without diabetes mellitus.

METHODS

Study Design and Participants

The Osteoporotic Fractures in Older Men Study (MrOS) enrolled 5,994 ambulatory men aged 65 and older (mean age 73) at six clinical sites in the United States to study healthy aging, with a particular emphasis on osteoporosis. The institutional review board at each clinical site approved the study protocol, and study participants provided written informed consent. Participants were studied initially between March 2000 and April 2002 and had a second clinic visit between March 2005 and May 2006. Details of this cohort have been described previously.^{17,18} Participants were excluded if they had missing data on dual-energy absorptiometry scan (DXA) measures of body composition at Visit 1 or 2; diabetes mellitus at Visit 1 or 2 (fasting glucose ≥ 126 mg/dL at Visit 1 or self-reported diabetes mellitus, insulin use, or hypoglycemic agent use at Visit 1 or 2); or missing data on baseline fasting glucose, insulin, high-density lipoprotein cholesterol (HDL-C) levels, triglycerides, systolic blood pressure, antihypertensive medication use, or lipid-lowering medication use. The analytical cohort comprised 3,132 men without diabetes mellitus with complete baseline metabolic parameters and body composition measures at Visits 1 and 2.

Clinic Visit Measurements

Weight in kilograms was obtained at Visits 1 and 2 using balance-beam scales at all sites except Portland, where a digital scale was used. Systolic blood pressure was taken using a mercury sphygmomanometer in duplicate at base-line, and values were averaged to calculate mean systolic blood pressure.

Body Composition Measurements

Total lean, appendicular lean, total fat, and truncal fat mass were derived from DXA (QDR 4,500W, Hologic, Inc., Bedford, MA) at Visits 1 and 2. The DXA operators adjusted the cut lines in the whole-body DXA scans to define regions according to standard Hologic procedures. Appendicular lean mass was the sum of lean mass in the arms and legs. Cut lines were drawn between the head of the humerus and the scapula at the glenoid fossa for delineation of the arm and across the midpoint of the femoral neck for delineation of the leg. For the derivation of truncal fat mass, these cut lines also served as the borders for the trunk, which extended to the jaw superiorly. A Hologic wholebody phantom was scanned three times weekly at each site for the calculation and application of correction factors to adjust for longitudinal drift in DXA measures as appropriate. Reproducibility of measurements was ensured by using a central quality control lab (San Francisco Coordinating Center, San Francisco, CA), using standardized scanning procedures across sites, and certifying DXA operators.

Serum Measurements

Fasting morning serum samples were collected at baseline and stored at -70°C . Previously unthawed serum was assayed for glucose using a hexokinase method and insulin using a two-site immune-enzymometric assay with autoanalyzers (Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA). The interassay coefficient of variation (CV) based on blind duplicates was less than 3% for glucose and inter- and intra-assay CVs were less than 10% for insulin. Insulin resistance was calculated using fasting glucose and insulin levels in the homeostasis model of insulin resistance (HOMA-IR) as (fasting glucose

$(\text{mg/dL}) \times \text{fasting insulin } (\mu\text{U/mL})/405$.¹⁹ HOMA-IR measurement of insulin resistance was highly correlated with euglycemic clamp measurement, and its CV in participants without diabetes mellitus was reported to be $9.4 \pm 0.7\%$.²⁰ Assays for HDL-C and triglycerides were performed on previously thawed and refrozen serum using a Roche COBAS Integra 800 automated analyzer (Roche Diagnostics Corp., Indianapolis, IN) at the Oregon Veterans Affairs Clinical Laboratory. Interassay CVs for HDL-C and triglycerides were 2.39% and 3.03%, respectively.

