Identification and Characterization of Metabolically Benign Obesity in Humans

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Background: Obesity represents a risk factor for insulin resistance, type 2 diabetes mellitus, and atherosclerosis. In addition, for any given amount of total body fat, an excess of visceral fat or fat accumulation in the liver and skeletal muscle augments the risk. Conversely, even in obesity, a metabolically benign fat distribution phenotype may exist.

Methods: In 314 subjects, we measured total body, visceral, and subcutaneous fat with magnetic resonance (MR) tomography and fat in the liver and skeletal muscle with proton MR spectroscopy. Insulin sensitivity was estimated from oral glucose tolerance test results. Subjects were divided into 4 groups: normal weight (body mass index [BMI] [calculated as weight in kilograms divided by height in meters squared], <25.0), overweight (BMI, 25.0-29.9), obese–insulin sensitive (IS) (BMI, ≥30.0 and placement in the upper quartile of insulin sensitivity), and obese–insulin resistant (IR) (BMI, ≥30.0 and placement in the lower 3 quartiles of insulin sensitivity).

Results: Total body and visceral fat were higher in the overweight and obese groups compared with the normal-weight group ($P<.05$); however, no differences were observed between the obese groups. In contrast, ectopic fat in skeletal muscle ($P<.001$) and particularly the liver (4.3%±0.6% vs 9.5%±0.8%) and the intima-media thickness of the common carotid artery (0.54±0.02 vs 0.59±0.01 mm) were lower and insulin sensitivity was higher (17.4±0.9 vs 7.3±0.3 arbitrary units) in the obese-IS vs the obese-IR group ($P<.05$). Unexpectedly, the obese-IS group had almost identical insulin sensitivity and the intima-media thickness was not statistically different compared with the normal-weight group (18.2±0.9 AU and 0.51±0.02 mm, respectively).

Conclusions: A metabolically benign obesity that is not accompanied by insulin resistance and early atherosclerosis exists in humans. Furthermore, ectopic fat in the liver may be more important than visceral fat in the determination of such a beneficial phenotype in obesity.

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THE PREVALENCE OF OBESITY IS increasing worldwide, and this epidemic is accompanied by a high incidence of type 2 diabetes mellitus and cardiovascular disease.[1] Although overall obesity delineates an important risk factor for these diseases, it is recognized that body fat distribution additionally represents an independent determinant. For any given amount of total body fat, individuals with a selective excess of intra-abdominal (visceral) adipose tissue, estimated by an increased waist circumference, are at substantially higher risk of being insulin resistant and having a cardiovascular risk profile.[2-8] Excess visceral fat accumulation results from the inability of adipose tissue to appropriately store the excess energy. According to this hypothesis, energy is deposited as fat intra-abdominally and in ectopic depots such as the liver and the skeletal muscle, resulting in an increased risk of type 2 diabetes mellitus and cardiovascular disease. In contrast, when extra energy is directed toward the subcutaneous depots or is burned within the mitochondria in the liver and muscle, the individual, although having a positive energy balance, will be protected against the development of these diseases.[9] Accordingly, it may be possible to identify a metabolically benign fat distribution phenotype even in the obese spectrum. Such individuals may be protected from type 2 diabetes mellitus and cardiovascular disease.

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With the present study, we set out to identify subjects with metabolically benign obesity and to determine what factors characterize this phenotype. The iden-

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tification of such a phenotype may allow better study of the pathophysiologic mechanisms of insulin resistance and cardiovascular disease and may facilitate a more careful selection of individuals for strategies to prevent these diseases. To test our hypotheses, we used precise phenotyping methods, such as magnetic resonance (MR) tomography to measure total body fat content and fat content in visceral as well as in subcutaneous depots and proton (^{1}H)–MR spectroscopy to determine fat deposition in ectopic tissues (liver and skeletal muscle).

METHODS

SUBJECTS

Data from 314 white adults from the southern part of Germany were included in the analyses. They participated in an ongoing study on the pathophysiologic mechanisms of type 2 diabetes mellitus.[10] Individuals were included in the study when they fulfilled at least 1 of the following criteria: a family history of type 2 diabetes mellitus, a body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of greater than 27, and a previous diagnosis of impaired glucose tolerance or gestational diabetes. All subjects had measurements of body fat distribution determined by MR imaging. They were considered healthy according to results of a physical examination and routine laboratory tests. The participants had no history of liver disease and did not consume more than 2 alcoholic drinks per day. Informed written consent was obtained from all participants and the local medical ethics committee approved the protocol.

