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Regional Anthropometric Measures and Hepatic Fibrosis in Patients With Nonalcoholic Fatty Liver Disease

Ayako Suzuki^{*}, Manal F. Abdelmalek^{*}, Aynur Unalp–Arida[‡], Katherine Yates[‡], Arun Sanyal[§], Cynthia Guy^{||}, and Anna Mae Diehl^{*}

^{*}Division of Gastroenterology, Duke University, Durham, North Carolina [‡]NASH CRN Data Coordinating Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

[§]Division of Gastroenterology, Virginia Commonwealth University, Richmond, Virginia

^{||}Department of Pathology, Duke University, Durham, North Carolina

Abstract

BACKGROUND & AIMS—In overnourished individuals, impaired peripheral fat storage (ie, reduced fat mass in extremities) can increase delivery of surplus calories to the organs other than peripheral adipose tissues, including the liver (ie, lipid overload), and facilitate disease progression in patients with nonalcoholic fatty liver disease (NAFLD). We investigated whether peripheral and/or abdominal adipose depot size correlates with stage of hepatic fibrosis in patients with NAFLD in sex- and/or menopausal stage-specific manners.

METHODS—We performed a cross-sectional analysis of 537 adult patients with NAFLD. Peripheral adipose depot size was defined as the sum of z-scores of 2 anthropometric parameters (middle upper arm circumference and hip circumference, relative to total body size) and expressed as extremity size. Abdominal adipose depot size was defined as waist circumference. Peripheral and abdominal adipose depot sizes were associated with fibrosis stage(s) (F0–F4) using multivariable analyses separately for men and pre- and post-menopausal women.

RESULTS—After adjusting for caloric intake and energy expenditure during physical activity (MET; hours/week), peripheral and/or abdominal adipose depot sizes were differentially associated with fibrosis stages in men and pre- and post-menopausal women. Men with smaller extremity size, premenopausal women with larger extremity size, and postmenopausal women with larger abdominal size were more likely to have higher stages of fibrosis.

CONCLUSIONS—In patients with NAFLD, regional anthropometric measures are associated with fibrosis severity in a sex- and menopausal stage-specific manner. Unlike premenopausal women, men with NAFLD who have small peripheral adipose depots are at an increased risk of having advanced fibrosis.

Keywords

Obesity; Regional Anthropometrics; Gender Difference; Reproductive Status

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Address requests for reprints to: Ayako Suzuki, MD, PhD, MSc, Duke University Medical Center, Division of Gastroenterology, Duke South Orange Zone, Room 0340, PO 3913, Durham, North Carolina 27710. suzuk004@mc.duke.edu; fax: (919) 681-8147.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at doi:10.1016/j.cgh.2010.08.005.

Conflicts of interest

The authors disclose no conflicts.

During the past decade, obesity has increased in an epidemic manner and has created a significant public health problem in most developed nations.¹⁻⁴ Nonalcoholic fatty liver disease (NAFLD) has been suggested to increase globally along with the steep increment of overweight and obese populations.^{5,6} A certain proportion of patients with NAFLD may progress to cirrhosis or end-stage liver disease.⁷ Insulin resistance, oxidative stress, altered hormonal milieu, and immunological deregulation may orchestrate and contribute to the disease progression of NAFLD.⁸ However, the exact mechanism underlying disease progression and who would likely develop cirrhosis has not been fully defined.

Obesity is a condition of excessive fat (ie, triglyceride) accumulation in adipose tissue as a consequence of impaired energy balance.⁹ In the setting of overnutrition (ie, a chronic state of positive energy balance), surplus calories are stored as fat in the white adipocytes, a cell group specifically designed to store excess fuel. When this storage capacity becomes saturated, it results in the ectopic accumulation of lipids (ie, triglycerides and other lipids such as fatty acids, fatty acid derivatives, and sphingolipids) in lean tissues such as muscle, pancreas, liver, heart, and blood vessels (ie, lipid overflow).¹⁰ The ectopic lipid accumulation could compromise normal functionality in these organs and, at least partially, facilitate the development of obesity-related diseases, such as insulin resistance, diabetes mellitus, fatty liver, and atherosclerosis.¹⁰⁻¹² Lipodystrophy provides an extreme example of abnormal lipid partitioning. In lipodystrophic patients, impaired peripheral fat storage increases nonadipose (ectopic) lipid accumulation (ie, muscle, liver) and causes insulin resistance and fatty liver.^{13,14} Indeed, the prevalence of NAFLD, especially the more severe form of NAFLD (ie, steatohepatitis associated with fibrosis), is increased in lipodystrophy.¹⁴⁻¹⁶ It is conceivable that impaired peripheral fat storage (ie, reduced fat mass in extremities) may also impact on NAFLD progression in nonlipodystrophic patients. Perlemuter et al recently showed that, as observed for cardiovascular risk factors, leg and trunk fat mass measured by dual-energy x-ray absorptiometry were independently oppositely associated with liver enzymes; leg fat mass was inversely correlated with liver enzymes while trunk fat mass was positively associated with liver enzymes.¹⁷ To date, however, whether peripheral adipose depot sizes are associated with severity of NAFLD remains unknown.