Questionnaire Data

Demographic information included age, race (white, African American, or other), education (<college degree or college degree), and study site. Lifestyle factors included alcohol use (none, light (<7 drinks/wk), or moderate to high (≥ 7 drinks/wk)), smoking status (current, past, or never users), physical activity using Physical Activity Scale for the Elderly (PASE) score, with higher scores indicating greater levels of physical activity,²¹ and self-reported health status (excellent or good vs fair, poor, or very poor). Participants self-reported medical conditions (including hypertension, hyperlipidemia, diabetes mellitus, stroke, myocardial infarction, angina pectoris, and congestive heart failure) and had assessment of prescription medication use (including insulin, hypoglycemic agents, betablockers, thiazide diuretics, angiotensin-converting enzyme inhibitors, calcium-channel blockers, angiotensin receptor blockers, nitrates, alpha-blockers, fibrates, and statins). Medications were matched to their ingredient(s) based on the Iowa Drug Information Service Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA), and these data were stored in an electronic medications inventory database (San Francisco Coordinating Center).²²

Statistical Analysis

All statistical analyses were performed using STATA/IC 11.0 (STATA Corp LP, College Station, TX). Differences in baseline characteristics according to quartiles of HOMA-IR were assessed using the chi-square test for categorical variables and analysis of variance for continuous variables.

Mean absolute and percentage changes in weight, total lean mass, appendicular lean mass, total fat mass, and truncal fat mass were calculated for each quartile of HOMA-IR. A significant absolute change in these measures was determined as $P < .05$ for paired t-test for baseline and 4.6-year follow-up measurements. A significant trend in the baseline and change measurements of body composition was determined as $P < .05$ for nonparametric test for trend across ordered groups (quartiles of HOMA-IR).

Because older men experience an average loss of total body mass, total lean mass, and appendicular lean mass but a gain in total and truncal fat,²³ binary variables were created to represent the loss or gain of body composition measurements over time as follows: loss of weight, total lean mass, and appendicular lean mass was defined as loss of 5% or more of these measurements, and gain in total and truncal fat mass was defined as gain of 5% or more. These categories were chosen based on the relevance of 5% change categories of weight to mortality.²⁴ Odds for loss of 5% or more of weight or lean mass or gain of 5% or more in fat mass by quartiles of HOMA-IR (with men in the lowest quartile of HOMA-IR as the reference group) were estimated using logistic regression, with the linear trend in odds ratios tested in each model. Because older men have opposite changes in weight, total lean mass, and appendicular lean mass from changes in total fat and truncal fat, likelihoods for loss in weight, total lean mass, and appendicular lean mass were presented separately from likelihoods for total and truncal fat gain. Odds ratios in the above logistic regression models were recalculated after exclusion of men who gained 5% or more weight, total lean mass, or appendicular lean mass, or lost 5% or more total or truncal fat mass in respective models to

ensure that the odds of loss or gain reflected a comparison with stability in the body composition measurement. Covariates associated with HOMA-IR and changes in body composition were examined in these logistic regression models and included in multiple logistic regression models if the magnitude of the associations between HOMA-IR and body composition changed by more than 10%. The influence of physical activity and change in physical activity on these relationships was assessed with further adjustment in the above models for PASE score at baseline and change in PASE score between baseline and 4.6-year follow-up visits. To control for the potential confounding effects of coexisting metabolic abnormalities, systolic blood pressure, HDL-C, triglycerides, and antihypertensive and lipid-lowering medication use were adjusted for in multivariable logistic regression models. Effect modification by baseline age and body mass index (BMI) was examined using interaction terms in logistic regression models.

RESULTS

At baseline, the mean age of these 3,132 men was 72.7 (range 65–92). As shown in Table 1, there were significant differences between quartiles of HOMA-IR in baseline age, education level, alcohol use, self-rated health, self-report of hypertension, HDL-C levels, triglyceride levels, use of antihypertensive and lipid-lowering agents, weight, BMI, physical activity level, fasting glucose, fasting insulin, and HOMA-IR.

