High Leptin/Adiponectin Ratio and Serum Triglycerides Are Associated With an "At-Risk" Phenotype in Young Severely Obese Patients

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"At-risk" severely obese subjects are characterized by insulin resistance, and higher visceral fat and plasma lipid levels compared with metabolically healthy obese (MHO) subjects, although both groups have a high BMI and fat mass. The aim of this study was to measure several serum adipokines and gastrointestinal hormones in a young severely obese population from Southern Italy to identify biochemical markers of the "at-risk" insulin-resistant obese profile. We studied 160 unrelated white young adults (mean age = 25.2 years, mean BMI = 44.9 kg/m², 65% women) affected by obesity for at least 5 years. Serum concentrations of glucagon, ghrelin, gastric inhibitory peptide, glucagon like peptide-1, interleukin-6, tumor necrosis factor α, leptin, adiponectin, adipsin, and visfatin were measured. The leptin/adiponectin (L/A) ratio and fatty liver index (FLI) were calculated. We found a prevalence of 21.3% of MHO patients in our young severely obese patients. At univariate analysis, the "at-risk" group had higher mean levels of BMI ($P < 0.0001$), leptin ($P = 0.039$, men) and the L/A ratio ($P = 0.003$), and lower mean levels of visfatin ($P = 0.026$) than the MHO group. The L/A ratio, serum triglycerides, and male sex were significantly associated with "at-risk" obesity and accounted for 19.5% of insulin resistance at multivariate analysis. In conclusion, we demonstrate that a high serum L/A ratio and high levels of serum triglycerides may be markers of "at-risk" obesity, independent of waist circumference (WC) and BMI, in young severely obese population.

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INTRODUCTION

The obese phenotype is widely heterogeneous: it includes an "at-risk" phenotype and a so-called "metabolically healthy phenotype" (MHO) that is present in 10% to over 30% of the obese population (1). "At-risk" obese subjects are characterized by insulin resistance and by higher visceral fat and plasma lipid levels compared with MHO subjects, although both groups have a high BMI and fat mass (2). Low visceral fat (2) and early obesity onset (<20 year of age) (3) accounted for 22% and 13% respectively of the insulin sensitivity observed in MHO patients, but 65% of the phenotype remained unexplained (2). The MHO phenotype has been well described in mild obesity (4,5), in postmenopausal obesity (3,6), and in a randomly selected population (7), but not in young severely obese people (8).

In the attempt to identify biochemical markers of the MHO and "at-risk" obese profiles, we measured several serum adipose and gastrointestinal hormones in a young severely obese population from Southern Italy. The identification of an "at-risk" profile, particularly in young subjects, could have important implications in their clinical management. In fact, "at-risk" obese subjects need aggressive treatment to prevent or delay obese-associated metabolic complications, whereas attempts to loose weight might be potentially harmful, or not effective in MHO individuals (9,10).

METHODS AND PROCEDURES

Study population

We studied 160 unrelated white young adults (mean age ± s.d. = 25.2 ± 9.6 years; mean BMI [95% confidence interval (CI)] = 44.9 [43.6–46.3] kg/m²; 65% women) from Southern Italy who had suffered from obesity for at least 5 years. The population was recruited at the Obesity Outpatient Clinic of the Department of Internal Medicine, Federico II University Hospital, Naples, Italy. Clinical, functional, and biochemical data were obtained from each patient at the baseline. Secondary causes of obesity were excluded, and no patient was an alcohol abuser or under pharmacological treatment for any disease. We measured: BMI (weight/height²; kg/m²), waist circumference (WC; cm), blood pressure (systolic blood pressure and diastolic blood pressure; mm Hg) and heart rate (beats/min) in each individual after they had been sitting for 5 min; we also recorded smoking habits and body composition (fat mass and

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Table 1 Physical and biochemical characteristics (mean and 95% CI) in MHO and "at-risk" severely obese young patients from Southern Italy

