

# Metabolically Healthy but Obese Women Have an Intermediate Cardiovascular Risk Profile Between Healthy Nonobese Women and Obese Insulin-Resistant Women

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Obesity is associated with metabolic and cardiovascular risk factors that include type 2 diabetes, hypertension, and dyslipidemia (1–4). A subset of obese subjects has been identified that appears to be protected from obesity-related metabolic abnormalities (5–11). These subjects, termed metabolically healthy but obese (MHO), are relatively insulin sensitive and have a rather favorable cardiovascular risk profile (5–11). Although the existence of MHO individuals has been recognized, only a few studies have examined in detail the metabolic characteristics associated with their protective profile (5–13). Whereas MHO individuals appear to have a more favorable cardiovascular risk profile than insulin-resistant obese (IRO) individuals, they show early signs of atherosclerosis compared with lean subjects, which could not be explained by alterations in cardiovascular risk factors (12). Among the factors that may account for the early atherosclerosis, insulin-like growth factor (IGF)-1 is a plausible candidate because low plasma IGF-1 concentrations are associated with type 2 diabetes, insulin resistance (14–16), and increased risk of coronary artery disease (17–22). To further characterize the protective profile of MHO individuals, we compared clinical characteristics, including cardiovascular risk factors,

plasma IGF-1 levels, and intima-media thickness (IMT) of the common carotid artery, of a group of MHO women from a cohort of nondiabetic Italian Caucasians with those of two age-matched groups comprising healthy nonobese or IRO women.

## RESEARCH DESIGN AND

**METHODS**— The study group consisted of 73 nonobese (BMI <27 kg/m<sup>2</sup>) and 80 obese (BMI >30 kg/m<sup>2</sup>) women, recruited by announcements in the Universities of Rome and Catanzaro areas. The inclusion criteria included the following: aged 19–48 years, absence of diabetes, and absence of known inflammatory disease or pathologies affecting glucose metabolism. A total of 68 women in the cohort used oral contraceptives, whereas the remaining had regular menses. Subjects underwent anthropometrical evaluation, a 75-g oral glucose tolerance test, and a euglycemic-hyperinsulinemic clamp, as previously described (23). Glucose disposal (*M*) was calculated as the mean rate of glucose infusion during the last 60 min of the examination and was expressed as milligrams per minute per kilogram fat-free mass (*M*<sub>FFM</sub>). IMT of the common carotid artery was measured by high-resolution B-mode ultrasound using an

ATL-HDI 3000 system equipped with a 5-MHz linear array transducer, as previously described (24). The protocol was approved by the ethics committees, and informed written consent was obtained from all participants. The investigations were performed in accordance with the principles of the Declaration of Helsinki. Plasma insulin and IGF-1 concentrations were determined by a chemiluminescence-based assay. Relationships between variables were sought by stepwise multivariate linear regression analysis.

**RESULTS**— Because insulin sensitivity is a continuous trait, there is no objective definition of insulin resistance. Therefore, the 80 obese subjects were stratified into quartiles based on their *M*<sub>FFM</sub> values, and women were defined as MHO if their *M*<sub>FFM</sub> value was in the upper quartile (>13.2 mg/min × kg<sub>FFM</sub>; *n* = 20). Women with *M*<sub>FFM</sub> values in the two lower quartiles (<9.9 mg/min × kg<sub>FFM</sub>; *n* = 40) were defined as IRO. A control group of 80 nonobese women was included in the study. Clinical characteristics of the three study groups are shown in Table 1. No differences in age, BMI, fat mass, and HDL cholesterol were observed between MHO and IRO individuals. By definition, insulin-stimulated glucose disposal was higher in MHO subjects who also exhibited significant lower lean body mass, fasting and 2-h postchallenge plasma glucose, fasting insulin, triglycerides, systolic and diastolic blood pressure, and carotid IMT compared with IRO individuals. No differences in age, lean body mass, total cholesterol, triglycerides, fasting and 2-h postchallenge plasma glucose, fasting insulin, and insulin-stimulated glucose disposal were observed between nonobese and MHO subjects (Table 1). However, MHO women had a less favorable risk profile compared with nonobese women with a significantly higher waist circumference, fat mass, blood pressure, and carotid IMT and lower concentrations of HDL cholesterol and IGF-1. As expected, IRO indi-

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**Abbreviations:** IGF, insulin-like growth factor; IMT, intima-media thickness; IRO, insulin-resistant obese; MHO, metabolically healthy but obese.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Anthropometric and biochemical characteristics of the study subjects