Baseline and 4.6-year follow-up visit measurements of weight and total lean, appendicular lean, total fat, and truncal fat mass were higher with increasing quartiles of HOMA-IR ($P < .001$ for trend) (Table 2). During the mean 4.6-year follow-up, there was a significant loss of weight, total lean mass, and appendicular lean mass in all quartiles of HOMA-IR ($P < .001$), although there was a significant trend toward greater absolute and percentage loss in weight, total lean mass, and appendicular lean mass with increasing quartiles of HOMA-IR ($P < .001$ for trend). Only the men in the lowest two quartiles of HOMA-IR had a significant increase in total fat mass during this same time period, whereas men in all quartiles of HOMA-IR had a significant increase in percentage fat mass, suggesting that the rise in percentage fat mass for men in the highest two quartiles of HOMA-IR result from the significant decrease in total lean mass. Men in the lowest quartile of HOMA-IR had a significant increase in the absolute amount and percentage of truncal fat, whereas men in the highest quartile of HOMA-IR had a decrease in truncal fat. Overall, there was a significant trend toward greater absolute and percentage gain in total fat mass, percentage fat mass, truncal fat, and percentage truncal fat with decreasing quartiles of HOMA-IR ($P < .001$ for trend).

There were progressively higher odds of loss of 5% or more weight, total lean mass, and appendicular lean mass loss with increasing quartiles of HOMA-IR (all P -values for trend $< .001$) (Table 3). The higher odds of weight loss, total lean mass loss, and appendicular lean mass loss associated with increasing HOMA-IR remained significant even after exclusion of men with 5% or more gain in weight, total lean mass, and appendicular lean mass from respective models. Further adjustment for baseline physical activity and changes in physical activity over 4.6 years had little influence on the odds of weight, total lean mass, or appendicular lean mass loss. Men in the highest two quartiles of HOMA-IR were still significantly more likely to experience loss of 5% or more weight, total lean mass, or appendicular lean mass loss over 4.6 years than men in the lowest quartile of HOMA-IR, even with a more than 10% attenuation of the odds by adjustments for metabolic comorbidities. There was a lack of effect modification by BMI or age on these associations (interaction P -values all $> .10$).

Men in all higher quartiles of HOMA-IR had significantly lower odds of 5% or more total body fat and truncal fat gain than those in the lowest quartile (reference group; Table 4).

There were progressively lower odds of gain in total fat mass and truncal fat mass with increasing quartiles of HOMA-IR (all P -values for trend $<.001$). Even after the exclusion of men with 5% or more loss of total fat mass and truncal fat mass from respective models, men in higher quartiles of HOMA-IR still had significantly lower odds of gain in total fat mass and truncal fat mass. These associations were attenuated but remained significant after adjustment for age, study site, and baseline weight. Adjustments for physical activity and changes in physical activity over 4.6 years or metabolic comorbidities did not alter the odds of gain in total fat mass or truncal fat mass associated with higher insulin resistance. There was no significant effect modification of the associations between HOMA-IR and total or truncal fat gain of age or BMI (interaction P -values all 4.10).

DISCUSSION

In this study of older men without diabetes mellitus, those who were the most insulin resistant had higher baseline weight and lean and fat mass but were more likely to lose weight and total lean and appendicular lean mass over 4.6 years than men with better insulin sensitivity. These insulin-resistant men were also less likely to gain total or truncal fat mass over the same period. These associations did not differ according to baseline age or BMI. By studying insulin resistance in men without diabetes mellitus and controlling for baseline physical activity, changes in physical activity, and metabolic comorbidities, the direct association between insulin resistance and greater likelihood of lean mass loss and lower likelihood of fat mass gain has been strengthened.

A substantial proportion of older men lose weight and total lean and appendicular lean mass as they age.^{15,24,25} These findings add to a previous report of weight loss in insulin-resistant older adults.¹⁶ Weight loss over 3 years was associated with greater risk of all-cause mortality in older men in a large longitudinal observational cohort study.²⁴ In addition, loss in extremity fat-free mass was related to greater risk of future disability for older men.²⁶ Thus, insulin-resistant men may have greater risks of disability and mortality associated with loss of weight and total and appendicular lean mass.