Sex and menopausal state influence regional fat distribution and adipocyte functionality via their different sex hormone levels.¹⁸ Sex hormones, both estrogen and androgen, have significant roles in site-specific adipocyte development.¹⁹⁻²¹ Accordingly, men and women have distinct regional fat distribution: android pattern (ie, upper body, truncal, central, abdominal, or visceral obesity) in men versus gynoid pattern (ie, lower body, gluteo-femoral, or peripheral obesity) in women. In women, fat distribution significantly changes along with menopause and aging; women increase subcutaneous as well as visceral abdominal fat after menopause.²² Therefore, sex and menopausal status may impact the associations between regional fat distribution and NAFLD severity. In several previous studies evaluating the associations between regional fat distribution and liver enzymes (fatty liver or histologic severity), menopausal status was not taken into consideration.^{17,23,24} A better understanding of how sex and reproductive status influence the associations between regional fat distribution and NAFLD severity is needed.

In this study, we conducted a pilot analysis to refine the hypothesis that impaired peripheral fat storage (ie, reduced fat mass in extremities) impacts on NAFLD progression in nonlipodystrophic patients, by evaluating the associations between regional fat distribution and NAFLD severity while taking into consideration sex and menopausal status. Our specific aim was to determine whether peripheral and/or abdominal adipose depot sizes (ie,

regional anthropometric measures used as surrogates) are correlated with stages of hepatic fibrosis in patients with NAFLD, in sex-and/or menopausal stage-specific manners.

Methods

Study Design and Population

We performed a hypothesis-driven, cross-sectional analysis using data from the NASH Clinical Research Network (NASH CRN), both the NAFLD database and Pioglitazone vs Vitamin E vs Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) study, of patients diagnosed with NAFLD who were enrolled from September 2004 to January 2008.^{25,26} The study design and data collected from the NASH CRN database and PIVENS study have been recently reported.^{25,26} Our study population was defined using the following criteria: (1) age at enrollment was ≥ 18 years; (2) the presence of liver histologic data; (3) no significant alcohol consumption (defined as >14 drinks or 168 g of alcohol per week in men or >7 drinks or 84 g of alcohol per week in women on average within the past year); (4) no chronic liver diseases other than NAFLD as assessed by serologies and/or histology; (5) if women, the presence of menopausal history data; and (6) the presence of study variables obtained at baseline and within 6 months of liver biopsy. Our study population ($n = 537$) consisted of 215 men, 119 premenopausal women, and 203 postmenopausal women. The NASH CRN studies were approved by the Institutional Review Boards at each participating center.

Liver Histology

The primary outcome in this study was severity of hepatic fibrosis on histology. All liver biopsies from the enrolled patients were stained with hematoxylin-eosin and Masson's trichrome stains, and reviewed and scored centrally by the Pathology Committee according to the published NASH CRN scoring system.²⁷ Briefly, the stage of hepatic fibrosis was assessed using a 5-point scale: 0 = none; 1 = zone 3 perisinusoidal or periportal fibrosis (1a = mild, zone 3, perisinusoidal; 1b = moderate, zone 3, perisinusoidal; 1c = portal/periportal only); 2 = zone 3, perisinusoidal and periportal fibrosis, any combination; 3 = bridging fibrosis; and 4 = cirrhosis. For the analyses, all the stage 1 (1a, 1b, and 1c) biopsies were combined and treated as stage 1 biopsies, and stage 3 and 4 biopsies were combined and treated as advanced fibrosis.

Study Variables

The primary predictors in this study were regional (ie, peripheral and abdominal) adipose depot sizes. Using available regional anthropometric measures in the database, we created a parameter describing "extremity size relative to total body size" in individuals to characterize their peripheral fat distribution within the study population. The parameter and abdominal circumference were utilized as surrogate measures of defining regional adipose depot sizes. Total caloric intake and physical activity were treated as covariates for the purposes of incorporating energy balance for individuals into the analysis.