ASSESSMENTS

Body fat was measured by the bioelectrical impedance method (RJL Systems, Detroit, Michigan). Waist circumference was measured at the midpoint between the lateral iliac crest and lowest rib, which corresponded to the level of the umbilicus in most subjects. Furthermore, we measured total, visceral, and subcutaneous abdominal fat with an axial T1-weighted fast spin-echo technique using a 1.5-T whole-body imager (Magnetom Sonata; Siemens Medical Solutions, Erlangen, Germany).[11]

The individuals completed a standardized self-administered and validated questionnaire to measure physical activity, and a habitual physical activity score was calculated.[12] Alcohol intake was also estimated from a standardized questionnaire.

Liver fat was measured by means of localized ^{1}H-MR spectroscopy.[13] The amount of intramyocellular lipids (IMCL) and lipids interlaced between the muscle fibers (extramyocellular lipid [EMCL]) of the tibialis anterior and soleus muscles were determined as previously described.[13] The discrimination between IMCL and EMCL was possible for 277 subjects within the tibialis anterior and for 218 subjects within the soleus muscles.

All individuals underwent a 75-g oral glucose tolerance test (OGTT). We obtained venous plasma samples at 0, 30, 60, 90, and 120 minutes for determination of plasma glucose, insulin, and C-peptide levels. Glucose tolerance was determined according to the 1997 World Health Organization diagnostic criteria.[14]

The intima-media thickness (IMT) of the common carotid artery was measured with high-resolution ultrasonography as previously described.[15]

ANALYTICAL PROCEDURES

The blood glucose level was determined using a bedside glucose analyzer (glucose oxidase method; Yellow Springs Instruments, Yellow Springs, Colorado). The plasma insulin concentration was determined using a microparticle enzyme immunoassay (Abbott Laboratories, Tokyo, Japan), and the serum free fatty acid (FFA) concentration was measured with an enzymatic method (WAKO Chemicals, Neuss, Germany). The plasma C-peptide level was measured using radioimmunoassay (Byk-Sangtec Diagnostica GmbH & Co KG, Dietzenbach, Germany). Plasma samples were frozen immediately and stored at –80°C, and fasting plasma levels of adiponectin were determined using enzyme-linked immunosorbent assays (Linco Research, Inc, St Charles, Missouri).

CALCULATIONS

Insulin sensitivity from the OGTT was calculated as proposed by Matsuda and DeFronzo[16] and with the homeostasis model assessment of insulin resistance index.[17] The area under the curve (AUC) for plasma insulin during the OGTT was calculated as $0.5 \times [(0.5 \times \mathrm{Ins}_0) + \mathrm{Ins}_{30} + \mathrm{Ins}_{60} + \mathrm{Ins}_{90} + (0.5 \times \mathrm{Ins}_{120})]$, where Ins_0, Ins_{30}, Ins_{60}, Ins_{90}, and Ins_{120} represent the plasma insulin level 0, 30, 60, 90, and 120 minutes, respectively, from the beginning of the OGTT. The AUC for plasma C-peptide was calculated analogously. Insulin clearance was estimated from the OGTT as the C-peptide AUC divided by the insulin AUC.

STATISTICAL ANALYSES

Unless otherwise stated, data are given as mean ± SE. Data that were not normally distributed (eg, liver fat, insulin sensitivity, and body fat distribution; Shapiro-Wilk *W* test) were logarithmically transformed and a normal distribution of these measurements was achieved. Subjects were first divided into 3 groups on the basis of their body mass index: normal weight (BMI, <25.0), overweight (BMI, 25.0-29.9), and obese (BMI, ≥30). In the obese group, men and women separately were further divided into quartiles according to their insulin sensitivity estimated from the OGTT results. Men and women in the upper quartiles were then combined and represented insulin-sensitive obese subjects (obese-IS group), while men and women in the other 3 quartiles represented insulin-resistant obese subjects (obese-IR group). Differences in group means were tested using the Tukey-Kramer test to accommodate different kinds of multiple comparisons. Receiver operating characteristic curve analyses were used to determine the predictive effect of variables to separate groups. $P \leq .05$ was considered statistically significant. We used the statistical software package JMP 4.0 (SAS Institute Inc, Cary, North Carolina).