A previous study reported higher appendicular lean mass loss in undiagnosed, older people with undiagnosed type 2 diabetes mellitus than in those without diabetes mellitus.⁸ The current analysis further elucidates the role of insulin resistance in loss of total and appendicular lean mass in older men without diabetes mellitus, independent of physical activity and metabolic comorbidities. Decreased responsiveness to insulin for stimulation of muscle protein synthesis and for inhibiting protein breakdown in insulin-resistant older men may cause greater lean mass loss.

Clinical studies have shown defects in the ability of insulin to stimulate muscle protein synthesis in older individuals than in younger ones, possibly because of lower muscle blood flow.⁷ Furthermore, the ability of insulin to inhibit protein breakdown is impaired in older adults.²⁷ Further studies are needed in insulin-resistant older men to examine the potential defects of insulin signaling that contribute to a net loss of muscle protein and lean mass.

In this study, insulin-resistant older men with greater total and truncal fat at baseline had lower odds of total and truncal fat gain independent of physical activity and metabolic comorbidities. A potential explanation for this finding may be poorer suppression of lipolysis by insulin in insulin-resistant individuals than in those who are not insulin resistant.²⁸ Clinical studies have also demonstrated greater basal and catecholamine-stimulated lipolysis in patients with insulin resistance.^{29,30} Higher rates of lipolysis in insulin-resistant individuals with high total and truncal adiposity may serve as a homeostatic mechanism to prevent further total and truncal fat gain. Other homeostatic effects of high

insulin levels on adiposity may involve signaling in the central nervous system to alter appetite and energy expenditure.^{31,32}

Strengths of this study include the excellent characterization of a large number of community-dwelling older men, including assessment of body composition using DXA scans. In addition, the longitudinal measurements of body composition aid in the investigation of potential factors associated with adverse changes in body composition, rather than correlates of cross-sectional measurements of body composition. A few limitations must also be acknowledged. The criterion standard technique for measuring peripheral insulin resistance is a hyperinsulinemic–euglycemic clamp, and the use of fasting glucose and insulin levels for calculating HOMA-IR may better reflect basal hepatic insulin resistance. Nevertheless, HOMA-IR is an acceptable and more-feasible, surrogate measure of peripheral insulin sensitivity for use in large epidemiological studies for multiple reasons: hepatic and skeletal muscle insulin sensitivity are usually proportional to each other, and HOMA-IR is reproducible with low coefficients of variability and correlates well with the criterion-standard, more-labor-intensive measurement of insulin resistance using a hyperinsulinemic–euglycemic clamp.^{20,33,34} Because oral glucose tolerance testing was not performed in MrOS, some study participants with impaired fasting glucose probably had undiagnosed type 2 diabetes mellitus. Despite this potential misclassification, the measurement of insulin resistance using HOMA-IR in participants with type 2 diabetes mellitus still correlates highly with hyperinsulinemic–euglycemic clamp measurements in this population.^{34,35} Furthermore, it is likely that there was little influence of medically advised lifestyle modification that would result in an attenuation of fat mass and decline in weight and lean mass in this group, given the absence of a formal diagnosis of type 2 diabetes mellitus. The minimal effect of adjustment for baseline or changes in physical activity on the odds of gaining fat mass or losing weight and lean mass for insulin-resistant men was evidence of this assumption, although this study cannot account for potential dietary changes on observed associations given the absence of longitudinal dietary measurements. The reason for weight loss is not clear, and other potential explanations for the associations between insulin resistance and changes in weight, lean mass, and fat mass may exist, because the effects of incident acute and chronic illnesses and initiation of medications on these associations were not examined. Because this cohort included only older men who were predominantly Caucasian, these findings may not generalize to older women, younger populations, or other ethnic groups.