Peripheral and abdominal adipose depot sizes—Body mass index (BMI; weight [kg]/height[m²]), the circumferences of waist (cm), hip (HIP; cm), and midupper arm (ARM; cm) were used to create anthropometric parameters to define peripheral and abdominal adipose depot sizes. In order to define the peripheral adipose depot size, the ratio of HIP and ARM to BMI were first calculated in each individual as HIP/BMI and ARM/BMI, to express sizes of lower and upper extremities relative to total body size (ie, BMI). Then, the distributions of the 2 variables, HIP/BMI and ARM/BMI, were each transformed to a z-score, $(x - \text{mean})/\text{SD}$, and then summed to calculate a parameter of total peripheral adipose depots, expressed as extremity size (EXT) ($\text{EXT} = \text{standardized [HIP/BMI]} +$

standardized [ARM/BMI]). EXT (summed z-score) of 0 indicates that the extremity size (relative to total body size) is average in this study population, while EXT of -2 (or -3) indicates that the extremity size is disproportionally smaller than average.

For the comparisons between men, pre-, and post-menopausal women, the above standardization was done using the total study population to determine the means and SDs of the parameters. In subgroup analyses, the standardization was computed within each subgroup. In order to define the abdominal adipose depot size, waist circumference was utilized. To be consistent with the EXT variable, standardized waist circumference (z-score) was used in all the models (hereafter WAIST). To classify women into pre- and postmenopause, we used self-reported postmenopausal status. All the women before or during menopause were classified as premenopause.

Other study variables—Demographic information, physical activity, current smoking (cigarette), and the presence or absence of comorbidities of diabetes or impaired fasting glucose (IFG) (patient report and/or use of antidiabetic medication and/or fasting glucose >100 g/dL), hypertension (patient report and/or use of antihypertensive medication), hyperuricemia (serum uric acid >5.5 mg/dL), hypertriglyceridemia (serum triglycerides >150 mg/dL), elevated low-density lipoprotein (LDL)-cholesterol (serum LDL-cholesterol $\geq$ 130 mg/dL), low high-density lipoprotein (HDL)-cholesterol (serum HDL-cholesterol <40 mg/dL in men and <50 mg/dL in women), and depression (patient report) were collected at the time of the study enrollment (within 6 months from liver biopsy) via case report forms developed by the NASH CRN Steering Committee. For race and ethnicity, we used a combination variable (white [non-Hispanic], Hispanic, and others). Total caloric intake (Kcal/day) was calculated based on self-reported usual eating habits over the prior year provided via the Block 98.2 nutrition questionnaire.²⁸ Levels of physical activity were calculated based on self-reported information on averaged daily activities and regular weekly recreational activities provided via the National Institutes of Health (NIH) physical activity questionnaire.²⁹ Specifically, averaged levels of daily activities (vigorous or strenuous, moderate, or light activities for nonrecreational activities) with time (numbers of hours per day) and all the recreational activities (engaged in at least 15 minutes per week) with time (hours and minutes per week) were self-recorded at enrollment and used to calculate estimated energy expenditures for nonrecreational and recreational physical activities (metabolic equivalent tasks; MET-hours/week).^{29,30} Information on alcohol consumption was collected through a standardized questionnaire (Alcohol Use Disorders Identification Test or AUDIT)³¹ as well as the Block 98.2 nutrition questionnaire and analyzed as a dichotomous variable (any amounts of alcohol within allowable limits for study inclusion vs no).

Statistical Analyses

Data are reported as mean $\pm$ SD for continuous variables or proportion of patients with a condition. We first compared clinical characteristics between the 3 groups: men, premenopausal women, and postmenopausal women by using analysis of variance (ANOVA) or χ^2 tests. Then, we assessed associations between clinical characteristics and fibrosis stages in men, premenopausal women, and postmenopausal women separately using analysis of variance (ANOVA) or χ^2 tests. For the 2 parameters of regional adipose depot sizes (EXT and WAIST) the associations of each depot size on fibrosis were also assessed using multiple linear regression models, adjusting for total caloric intake (Kcal/day) and recreational/nonrecreational MET-hours/week (in order to take into account the magnitude of excess energy). In the models, 3 indicator variables were used for fibrosis stage (1 = stage 1, 2 = stage 2, 3 = advanced, stage 3 or 4) with stage 0 as the reference group to compute adjusted mean differences (vs stage 0), expressed as beta-coefficients.