RESULTS

STUDY GROUP CHARACTERISTICS

The 314 subjects (121 men and 193 women) had a mean age of 45 (range, 18-69) years. Anthropometrics and metabolic characteristics covered a wide range that was particularly large for total body fat, body fat distribution, ectopic fat in the liver and skeletal muscle, and insulin sensitivity. Glucose tolerance measured by the OGTT ranged from 72.0 to 277.5 mg/dL (to convert glucose to millimoles per liter, multiply by 0.0555), and 10 subjects were found to have undiagnosed type 2 diabetes mellitus. A total of 102 subjects had fatty liver (liver fat, >5.56%).[18] Insulin sensitivity estimated from the OGTT strongly correlated with measures of adiposity as BMI ($r = -0.45$, $P < .001$), waist circumference ($r = -0.42$, $P < .001$), total body fat (as determined by MR tomography) ($r = -0.36$, $P < .001$), subcutaneous abdominal fat ($r = -0.38$, $P < .001$), and vis-

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Table 1. Subject Characteristics

Characteristic	Group[a]				*P* Value[b]
			Obese		
	Normal Weight	Overweight	Obese-IS	Obese-IR	
Demographic and anthropometric					
Sex, No. F/M	45/9	70/63	19/12	59/37	<.001[c]
Age, y	44.8 ± 1.6*	45.6 ± 1.0*	46.5 ± 1.9*	45.8 ± 1.2*	.92
Weight, kg	64.8 ± 1.0*	82.9 ± 0.8†	99.6 ± 2.2‡	98.7 ± 1.4‡	<.001
Height, cm	169.0 ± 1.0*	172.0 ± 1.0*	172.0 ± 1.0*	170.0 ± 1.0*	.03
Waist circumference, cm	79.2 ± 1.0*	94.0 ± 0.7†	104.6 ± 1.7‡	107.4 ± 1.0‡	<.001
Body fat, %[d]	26.9 ± 1.0*	29.9 ± 0.6†	36.6 ± 1.3‡	36.9 ± 0.8‡	<.001
Fatty liver, % of subjects	6*	27†	29†	56‡	<.001[c]
Metabolic					
Fasting glucose level, mg/dL	92.25 ± 1.44*	95.14 ± 0.09*†	91.17 ± 1.26*	97.30 ± 0.09†	.001
2-h Glucose level, mg/dL	125.41 ± 5.05*	124.50 ± 2.70*	122.34 ± 5.95*	135.32 ± 3.96*	.08
Fasting insulin level, μIU/mL	5.33 ± 0.29*	7.92 ± 0.43†	5.62 ± 0.29*	13.10 ± 0.58‡	<.001
Fasting FFA level, mg/dL	19.7 ± 0.9*	17.0 ± 0.6†	21.7 ± 2.2*	19.0 ± 0.6*	.001
Cholesterol level, mg/dL					
Total	198 ± 5*	195 ± 3*	193 ± 6*	193 ± 3*	.91
LDL	121 ± 4*	125 ± 3*	117 ± 5*	127 ± 3*	.24
HDL	61 ± 2*	51 ± 1†	53 ± 2†	49 ± 1†	<.001
Triglycerides level, mg/dL	96 ± 5*	122 ± 8*†	142 ± 30*†	132 ± 10*†	.02
HOMA-IR value, AU	1.43 ± 0.10*	2.16 ± 0.12†	1.45 ± 0.06*	3.63 ± 0.15‡	<.001
Insulin clearance, AU	6.75 ± 0.30*	5.73 ± 0.16†	6.35 ± 3.10*†	4.37 ± 0.11‡	<.001
Adiponectin level, μg/mL	18.53 ± 1.74*	13.11 ± 0.59†	16.55 ± 1.73*†	12.41 ± 0.61†	<.001

Abbreviations: AU, arbitrary units; FFA, free fatty acids; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance index; LDL, low-density lipoprotein; obese-IR, obese–insulin resistant; obese-IS, obese–insulin sensitive.