In a population of older men without diabetes mellitus, greater insulin resistance was associated with higher baseline BMI and adiposity, although these insulin-resistant older men had a greater likelihood of experiencing significant loss in weight, total lean mass, and appendicular lean mass and less likelihood of experiencing a significant gain in total fat mass or truncal fat mass. These data indicate that greater insulin resistance may contribute to the development of sarcopenia. Future studies to understand the mechanism of lean mass loss in insulin-resistant older men are needed. Furthermore, intervention studies to determine whether lean mass loss can be prevented with treatment of insulin-resistance in older men are warranted.

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Table 1
Baseline Characteristics According to Quartile (Q) of Homeostasis Model of Insulin Resistance (HOMA-IR)

Characteristic	More Insulin Sensitive ← → More Insulin Resistant				P-Value
	Q1 (n = 783)	Q2 (n = 783)	Q3 (n = 784)	Q4 (n = 782)	
Age, mean ± SD	72.9 ± 5.8	73.3 ± 5.5	72.7 ± 5.4	72.0 ± 4.9	<.001
Smoking, %					.09
Never	43.4	39.6	39.7	36.4 *	
Former	53.3	58.1	57.8	60.2	
Current	3.3	2.3	2.3	2.9	
Race, %					.16
Caucasian	93.2	92.0	92.0	91.7	
African American	2.7	2.2	2.0	3.7	
Other	4.1	5.9	6.0	4.6	
College degree, %	67.0	59.9	53.2	47.8	<.001
Alcohol use, %					<.001
None	25.5 *	30.4	32.1	35.6	
Moderate	41.8	38.7	43.6	42.8	
High	32.7	30.9	24.2	21.6	
Excellent to good self-rated health, %	94.4	90.7	90.9	89.1	.002
Cancer, %	30.0	29.1	28.6	25.7	.26
Congestive heart failure, %	2.6	3.8	2.8	4.0	.29
Myocardial infarction, %	8.6	11.5	10.5	11.6	.17
Angina pectoris, %	9.7	11.1	11.6	12.3	.42
Stroke, %	4.5	4.5	4.0	2.7	.22
Hypertension, %	28.7	36.1	39.7	47.8	<.001
Systolic blood pressure, mmHg, mean ± SD	136.2 ± 19.9	135.6 ± 18.8	137.0 ± 16.9	137.8 ± 16.4	.07
High-density lipoprotein cholesterol, mg/dL, mean ± SD	56.8 ± 15.0	51.7 ± 12.9	48.1 ± 13.1	43.3 ± 11.3	<.001
Triglycerides, mg/dL, mean ± SD	106.9 ± 58.4	124.1 ± 62.3	152.5 ± 92.2	180.0 ± 99.5	<.001
Antihypertensive use, %	38.7	46.4	49.1	56.0	<.001

Characteristic	More Insulin Sensitive ←			→ More Insulin Resistant			P-Value
	Q1 (n = 783)	Q2 (n = 783)	Q3 (n = 784)	Q4 (n = 782)	Q5 (n = 782)	Q6 (n = 782)	
Lipid-Lowering drugs use, %	22.0	26.3	28.3	28.8	28.8	28.8	.009
Weight, kg, mean ± SD	75.3 ± 9.5	80.2 ± 10.6	84.3 ± 11.1	90.1 ± 13.1	90.1 ± 13.1	90.1 ± 13.1	<.001
Body mass index, kg/m ² , mean ± SD	24.7 ± 2.6 [†]	26.3 ± 3.0	27.5 ± 3.1	29.5 ± 3.6	29.5 ± 3.6	29.5 ± 3.6	<.001
Physical Activity Scale for the Elderly score, mean ± SD	158.8 ± 69.7	153.1 ± 67.4	158.0 ± 66.7 [‡]	147.0 ± 66.4	147.0 ± 66.4	147.0 ± 66.4	.002
Fasting glucose, mg/dL, mean ± SD	93.0 ± 7.8	97.1 ± 8.0	99.8 ± 8.8	104.4 ± 9.0	104.4 ± 9.0	104.4 ± 9.0	<.001
Fasting insulin, (IU/mL), mean ± SD	3.9 ± 0.9	6.2 ± 0.9	8.9 ± 1.2	15.9 ± 6.1	15.9 ± 6.1	15.9 ± 6.1	<.001
HOMA-IR, mean ± SD	0.9 ± 0.2	1.5 ± 0.2	2.2 ± .3	4.1 ± 1.6	4.1 ± 1.6	4.1 ± 1.6	<.001