Multiple ordinal logistic regression models of fibrosis stage on regional adipose depot sizes (EXT and WAIST) were then developed separately. We first included all the potential confounder variables (listed in the “Other study variables”). Then, by manually removing variables that did not influence odds ratios of the primary predictors (ie, EXT and WAIST), we developed the final models. The proportional odds assumption was tested as previously described.³² In cases where the proportional odds assumption was not met, multiple logistic regression analysis using advanced fibrosis (stages 3–4) as a dependent variable was also used. Adjusted cumulative odds ratios (COR) were estimated from the final models developed in each subgroup.³³ *P* values were determined from a likelihood ratio test.

For analyses, we used JMP statistical software version 7.0 (SAS Institute, Inc, Cary, North Carolina) and considered differences statistically significant when the *P* values were less than .05. All *P* values presented are 2-sided and have not been adjusted for multiple comparisons.

Results

Clinical Characteristics

In the total population of 537 subjects, mean age and BMI were 48.0 ± 12.4 years old and 34.6 ± 6.5 ; 39.9% were men, 52.3% had hypertension, 45.3% had diabetes or impaired fasting glucose, 49.2% had hypertriglyceridemia, 64.4% had low HDL-cholesterolemia, 38.0% had high LDL-cholesterolemia, 60.9% had hyperuricemia, and 63.0% of women were postmenopausal. The comparisons of clinical characteristics among men, pre-, and post-menopausal women are presented in Supplementary Table 1 (see supplementary material online at www.cghjournal.org). The prevalence of advanced fibrosis (stage 3 or 4) was significantly different among groups and was highest in postmenopausal women (17.7%, 13.5%, and 36.1% for men, pre-, and post-menopausal women, respectively) (χ^2 test, *P* < .0001 with the alpha-level of .017 for multiple comparison).

The Associations of Peripheral and Abdominal Adipose Depot Sizes With the Stage of Hepatic Fibrosis

The results of the comparisons between clinical characteristics and stages of fibrosis in the 3 subgroups are summarized in Table 1 (A, men; B, premenopausal women; and C, postmenopausal women). In univariate analyses, parameters of regional adipose depot sizes, extremity size (EXT) (*P* = .029), and abdominal size (waist circumference) (*P* = .004) were associated with fibrosis stages only in postmenopausal women (Table 1, C); smaller extremity size (EXT) and larger abdominal size (waist circumference) appeared to be associated with more severe fibrosis.

The correlations between regional adipose depot sizes and fibrosis stages after adjusting for total caloric intake and MET-hours/week from physical activity levels are shown in Figure 1A–C, for men, pre-, and post-menopausal women, respectively. The correlation results differ, depending on sex and menopausal status. There was a positive correlation between fibrosis stage and extremity size (EXT) in premenopausal women, while a negative correlation exists between fibrosis stage and extremity size (EXT) in men and postmenopausal women. These findings implicate that, with a given magnitude of excess energy, men with severe fibrosis (stage 3 or 4) had smaller peripheral adipose depot size compared with ones with stage 0 (difference in adjusted mean, ie, beta coefficient, of extremity size [EXT] = $-.944$, *P* = .03), while premenopausal women with severe fibrosis had larger peripheral adipose depot size compared with ones with stage 0 (beta coefficient and *P* value = 2.218 , *P* = .002). Also, a positive correlation between abdominal size (WAIST) and fibrosis stages in men and postmenopausal women, but not in premenopausal

women, was noted. Based on the models, with a given magnitude of excess energy, men with severe fibrosis had larger abdominal adipose depot size compared with ones with stage 0 (difference in adjusted mean, ie, beta coefficient, of abdominal size [WAIST] = .39, $P = .08$), while postmenopausal women with moderate (stage 2) or severe fibrosis (stages 3–4) had larger abdominal adipose depot size compared with ones with stage 0 (beta coefficient = .63, $P = .005$ for stage 2 and beta coefficient = .53, $P = .01$ for stages 3–4). As expected, there was significant interaction between premenopausal women versus men ($P = .006$) or postmenopausal women ($P = .009$) in the association between fibrosis stage and extremity size (but not waist).