SI conversion factors: To convert total, HDL, and LDL cholesterol to millimoles per liter, multiply by 0.0259; FFA to millimoles per liter, by 0.0355; glucose to millimoles per liter, by 0.0555; insulin to picomoles per liter, by 6.945; and triglycerides to millimoles per liter, by 0.0113.

[a] Data are given as mean ± SE unless otherwise indicated. Values that are not connected by the same symbol (*, †, ‡) are statistically different from each other.

[b] Determined by 1-way analysis of variance.

[c] By χ^2 test.

[d] Body fat was measured using the bioelectrical impedance method.

ceral fat (r=–0.41, P<.001), as well as IMCL (r=–0.27, P<.001), liver fat (r=–0.54, P<.001), and plasma adiponectin level (r=0.22, P<.001).

INDIVIDUAL GROUP CHARACTERISTICS

Demographics and Simple Measurements of Adiposity

The characteristics of the 4 groups are shown in **Table 1**. The sex distribution was different between the normal-weight (17% men), overweight (47% men), and obese (both groups, 39% men) groups. Of importance, the sex distribution was identical between the obese groups. There were also no statistically significant differences in age and height between these groups. The habitual physical activity score decreased with increasing BMI (total n=308; normal-weight group, 8.34±0.15; overweight, 8.14±0.10; obese-IS, 8.05±0.22; and obese-IR, 7.81±0.11; 1-way analysis of variance, P=.04); however, the differences between the obese groups were not statistically significant (P=.32). Subjects who never (n=46), rarely (n=234), or regularly (≤2 alcoholic drinks per day, n=28) consumed alcohol were evenly represented in the groups (χ^2 test=0.42). Upon stratification, we expected to find differences in body weight, BMI (**Figure 1**A), body fat, and waist circumference between the normal-weight, overweight, and obese groups. However, we did not expect to find very similar measurements that were not statistically significantly different for these variables between the obese-IS and obese-IR groups.

Body Fat Distribution Measured by MR Tomography

We further investigated whether similar findings were apparent when we more precisely determined total adiposity and body fat distribution applying the MR techniques. Again, although differences between the normal-weight, overweight, and both obese groups analyzed together were detected for total body fat (Figure 1B), subcutaneous abdominal fat (Figure 1C), and visceral fat (Figure 1D), we did not expect to find similar and statistically nonsignificant results for visceral fat between the obese-IS and obese-IR groups.

Ectopic Fat Measured by ^{1}H-MR Spectroscopy

We found no difference in IMCL between the normal-weight, overweight, and obese-IR groups for the tibialis anterior and soleus muscles. However, the obese-IS group had significantly lower IMCL in the tibialis anterior muscle than did the obese-IR group (Figure 1E). Intramyocellular fat in the soleus muscle was also lower in the obese-IS group compared with the obese-IR group; however, this