* Missing data for 1 participant.

[†] Missing data for 2 participants.

SD = standard deviation.

Table 2

Measures of Mean Weight, Total Lean Mass, Appendicular Lean Mass, Total Fat Mass, Total Percentage Fat Mass, Truncal Fat Mass, and Percentage Truncal Fat Mass at Visits 1 and 2 and Median Absolute and Percentage Change (A) in Body Composition Measurements Between Visits 1 and 2 (V1-V2) According to Quartile (Q) of Insulin Resistance Measured Using the Homeostasis Model of Insulin Resistance (HOMA-IR)

Measure	Q1	Q2	Q3	Q4
Weight				
Baseline, kg (mean $\pm$ SD) [†]	75.3 (9.5)	80.2 (10.6)	84.4(11.1)	90.1 (13.1)
Visit 2, kg (mean $\pm$ SD) [†]	74.7(10.2) [*]	79.2(11.2) [*]	82.8(11.9) [*]	88.4(13.6) [*]
Absolute Δ V1-V2, kg, median (IQR) [†]	-0.5 (-2.7-1.6)	-0.9 (-3.4-1.5)	-1.4 (-3.9-1.2)	-1.3 (-4.2-1.3)
Percentage Δ V1-V2, median (IQR)% [†]	-0.7 (-3.5-2.1)	-1.2 (-4.3-1.9)	-1.7 (-4.6-1.5)	-1.5 (-4.9-1.5)
Total lean mass				
Baseline, kg (mean $\pm$ SD) [†]	54.6 (6.2)	55.9 (6.4)	57.4 (6.6)	59.4 (7.4)
Visit 2, kg (mean $\pm$ SD) [†]	53.8 (6.4) [*]	54.9 (6.5) [*]	56.2 (6.9) [*]	58.1 (7.5) [*]
Absolute Δ V1-V2, kg, median (IQR) [†]	-0.9 (-1.9-0.4)	-0.9 (-2.2-0.3)	-1.1 (-2.5-0.2)	-1.2 (-2.9-0.3)
Percentage Δ V1-V2, median (IQR) [†]	-1.6 (-3.6-0.7)	-1.6 (-3.7-0.6)	-1.9 (-4.5-0.3)	-2.0 (-4.8-0.5)
Appendicular lean				
Baseline, kg (mean $\pm$ SD) [†]	23.5 (3.1)	23.9 (3.1)	24.6 (3.2)	25.4 (3.6)
Visit 2, kg (mean $\pm$ SD) [†]	22.9 (3.2) [*]	23.2 (3.2) [*]	23.8 (3.4) [*]	24.5 (3.7) [*]
Absolute Δ V1-V2, kg, median (IQR) [†]	-0.6 (-1.2-0.0)	-0.6 (-1.3-0.0)	-0.8 (-1.5-0.0)	-0.8 (-1.7-0.0)
Percentage Δ V1-V2, median (IQR) [†]	-2.5 (-5.2-0.2)	-2.6 (-5.7-0.1)	-3.2 (-6.2 to -0.1)	-3.2 (-6.7 to -0.2)
Total fat mass				
Baseline, kg (mean $\pm$ SD) [†]	16.4 (4.9)	20.0 (5.5)	22.4 (5.7)	26.0 (6.8)
Visit 2, kg (mean $\pm$ SD) [†]	17.0 (5.3) [*]	20.2 (6.0) [*]	22.4 (6.1)	25.9 (7.3)
Absolute Δ V1-V2, kg, median (IQR) [†]	0.5 (-0.9-2.1)	0.3 (-1.4-1.9)	0.1 (-1.6-1.7)	0.0 (-1.7-1.9)
Percentage Δ V1-V2, median (IQR) [†]	3.5 (-6.3-13.7)	1.5 (-7.1-10.7)	0.5 (-7.1-8.1)	0.0 (-6.6-7.2)
Total % fat mass [†]				
Baseline, % (mean $\pm$ SD) [†]	22.0 (4.9)	25.1 (4.6)	26.9 (4.4)	29.1 (4.5)
Visit 2, % (mean $\pm$ SD) [†]	22.8 (5.1) [*]	25.6 (4.9) [*]	27.3 (4.6) [*]	29.5 (4.9) [*]
Absolute Δ V1-V2, %, median (IQR) [†]	0.8 (-0.9-2.4)	0.5 (-1.0-2.1)	0.3 (-1.0-1.8)	0.4 (-0.9-1.8)
Percentage Δ V1-V2, median (IQR) [†]	3.7 (-3.7-11.4)	2.1 (-3.8-8.7)	1.1 (-3.97.0)	1.3 (-3.1-6.4)
Truncal fat				
Baseline, kg (mean $\pm$ SD) [†]	8.8 (3.0)	11.0(3.2)	12.8(3.3)	14.9(3.9)
Visit 2, kg (mean $\pm$ SD) [†]	9.1 (3.2) [*]	11.1 (3.5)	12.7(3.6)	14.8(4.2) [*]
Absolute Δ V1-V2, kg, median (IQR) [†]	0.3 (-0.7-1.3)	0.2 (-1.0-1.2)	0.0 (-1.2-1.1)	-0.1 (-1.2-1.1)
Percentage Δ V1-V2, median (IQR) [†]	3.6 (-8.1-16.4)	1.5 (-9.2-11.7)	0.3 (-9.2-8.5)	-0.8 (-7.7-7.5)