Multiple ordinal logistic regression models developed in the 3 subgroups are summarized in Table 2. After adjusting for other factors, larger extremity size (EXT) was less likely associated with higher histologic stages of fibrosis among men (COR = 0.7, $P = .008$). In contrast, larger extremity size (EXT) was more likely associated with higher histologic stages of fibrosis among premenopausal women (COR = 1.6, $P = .003$). Among postmenopausal women, larger abdominal size (WAIST), but not extremity size (EXT), was more likely associated with higher histologic stages of fibrosis (COR = 1.6, $P = .032$).

In the premenopausal women, the assumption for use of a proportional logistic regression model was weakly met ($P = .04$); therefore, we also performed multiple logistic regression analysis using a binary fibrosis variable (stage 3–4 vs others). The logistic regression model showed consistent results; larger extremity size (EXT) was associated with an increased likelihood of advanced fibrosis (adjusted OR of having advanced fibrosis for 1 U increase in extremity size [EXT] = 3.9 [95% confidence interval, 1.4–10.8], $P = .008$).

Discussion

We have conducted a pilot analysis using data from the NASH CRN, taking into account sex and menopausal status for the purpose of validating our preliminary hypothesis. Our analyses revealed that after adjusting for energy balance (total caloric intake and energy expenditure from physical activity levels), regional anthropometric measures (as surrogates for peripheral and/or abdominal adipose depot sizes) were significantly associated with hepatic fibrosis in sex- and menopausal status-specific manner. Men who preferentially stored fat in peripheral adipose depots (as evidenced by larger extremities with smaller abdominal girths) were less likely to have severe hepatic fibrosis than men who stored less fat in peripheral adipose depots (smaller extremities with larger abdominal girths). In contrast, premenopausal women who had enlarged extremities were at an increased risk of having more severe liver fibrosis. After menopause, however, the relationship between adipose depot size and liver fibrosis became more male-like; postmenopausal women with larger waist circumference were at an increased risk of having more severe hepatic fibrosis.

In this study we investigated the cross-sectional associations between the 2 anthropometric parameters (ie, peripheral and abdominal adipose depot sizes) and fibrosis stages after adjusting for other potentially confounding factors, to provide a basis for future validation studies. The limitations of retrospective cross-sectional association studies preclude assessment of causality and/or pathogenic mechanisms underlying the observed associations. However, the strength of the observed associations justifies further animal, preclinical, and/or clinical studies to elucidate the involved mechanisms.

Previous studies have also suggested an association between regional fat distribution and NAFLD. For example, Cheung et al reported that the presence of dorsocervical lipohypertrophy (ie, buffalo hump) is a strong predictor of the severity of steatohepatitis.²³ The mechanisms underlying the development of a “buffalo hump” remain unknown and

warrant further investigation. Nonetheless, the data are intriguing and potentially pertinent to abnormalities in lipid partitioning because buffalo hump is 1 of the clinical features in patients with lipodystrophy, a condition of impaired peripheral fat storage.^{14,34} Jun et al investigated the associations between regional fat distribution (measured by computed tomography) and the presence of fatty liver disease (as diagnosed by ultrasound) in men and women.²⁴ Among women (but not men), low femoral subcutaneous fat was independently associated with the presence of fatty liver. Further, Perlemuter et al showed by using dual-energy x-ray absorptiometry that leg fat mass was inversely correlated with liver enzymes while trunk fat mass was positively associated with liver enzymes.¹⁷ Unfortunately, these studies did not distinguish pre- from post-menopausal women in their analysis, which may have significantly influenced regional fat distribution and NAFLD susceptibility. Lacking such information, it is difficult to compare the results of these earlier studies with our current work.

The safest place to store surplus calories is peripheral white adipose tissue. When the storage capacity of the peripheral white adipose tissue becomes saturated (eg, due to the lack of preadipocyte differentiation or adipocyte maturation), surplus calories (ie, lipids) will be distributed to visceral adipose tissue or normally lean nonadipose tissues, as seen in patients with lipodystrophy. Thus, it is reasonable to speculate that obese patients who have disproportionately smaller extremities relative to total adiposity (reflecting less-utilized subcutaneous fat depots) may deliver excessive lipids to normally lean tissues, such as the liver, thereby causing “lipotoxicity.” As age advances, peripheral adipogenesis becomes relatively impaired and, at the same time, visceral fat depots increase in size.³⁵ The increase in age and abdominal fat, along with the decrease in energy expenditure and physical activity, are especially notable risk factors for NAFLD among women following menopause.²² Thus, postmenopausal women may suffer from increased lipid delivery to the liver, which could partially explain their higher prevalence of advanced NAFLD. The positive association between extremity sizes and hepatic fibrosis that we observed in premenopausal women is hard to explain at this point. This association was not eliminated or altered after adding the combined ethnicity/race variable in the model, suggesting that the association may not be explained by ethnicity/race (data are not shown). Mechanisms other than lipotoxicity (eg, obesity-related hyperleptinemia with consequent activation of hepatic stellate cells to myofibroblasts or other adipose derived hormones/cytokines) may be involved in fibrosis progression under sufficient estrogen supply. Further investigation is required to delineate the specific mechanisms involved in premenopausal women.