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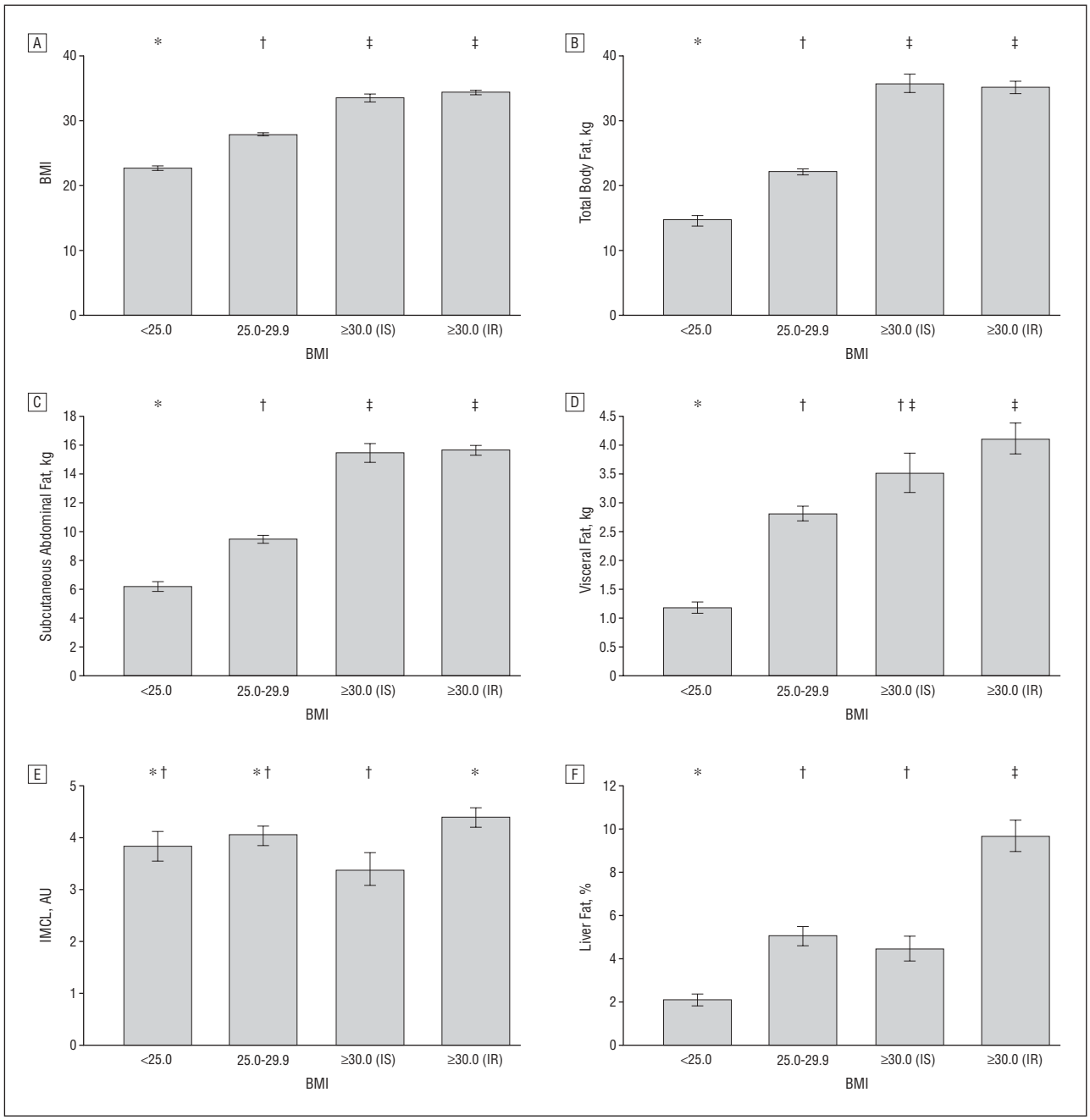

Figure 1. Body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) (A), total body fat (B), subcutaneous abdominal body fat (C), visceral fat (D), intramyocellular lipids (IMCL) in the tibialis anterior muscle (E), and liver fat (F) among subjects characterized for BMI and insulin sensitivity (obese individuals). Obese individuals were divided into those who were insulin sensitive (IS) (defined as being in the upper quartile of insulin sensitivity) and those who were insulin resistant (IR) (defined as being in the lower 3 quartiles of insulin sensitivity). Bars and limit lines represent mean and standard error values, respectively. Values that are not connected by the same symbol are statistically different from each other at $P < .05$ after correction for multiple comparisons.

difference was not statistically significant, possibly owing to the smaller sample size. The percentage of liver fat was lower in the normal-weight group compared with the overweight and obese-IS groups, not statistically significantly different between the overweight and obese-IS groups, and highest in the obese-IR group (Figure 1F). The latter observation was statistically different compared with all other groups (eg, obese-IR group vs obese-IS group, 9.5%±0.8% vs 4.3%±0.6%). Similar findings were obtained when we determined the prevalence of fatty liver among the 4 groups (Table 1) (percentage of liver fat in 102 subjects with fatty liver: normal-weight group, 7.49%±1.16%; overweight group, 11.97%±0.98%; obese-IS group, 9.02%±0.68%; and obese-IR group, 14.60%±0.89%).