Measure	Q1	Q2	Q3	Q4
Percentage truncal fat				
Baseline, % (mean $\pm$ SD [†])	23.5 (5.9)	27.3 (5.2)	29.8 (4.8)	32.4 (4.9)
Visit 2, % (mean $\pm$ SD [†])	24.1 (6.1) *	27.5 (5.5)	29.8 (5.2)	32.3 (5.3)
Absolute Δ V1-V2, %, median (IQR) [†]	0.7 (−1.5–2.8)	0.4 (−1.7–2.2)	0.2 (−1.7–1.9)	0.1 (−1.6–1.6)
Percentage Δ V1-V2, median (IQR) [†]	2.9 (−6.5–11.0)	1.2 (−6.1–7.6)	0.5 (−5.9–5.9)	0.3 (−5.0–4.9)

* P .05 for *t* test between V2 and baseline measure.

[†]P .001 for trend across categories of HOMA-IR.

SD = standard deviation; IQR = interquartile range.

Table 3

Odds of Loss of 5% or More in Weight, Total Lean Mass, and Appendicular Lean Mass According to Quartile (Q) of Insulin Resistance Measured Using the Homeostasis Model of Insulin Resistance (HOMA-IR)

Quartile	Odds Ratio (95% Confidence Interval)			
	Model 1 [*]	Model 2 [†]	Model 3 [‡]	Model 4 [§]
Weight loss				
Q1	Reference	Reference	Reference	Reference
Q2	1.55(1.19–2.01) //	1.40(1.07–1.83) [#]	1.39(1.06–1.82) [#]	1.36(1.03–1.78) [#]
Q3	1.69(1.30–2.19) //	1.53(1.16–2.01) //	1.51 (1.15–1.99) //	1.41 (1.07–1.87) [#]
Q4	1.88 (1.46–2.43) //	1.69(1.27–2.25) //	1.65(1.24–2.21) //	1.49(1.10–2.01) //
Lean mass loss				
Q1	Reference	Reference	Reference	Reference
Q2	1.26 (0.95–1.67)	1.16(0.87–1.56)	1.15(0.86–1.55)	1.10(0.82–1.48)
Q3	1.80(1.37–2.36) //	1.73(1.30–2.31) //	1.72(1.29–2.30) //	1.56(1.16–2.09) //
Q4	2.09(1.60–2.73) //	2.05(1.52–2.77) //	2.01 (1.49–2.73) //	1.73(1.26–2.38) //
Appendicular lean mass loss				
Q1	Reference	Reference	Reference	Reference
Q2	1.24 (0.99–1.54)	1.15(0.91–1.44)	1.14(0.90–1.43)	1.13(0.89–1.42)
Q3	1.46(1.18–1.82) //	1.41 (1.12–1.78) //	1.42(1.12–1.79) //	1.34(1.06–1.71) [#]
Q4	1.57 (1.27–1.95) //	1.54(1.20–1.97) //	1.53(1.19–1.96) //	1.42(1.10–1.85) //

^{*} Unadjusted.