We acknowledge several limitations in this study. We did not assess regional fat mass directly, but used regional anthropometric measures as surrogates. Although our separate analyses in men, pre-, and post-menopausal women partially controlled some differences in lean body mass, our results may have been confounded by variance in lean body mass. Validation studies using more accurate measures for fat distribution (eg, dual energy x-ray absorptiometry scanning or magnetic resonance imaging) are warranted. Further, the cross-sectional study design and analysis does not allow us to address any causality. Regardless of these limitations, our study identified significant associations between regional anthropometric measures and hepatic fibrosis in a sex- and menopausal status-specific manner. Further investigation of peripheral adipogenesis as well as hepatic abilities to guard against lipotoxicity, while taking into account individual energy balance and sex hormone levels in patients with NAFLD, may enrich our understanding of clinical pathobiology and facilitate more individualized diagnostic and therapeutic approaches in the future.

In summary, our analyses show that after normalizing energy balance among a large group of obese/overweight NAFLD patients, regional anthropometric measures that reflect sizes of different adipose depots significantly correlate with severity of hepatic fibrosis in a sex- and

hormonal status-specific manner. Given the limitations and preliminary nature of this study, it remains hypothetical whether impaired peripheral fat storage has a significant impact on disease progression of NAFLD among obese patients. However, further investigation, both basic and clinical, is justified to delineate the dynamic mechanism(s) associated with peripheral and abdominal adipose depot sizes and disease progression in NAFLD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper

ARM	circumference of midupper arm (cm)
BMI	body mass index
COR	cumulative odds ratio
EXT	calculated parameter indicating extremity size
HDL	high-density lipoprotein
HIP	circumference of hip (cm)
IFG	impaired fasting glucose
LDL	low-density lipoprotein
MET	metabolic equivalent of task
NAFLD	nonalcoholic fatty liver disease
WAIST	standardized waist circumference (z-score)

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Figure 1.

The association between regional anthropometric parameters and hepatic fibrosis after adjusting for total calorie intake and physical activity levels. (A) Men, (B) premenopausal women, and (C) postmenopausal women depict the associations between severity of hepatic fibrosis and parameters of peripheral and abdominal adipose depot sizes after taking into consideration the magnitude of excess energy. In each figure, the *horizontal axis* represents fibrosis stages, and the *vertical axis* represents beta coefficients and 95% confidence intervals (*bars and lines*) from the multiple linear regression models.

Table 1
Comparisons of Clinical Characteristics Among Different Fibrosis Stages in NAFLD

	Fibrosis stage				P value ^a
	0	1	2	3-4	
A. Men	n = 62	n = 71	n = 44	n = 38	
Age, y	41 ± 11	44 ± 13	44 ± 12	49 ± 13	.009
Race and ethnicity					.059 ^b
White, %	54.8	68.6	75.0	79.0	
Hispanic, %	29.0	11.4	13.6	7.9	
Other, %	16.1	20.0	11.4	13.2	
Abdominal size (waist circumference, cm)	109.4 ± 12.9	112.9 ± 13.8	111.8 ± 12.6	112.9 ± 15.6	.463
Extremity size (EXT)	0.333 ± 1.756	-0.012 ± 1.926	-0.101 ± 1.466	-0.260 ± 2.042	.486
Current smoking, yes vs no	4.8%	7.0%	4.6%	7.9%	.877 ^b
Current alcohol use, yes vs no	73.7%	64.1%	57.5%	47.4%	.065 ^b
Total calorie intake, Kcal/d	2214 ± 1048	1971 ± 775	2419 ± 1382	2039 ± 964	.136
Nonrecreational physical activities, MET-hours/wk	146.3 ± 97.2	126.5 ± 80.8	147.3 ± 124.2	113.3 ± 77.7	.306
Recreational physical activities, MET-hours/wk	38.9 ± 30.7	38.2 ± 36.5	37.8 ± 45.5	36.0 ± 34.6	.987
Sleep apnea, yes vs no	14.5%	22.5%	13.6%	23.7%	.428 ^b
Hypertension, yes vs no	38.7%	43.7%	59.1%	63.2%	.041 ^b
Diabetes mellitus/IFG, yes vs no	32.3%	45.1%	50.0%	52.6%	.151 ^b
Hypertriglyceridemia, yes vs no	38.7%	57.8%	68.2%	39.5%	.007 ^b
Low-HDL cholesterol, yes vs no	54.8%	69.0%	63.6%	55.3%	.313 ^b
High-LDL cholesterol, yes vs no	33.9%	40.9%	49.0%	23.7%	.282 ^b
Hyperuricemia, yes vs no	85.5%	88.7%	79.6%	57.9%	<.001 ^b
Depression, yes vs no	5.3%	12.5%	18.0%	6.1%	.173 ^b
HOMA-IR	4.2 ± 2.5	7.4 ± 10.0	5.5 ± 3.7	7.1 ± 5.9	.033
B. Premenopausal women	n = 36	n = 41	n = 26	n = 16	
Age, y	38 ± 9	39 ± 9	42 ± 10	41 ± 10	.460
Race and ethnicity					.377 ^b