We next analyzed the relationships between ectopic fat and the 4 groups separately in women and men. Similar to the results of the previous analyses, in women (n=193), the percentage of liver fat was lower in the normal-weight group compared with all other groups, was

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Table 2. Ectopic Fat in the Liver and the Tibialis Anterior Muscle in Females and Males

	Group[a]				
			Obese		
	Normal Weight	Overweight	Obese-IS	Obese-IR	*P* Value[b]
Women, No.	45	70	19	59	
Liver fat, %	1.95 ± 0.29*	3.80 ± 0.53†	3.53 ± 0.66†	8.80 ± 1.01‡	<.001
Intramyocellular lipids, AU[c]	3.77 ± 0.33*	4.00 ± 0.22*†	4.04 ± 0.40*†	4.62 ± 0.23†	.03
Men, No.	9	63	12	37	
Liver fat, %	2.27 ± 0.46*	6.21 ± 0.74†	5.63 ± 1.10*†‡	10.53 ± 1.23‡	<.001
Intramyocellular lipids, AU[c]	4.01 ± 0.67*	4.06 ± 0.26*	2.29 ± 0.37†	4.08 ± 0.26*	<.001

Abbreviations: AU, arbitrary units; obese-IR, obese–insulin resistant; obese-IS, obese–insulin sensitive.
[a]Data are given as mean ± SE unless otherwise indicated. Values that are not connected by the same symbol (*, †, ‡) are statistically different from each other.
[b]Determined by 1-way analysis of variance.
[c]Determined in the tibialis anterior muscle. Data were available in 170 women and 107 men.

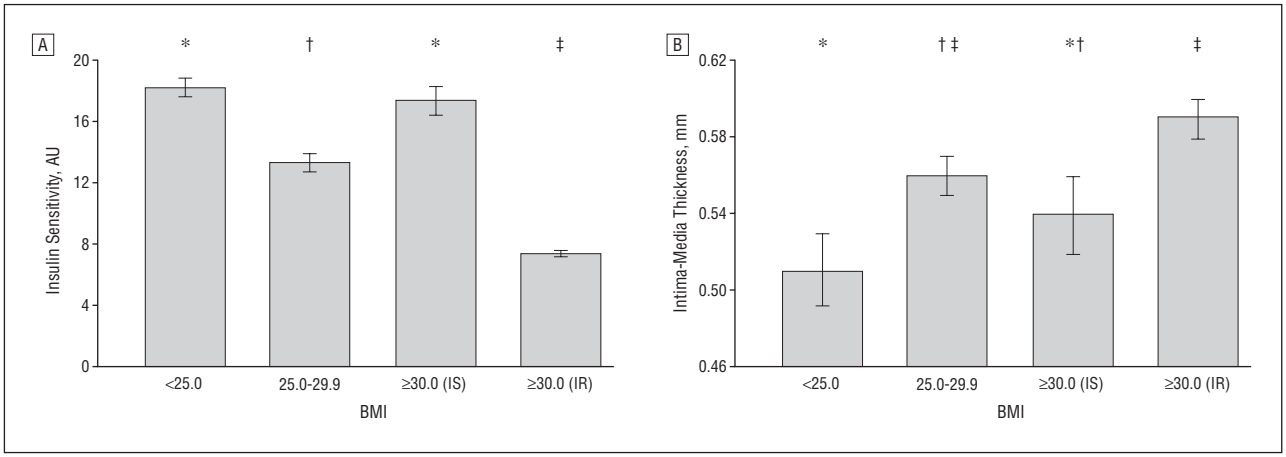

Figure 2. Insulin sensitivity (A) and intima-media thickness of the carotid artery (B) among subjects characterized for body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) and insulin sensitivity (obese individuals). Obese individuals were divided into those who were insulin sensitive (IS) (defined as being in the upper quartile of insulin sensitivity) and those who were insulin resistant (IR) (defined as being in the lower 3 quartiles of insulin sensitivity). Bars and limit lines represent mean and standard error values, respectively. Values that are not connected by the same symbol are statistically different from each other at $P < .05$ after correction for multiple comparisons.

not statistically different between the overweight and obese-IS groups, and was highest in the obese-IR group (**Table 2**). The level of IMCL in the tibialis anterior muscle was not different between the normal-weight, overweight, and obese-IS groups. The normal-weight group had a significantly lower IMCL measurement in the tibialis anterior muscle than did the obese-IR group (Table 2). In men (n = 121), the percentage of liver fat was lower in the normal-weight group compared with the overweight and obese-IR groups and was not statistically different compared with the obese-IS group. The percentage of liver fat was lower in the obese-IS group compared with the obese-IR group; however, this difference was not statistically significant ($P = .054$), most likely because of the small sample size. The level of IMCL was lowest in the obese-IS group, although it was not statistically significantly different among the other groups (Table 2).