[†] Adjusted for age, study site and baseline weight.

[‡] Adjusted for Model 2 covariates plus baseline Physical Activity Scale for the Elderly (PASE) score and change in PASE score.

[§] Adjusted for Model 2 covariates plus systolic blood pressure, use of antihypertensive medications, triglycerides, high-density lipoprotein cholesterol, and use of lipid-lowering agents.

// $P < .01$

[#] $P < .05$ for comparison with Q1 of HOMA-IR.

Table 4

Odds of Gain in 5% or more in Total Fat Mass or Truncal Fat Mass by Quartiles (Q) of Insulin Resistance Measured Using the Homeostasis Model of Insulin Resistance (HOMA-IR)

Odds Ratio (95% Confidence Interval)				
Quartile	Model 1 [*]	Model 2 [†]	Model 3 [‡]	Model 4 [§]
Total fat gain				
Q1	Reference	Reference	Reference	Reference
Q2	0.74 (0.61–0.91) //	0.79 (0.64–0.97) [#]	0.79 (0.64–0.97) [#]	0.79 (0.64–0.98) [#]
Q3	0.60 (0.49–0.73) //	0.64 (0.51–0.79) //	0.64 (0.51–0.79) //	0.66 (0.53–0.82) //
Q4	0.56 (0.45–0.68) //	0.61 (0.48–0.76) //	0.61 (0.48–0.77) //	0.64 (0.50–0.81) //
Truncal fat gain				
Q1	Reference	Reference	Reference	Reference
Q2	0.72 (0.59–0.88) //	0.78 (0.64–0.96) [#]	0.79 (0.64–0.97) [#]	0.80 (0.65–0.98) [#]
Q3	0.64 (0.52–0.78) //	0.71 (0.57–0.88) //	0.71 (0.57–0.88) //	0.75 (0.60–0.93) //
Q4	0.52 (0.42–0.64) //	0.60 (0.48–0.76) //	0.60 (0.48–0.76) //	0.65 (0.51–0.83) //

^{*} Unadjusted.

[†] Adjusted for age, study site and baseline weight.

[‡] Adjusted for Model 2 covariates plus baseline Physical Activity Scale for the Elderly (PASE) score and change in PASE score.

[§] Adjusted for Model 2 covariates plus systolic blood pressure, use of antihypertensive medications, triglycerides, high-density lipoprotein cholesterol, and use of lipid-lowering agents.

// $P < .01$

[#] $P < .05$ for comparison with Q1 of HOMA-IR.