	Fibrosis stage				P value ^a
	0	1	2	3-4	
White, %	66.7	63.4	65.4	81.3	
Hispanic, %	33.3	26.8	26.9	12.5	
Other, %	0.0	9.8	7.7	6.3	
Abdominal size (waist circumference, cm)	110.3 ± 14.1	107.6 ± 14.1	110.2 ± 13.8	115.0 ± 13.8	.365
Extremity size (EXT)	-0.494 ± 1.375	0.198 ± 1.982	0.061 ± 1.895	0.330 ± 1.884	.330
Current smoking, yes vs no	11.1%	14.6%	11.5%	18.8%	.876 ^b
Current alcohol use, yes vs no	60.6%	55.0%	48.0%	37.5%	.455 ^b
Total calorie intake, Kcal/d	1734 ± 795	1798 ± 900	1525 ± 786	1707 ± 700	.613
Nonrecreational physical activities, MET-hours/wk	120.9 ± 76.2	124.9 ± 101.6	140.1 ± 97.0	78.9 ± 50.6	.318
Recreational physical activities, MET-hours/wk	37.0 ± 33.6	39.7 ± 39.1	39.5 ± 32.9	22.0 ± 22.4	.496
Sleep apnea, yes vs no	2.8%	9.8%	19.2%	25.0%	.070 ^b
Hypertension, yes vs no	8.3%	41.5%	31.7%	50.0%	.001 ^b
Diabetes mellitus/IFG, yes vs no	36.1%	39.0%	46.2%	37.5%	.877 ^b
Hypertriglyceridemia, yes vs no	55.6%	58.5%	42.3%	50.0%	.604 ^b
Low-HDL cholesterol, yes vs no	75.0%	73.2%	88.5%	75.0%	.493 ^b
High-LDL cholesterol, yes vs no	38.9%	24.4%	42.3%	50.0%	.228 ^b
Hyperuricemia, yes vs no	50.0%	41.5%	57.7%	56.3%	.562 ^b
Depression, yes vs no	26.7%	27.5%	20.8	18.2%	.879 ^b
HOMA-IR	4.9 ± 3.7	5.1 ± 3.9	5.3 ± 3.2	7.1 ± 3.3	.226
C. Postmenopausal women	n = 42	n = 46	n = 41	n = 73	
Age, y	56 ± 8	56 ± 8	56 ± 7	59 ± 7	.036
Race and ethnicity					.955 ^b
White, %	81.0	87.0	82.9	78.1	
Hispanic, %	7.1	6.5	9.8	6.9	
Other, %	11.9	6.5	7.3	15.1	
Abdominal size (waist circumference, cm)	102.1 ± 12.9	103.8 ± 14.4	110.7 ± 12.7	109.9 ± 14.5	.004
Extremity size (EXT)	0.393 ± 1.218	0.383 ± 1.559	-0.078 ± 2.461	-0.441 ± 1.491	.029
Current smoking, yes vs no	9.5%	8.7%	4.9%	11.0%	.748 ^b