Insulin Sensitivity

We then investigated the magnitude of the differences in insulin sensitivity between the groups. As expected, we found lower insulin sensitivity in the overweight (13.3 ± 0.6 AU) and obese-IR (7.3 ± 0.3 AU) groups compared with the normal-weight group. Although insulin sensitivity was lower in the overweight group compared with the normal-weight group, we found the obese-IS group (mean BMI, 34) to have insulin sensitivity that was almost identical to that in the normal-weight group (mean BMI, 23; 17.4 ± 0.3 vs 18.2 ± 0.9 AU) (**Figure 2**A). Similar results were observed when we determined the homeostasis model assessment of insulin resistance index value and when we calculated insulin clearance (Table 1). Circulating adiponectin levels were highest in the normal-weight group, significantly different when the normal-weight group was compared with the overweight and obese-IR groups, but not statistically different when the normal-weight group was compared with the obese-IS group (Table 1).

Intima-Media Thickness

Finally, to search for differences in early markers of atherosclerosis between the groups, we measured the IMT

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of the common carotid artery. The IMT (adjusted for its strong determinant age) was lowest in the normal-weight group (0.51±0.02 mm), and the value was statistically significant compared with the other groups except for the obese-IS group. The obese-IS group also had significantly lower IMT measurements compared with the obese-IR group (0.54±0.02 vs 0.59±0.01 mm; Figure 2B).

Markers of High Insulin Sensitivity in Obesity

Having established that a group of insulin-sensitive individuals with low IMT can be identified among obese subjects, we investigated which circulating measures in blood may serve as markers for such a metabolically benign obesity. For this we analyzed the predictive values of fasting insulin, glucose, and C-peptide levels, which are widely used measurements in clinical routine, as well as adiponectin and FFA concentrations. We found the following AUCs for predicting high insulin sensitivity (being in the obese-IS group) among all obese subjects: insulin (0.97), C-peptide (0.91), glucose (0.70), adiponectin (0.63), and FFA (0.58). For the strongest determinant, fasting insulin, a value below 7.63 μIU/mL (to convert insulin to picomoles per liter, multiply by 6.945) predicted being in the obese-IS group with a sensitivity of 0.97 and a specificity of 0.88.

COMMENT

In the present study, we identified subjects who were obese but had high insulin sensitivity and low IMT, an early marker of atherosclerosis. Compared with normal-weight individuals, we expected to find a moderate decrease in insulin sensitivity in obese but relatively insulin-sensitive subjects. However, insulin sensitivity in these subjects was similar and not statistically different compared with normal-weight individuals. Altogether, 10% of the study population and 25% of the obese subjects had a high insulin sensitivity phenotype or "metabolically benign obesity." When we undertook these analyses, we hypothesized that such a phenotype may exist. This assumption was based on data from the literature.[19] In a small study in Pima Indians and white subjects, insulin sensitivity was shown to decline with increasing obesity.[20] However, in heavily obese Pima Indians, a further decline in insulin sensitivity was absent and, after correction for aerobic fitness, increased adiposity accounted for only 25% of the variability in insulin sensitivity.[20] In a study aimed at identifying insulin-resistant individuals, 17% of the overweight and obese subjects were found to be relatively insulin sensitive.[21] Moreover, as reviewed by Karelis et al,[22] approximately 20% of the general population can be categorized as obese but metabolically healthy. In contrast, 18% of the population were found to have a normal body weight or were slightly overweight but displayed severe metabolic abnormalities.[22] With the present data, we substantiate the hypothesis that a metabolically benign obesity for the phenotypes insulin sensitivity and early atherosclerosis can be identified in a population at risk for type 2 diabetes mellitus. Therefore, in the context that insulin sensitivity largely varies in obesity and strongly predicts impaired glucose tolerance and the metabolic syndrome,[23] it is necessary to characterize individuals for body fat distribution and insulin sensitivity in addition to total adiposity.