	Nonobese subjects	MHO subjects	Insulin resistant obese subjects	P*	P†	P‡
Age (years)	34 ± 9	35 ± 8	37 ± 8	0.43	0.10	0.53
BMI (kg/m <sup>2</sup> )	23.8 ± 2.8	37.7 ± 9.9	39.0 ± 7.4	0.0001	0.0001	0.56
Waist circumference (mm)	76 ± 8	100 ± 13	108 ± 14	0.0001	0.0001	0.07
Fat mass (kg)	20 ± 6	51 ± 19	47 ± 15	0.0001	0.0001	0.27
Lean body mass (kg)	42 ± 6	44 ± 15	56 ± 10	0.51	0.0001	0.001
Systolic blood pressure (mmHg)	113 ± 11	122 ± 12	132 ± 19	0.002	0.0001	0.05
Diastolic blood pressure (mmHg)	73 ± 8	77 ± 10	84 ± 9	0.02	0.0001	0.02
Total cholesterol (mg/dl)	186 ± 34	184 ± 46	205 ± 41	0.82	0.01	0.07
HDL cholesterol (mg/dl)	64 ± 15	49 ± 9	52 ± 13	0.0001	0.0001	0.28
Triglyceride (mg/dl)	77 ± 32	98 ± 45	152 ± 98	0.06	0.0001	0.008
Fasting glucose (mg/dl)	85 ± 10	85 ± 10	92 ± 9	0.85	0.0001	0.01
2-h glucose (mg/dl)	101 ± 28	108 ± 28	128 ± 33	0.32	0.0001	0.02
Fasting insulin (μU/ml)	7 ± 4	11 ± 3	20 ± 18	0.0001	0.0001	0.004
IGF-1 (ng/ml)	244 ± 92	194 ± 97	143 ± 54	0.02	0.0001	0.08
IMT (mm)	0.68 ± 0.11	0.79 ± 0.08	0.89 ± 0.14	0.0001	0.0001	0.03
Insulin-stimulated glucose disposal (mg/min × kg <sub>FFM</sub> )	14.3 ± 4.3	15.1 ± 1.8	6.4 ± 2.3	0.14	0.0001	0.0001

Data are means ± SD. Differences of continuous variables between two groups were compared using unpaired Student's *t* test. \*Nonobese vs. MHO subjects; †insulin-resistant obese vs. nonobese subjects; ‡insulin-resistant obese vs. MHO subjects.

viduals had high-risk metabolic and cardiovascular profiles compared with those of nonobese subjects (Table 1).

A stepwise multivariate regression analysis in a model, including metabolic and cardiovascular risk factors in the whole study group, showed that the three variables that remained significantly associated with carotid IMT were waist circumference (partial  $r^2 = 0.333$ ;  $P < 0.0001$ ), IGF-1 levels (partial  $r^2 = 0.095$ ;  $P < 0.001$ ), and insulin-stimulated glucose disposal (partial  $r^2 = 0.037$ ;  $P < 0.03$ ), accounting for 46.5% of its variation. A second stepwise multivariate regression analysis performed to identify the possible determinants of insulin sensitivity showed that the two variables that remained significantly associated with insulin-stimulated glucose disposal were waist circumference (partial  $r^2 = 0.30$ ;  $P < 0.0001$ ) and triglycerides (partial  $r^2 = 0.056$ ;  $P < 0.01$ ), accounting for 35.6% of its variation.

**CONCLUSIONS**— We provide evidence that MHO subjects have a metabolic and cardiovascular risk profile that is intermediate between that observed in healthy nonobese women and that of IRO women. Carotid IMT, an early sign of atherosclerosis (25,26), was lower in MHO compared with IRO women. Waist circumference was the strongest risk factor associated with IMT in a stepwise multivariate regression analysis. It is likely that

free fatty acids and adipokines such as tumor necrosis factor- $\alpha$  and interleukin-6, which are predominantly secreted from visceral fat and affect vasculature (27–30), may be responsible for the strong relationship between central obesity and early atherosclerosis. Interestingly, we found that plasma IGF-1 levels were independently associated with carotid IMT, suggesting that low IGF-1 levels could contribute to early atherosclerosis observed in IRO and MHO women compared with nonobese women. IGF-1 plays an important role in endothelial cells stimulating nitric oxide production (31–33). Moreover, low-tissue IGF-1 levels and reduced IGF-1 receptor expression have been found in atherosclerotic plaques (34). We also found that insulin-stimulated glucose disposal was independently associated with carotid IMT. This finding is consistent with previous studies supporting the concept that insulin sensitivity rather than plasma insulin levels is associated with early atherosclerosis in nondiabetic individuals (23,35). Given the relatively small sample size of this study, replication studies are required to assess the applicability of our conclusions to other sets of obese patients.

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