	Fibrosis stage				P value ^a
	0	1	2	3-4	
Current alcohol use, yes vs no	46.2%	52.3%	46.2%	33.3%	.213 ^b
Total calorie intake, Kcal/d	1691 ± 738	1728 ± 801	1747 ± 884	1626 ± 998	.888
Nonrecreational physical activities, MET-hours/wk	107.0 ± 68.1	94.6 ± 57.9	107.3 ± 63.5	81.9 ± 49.9	.125
Recreational physical activities, MET-hours/wk	50.0 ± 41.1	33.4 ± 28.5	38.9 ± 38.6	35.6 ± 31.4	.148
Sleep apnea, yes vs no	7.1%	15.2%	17.1%	30.1%	.018 ^b
Hypertension, yes vs no	52.4%	65.2%	61.0%	76.7%	.054 ^b
Diabetes mellitus/IFG, yes vs no	40.5%	34.8%	51.2%	64.4%	.008 ^b
Hypertiglyceridemia, yes vs no	50.0%	58.7%	31.7%	42.5%	.072 ^b
Low-HDL cholesterol, yes vs no	61.9%	56.5%	56.1%	64.4%	.770 ^b
High-LDL cholesterol, yes vs no	42.9%	43.5%	61.0%	26.0%	.003 ^b
Hyperuricemia, yes vs no	47.6%	52.2%	46.3%	43.8%	.849 ^b
Depression, yes vs no	29.0%	27.5%	29.7%	42.1%	.371 ^b
HOMA-IR	4.7 ± 3.4	5.9 ± 5.7	5.8 ± 4.4	9.0 ± 7.3	<.001

EXT, calculated parameter indicating extremity size; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model of Assessment - Insulin Resistance; IFG, impaired fasting glucose; LDL, low-density lipoprotein; MET, metabolic equivalent of task; NAFLD, nonalcoholic fatty liver disease.

^a P values were from χ^2 test or analysis of variance (ANOVA).

^b χ^2 test.

Table 2

Adjusted Cumulative Odds Ratios of Adipose Depot Sizes and Their Association With the Severity of Fibrosis in Men, Premenopausal, and Postmenopausal Women

	Men			Premenopausal women			Postmenopausal women		
	COR (95% CI)	P value		COR (95% CI)	P value		COR (95% CI)	P value	
Age, 10-y increase	1.4 (1.0–1.8)	.021		—	—		1.7 (1.1–2.6)	.014	
Race, white	2.3 (1.1–4.7)	.021		—	—		—	—	
Extremity size (EXT), 1 U increase	0.7 (0.6–0.9)	.008		1.6 (1.2–2.2)	.003		1.0 (0.8–1.3)	.711	
Abdominal size (WAIST), 1 U increase	0.8 (0.5–1.2)	.310		1.3 (0.7–2.5)	.357		1.6 (1.0–2.5)	.032	
Current smoking	—	—		—	—		—	—	
Current alcohol use	0.5 (0.3–0.8)	.008		—	—		—	—	
Total calorie intake, 500 Kcal/d increase	0.9 (0.8–1.1)	.315		1.0 (0.8–1.3)	.955		0.9 (0.8–1.1)	.424	
Nonrecreational physical activities, 10 MET-h/wk increase	1.0 (1.0–1.1)	.970		1.0 (0.9–1.0)	.820		1.0 (0.9–1.0)	.562	
Recreational physical activities, 10 MET-h/wk increase	1.0 (1.0–1.0)	.375		0.9 (0.8–1.0)	.074		1.0 (0.9–1.0)	.861	
Sleep apnea	1.5 (0.7–3.5)	.331		2.6 (0.6–10.6)	.181		1.4 (0.6–3.4)	.440	
Diabetes mellitus	1.5 (0.8–2.8)	.169		—	—		—	—	
Hypertension	—	—		2.1 (0.9–4.8)	.078		—	—	
Hypertriglyceridemia	—	—		0.3 (0.1–0.7)	.009		—	—	
Low-HDL cholesterol	—	—		1.5 (0.5–4.2)	.442		—	—	
High-LDL cholesterol	—	—		—	—		0.7 (0.4–1.2)	.179	
Hyperuricemia	0.2 (0.1–0.5)	<.001		1.8 (0.8–4.4)	.183		—	—	
Homa-IR, 5 U increase	—	—		1.2 (0.7–2.2)	.555		1.4 (1.0–1.8)	.040	

CI, confidence interval; COR, adjusted cumulative odds ratio; EXT, calculated parameter indicating extremity size; MET, metabolic equivalent of task; WAIST, standardized waist circumference (z-score).