The second finding of the present study was that measurement of visceral fat provided a powerful tool to discriminate between insulin-sensitive and insulin-resistant subjects within the normal-weight and overweight range; however, in the obese spectrum, the predictive effect of visceral fat was relatively weak. Visceral fat was lower in the obese-IS group compared with the obese-IR group, but this difference was not statistically significant. In addition, waist circumference was almost identical between the groups. These findings were unexpected considering the interesting data from Wajchenberg et al,[24] who showed that obese women with high visceral fat mass were more insulin resistant than obese women with lower visceral fat. There are 2 explanations for the different results of the studies. In the study by Wajchenberg et al, women with lower levels of visceral fat had a BMI that was lower by 2.5 compared with women who had high levels of visceral fat. Although this difference was not statistically significant, it may have affected the results. Furthermore, we used a whole-body MR imaging technique to measure total visceral fat volume, whereas Wajchenberg et al used computed tomography at the L4-L5 level as a measurement of visceral fat. Thus, methodological differences in the estimation of visceral adiposity may explain the results. Nevertheless, in agreement with that study, we consider that excess fat,[25-28] and particularly visceral fat[29] when it is inflamed, largely affects insulin sensitivity; however, with increasing total adiposity, factors other than excess visceral fat may become more important for regulating insulin sensitivity. This hypothesis is supported by our data showing that plasma adiponectin levels, which are strongly associated with visceral fat mass,[30] did not differ between the obese groups.

Factors regulating lipid oxidation and lipogenesis in ectopic tissues such as the liver and muscle may be relevant. Our third finding—different amounts of ectopic fat in skeletal muscle and the liver—substantiates this hypothesis. Among all of the phenotypes and metabolic variables tested, the difference in liver fat emerged as the largest, with the obese-IS group having 54% less fat accumulation in the liver than the equally fat obese-IR group. Several studies have consistently documented the predominant role of fatty liver in the regulation of glucose and lipid metabolism.[31-34] Elevated fat accumulation in the liver is accompanied by atherosclerosis and the metabolic syndrome,[35-39] even independent of visceral adiposity.[40,41] Thus, our present data identifying the percentage of liver fat as a key determinant of a metabolically benign obesity further underscores that the prevention and reduction of fat accumulation in the liver may provide a powerful tool for maintaining insulin sensitivity and for preventing atherosclerosis even under the growing burden of increasing adiposity.

Having identified such a beneficial phenotype, we tested the power of circulating variables to predict this condition. Fasting insulin level turned out to be the strongest predictor. The cutoff of 7.63 μIU/mL for fasting insulin concentrations identified subjects with

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this beneficial phenotype with a relatively high sensitivity and specificity among obese individuals in our population.

Mechanisms that are involved in the generation of a metabolically benign obesity are not fully understood. Because the cannabinoid 1 receptor is expressed in the liver, where it enhances the expression of the lipogenic transcription factors,[42] the endocannabinoid system may play a role in the determination of the observed phenotypes. Genetic variations in genes involved in lipid metabolism, such as adiponectin receptor 1 (*ADIPOR1* [OMIM 607945]) and hepatic lipase (*LIPC* [OMIM 151670]), as well as the upstream transcription factor 1, displaying modulatory effects on hepatic lipase, which are associated with fat accumulation in the liver,[13,43] may also represent candidates for a metabolically benign obesity. In support of this hypothesis, in a subgroup of 51 individuals, both protective alleles at the single-nucleotide polymorphisms –8503G in *ADIPOR1* and –514C in *LIPC*, were more frequently found in the obese-IS group compared with the obese-IR group (χ^2 test, $P = .005$ and $P < .001$, respectively; data not shown). Furthermore, increased aerobic fitness, which is associated with less fat accumulation in the skeletal muscle in untrained subjects[44] and with less fat accumulation in the liver,[45] may be important. In the present study, maximal aerobic capacity on a cycle ergometer, an estimate of aerobic fitness, was not different between the obese groups (data not shown). Nevertheless, because our group of obese subjects was relatively small, we cannot definitively answer whether the aforementioned factors play a major role in the determination of metabolically benign obesity. Accordingly, this is a limitation of the present study. Furthermore, it remains to be determined whether our findings in white subjects can be replicated in other races.

In conclusion, we provide evidence that a metabolically benign obesity can be identified and that it may protect from insulin resistance and atherosclerosis. Furthermore, our data suggest that ectopic fat accumulation in the liver may be more important than visceral fat in the determination of such a beneficial phenotype in obesity.

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