	MHO (*n* = 34)		M vs. F	"At risk" (*n* = 126)		M vs. F	MHO vs. "at risk"
Characteristics[a]	Mean	95% CI	*P* value[c]	Mean	95% CI	*P* value[c]	*P* value[c]
Age (years)[b]	22.6	19.7–25.5	Ns	25.8	24.1–27.6	Ns	Ns
BMI (kg/m^2)[b]	41.1	38.9–43.3	Ns	46.1	44.5–47.7	Ns	0.003
WC (cm)[b]	122.5	118.0–127.0	Ns	(M) 140.8 (F) 128.6	135.2–146.5 124.8–132.3	<0.0001	Ns
RQ	0.9	0.82–0.89	Ns	0.9	0.85–0.88	Ns	Ns
FFM (%)	(M) 56.3 (F) 50.0	50.4–62.2 47.9–52.1	0.010	(M) 53.9 (F) 50.2	52.2–55.6 48.9–51.3	0.001	Ns
FM (%)[b]	(M) 43.6 (F) 49.9	37.7–49.6 47.9–52.1	0.010	(M) 46.1 (F) 50.1	44.4–47.8 48.9–51.3	<0.0001	Ns
SBP (mm Hg)[b]	119.4	117.7–121.1	Ns	122.1	120.5–123.7	Ns	Ns
DBP (mm Hg)	77.4	75.7–79.1	Ns	78.7	77.6–79.8	Ns	Ns
Heart rate (beats/min)	76.8	74.4–79.2	Ns	78.6	77.5–79.8	Ns	Ns
Glucose (mmol/l)	4.1	3.9–4.3	Ns	4.7	4.5–4.9	Ns	<0.0001
Total cholesterol (mmol/l)	4.3	3.9–4.7	Ns	(M) 4.4 (F) 4.6	4.1–4.7 4.4–4.8	0.041	Ns
HDL cholesterol (mmol/l)	(M) 1.0 (F) 1.2	0.8–1.2 1.1–1.3	0.032	(M) 1.0 (F) 1.2	0.9–1.1 1.1–1.3	0.007	Ns
Triglycerides (mmol/l)[b]	1.0	0.8–1.2	Ns	1.5	1.4–1.7	Ns	<0.0001
AST (U/l)	(M) 25.9 (F) 18.6	20.6–31.2 17.2–19.9	0.002	(M) 35.1 (F) 23.8	25.4–44.9 20.8–26.8	<0.0001	(F) 0.029
ALT (U/l)	(M) 39.3 (F) 20.9	28.7–49.9 18.0–23.9	<0.0001	(M) 52.2 (F) 30.7	41.1–63.2 26.3–35.1	<0.0001	Ns
GGT (U/l)[b]	(M) 29.4 (F) 15.1	20.2–38.7 13.2–17.0	<0.0001	(M) 34.5 (F) 29.3	24.4–44.6 21.4–37.2	0.002	(F) 0.001
FLI[b]	86.7	81.4–92.1	Ns	94.4	92.7–96.1	Ns	<0.0001
Fibrinogen (μmol/l)	11.2	10.5–12.0	Ns	12.0	11.6–12.5	Ns	Ns
Creatinine (μmol/l)	(M) 79.5 (F) 61.8	70.7–88.4 53.0–62.0	<0.0001	(M) 70.7 (F) 61.8	61.8–79.5 53.0–62.0	<0.0001	(M) 0.042
Urea (mmol/l)[b]	4.6	4.2–5.0	Ns	5.1	4.9–5.3	Ns	0.039
C-peptide (ng/ml)	2.4	2.1–2.7	Ns	(M) 4.4 (F) 4.0	4.0–4.7 3.7–4.4	0.046	<0.0001
Insulin (mIU/l)	8.7	7.8–9.7	Ns	23.9	21.8–26.0	Ns	<0.0001
HOMA	1.5	1.4–1.7	Ns	(M) 4.5 (F) 3.8	4.0–4.9 3.5–4.1	0.009	<0.0001
Glucagon (ng/ml)	0.96	0.91–1.02	Ns	0.94	0.91–0.97	Ns	Ns
Ghrelin (pg/ml)	122.0	104.4–139.7	Ns	116.5	105.8–127.3	Ns	Ns
GIP (pg/ml)	61.2	50.8–71.5	Ns	55.1	50.5–59.8	Ns	Ns
GLP-1 (ng/ml)	1.1	0.8–1.3	Ns	0.9	0.8–1.1	Ns	Ns
IL-6 (pg/ml)	14.1	11.4–16.8	Ns	12.5	11.2–13.7	Ns	Ns
TNFα (pg/ml)	39.7	30.5–48.8	Ns	36.7	32.3–41.0	Ns	Ns
Leptin (ng/ml)	(M) 4.3 (F) 6.9	2.1–6.4 5.6–8.3	0.010	(M) 6.9 (F) 8.2	5.8–7.9 7.3–9.0	Ns	(M) 0.023
Adiponectin (μg/ml)	28.0	24.7–31.3	Ns	24.1	22.3–25.8	Ns	Ns
L/A ratio[b]	0.25	0.19–0.31	Ns	0.37	0.32–0.41	Ns	0.003
Adipsin (ng/ml)	592.2	507.9–676.4	Ns	503.3	460.7–545.9	Ns	Ns
Visfatin (ng/ml)[b]	7.6	6.0–9.2	Ns	5.8	5.1–6.5	Ns	0.026

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; F, females; FLI, fatty liver index; FFM, fat free mass; FM, fat mass; GIP, gastric inhibitory peptide; GGT, γ-glutamyl transferase; GLP-1, glucagon-like peptide-1; HOMA, homeostasis model assessment; IL-6, interleukin-6; L/A, leptin/adiponectin ratio; M, males; MHO, metabolically healthy obese subjects; Ns, not significant; RQ, respiratory quotient; SBP, systolic blood pressure; TNFα, tumor necrosis factor-α; WC, waist circumference.

[a]Reported as mean and 95% confidence interval (CI). [b]Variables used in the logistic model to assess their association with the "at-risk" characteristic in our obese population. [c]At Mann–Whitney or Student's t-test, as appropriate.

fat free mass using the bioelectrical impedance technique). The physical and biochemical characteristics of the population are reported in **Supplementary Table S1** online. A venous blood sample was collected from each patient at 8.00 AM after an overnight fast. The families of all subjects had lived in Southern Italy for at least three generations and all subjects gave their informed consent to the study. The research was approved by the Ethics Committee of the Faculty of Medicine, University of Naples Federico II, and was carried out according to the Helsinki II Declaration.

Laboratory investigations

Serum glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase (GGT), fibrinogen, creatinine, urea, C-peptide and insulin were measured by routine laboratory methods. Insulin resistance was estimated according to the homeostasis model assessment and the formula: fasting insulin (mIU/l) × fasting glucose (mmol/l)/22.5. We calculated the fatty liver index (FLI) according to the formula $FLI = (e^{0.953 \times \ln(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \ln(\text{GGT}) + 0.053 \times \text{waist circumference} - 15.745})/(1 + e^{0.953 \times \ln(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \ln(\text{GGT}) + 0.053 \times \text{waist circumference} - 15.745}) \times 100$ as a measure of hepatic steatosis (11).

Serum glucagon, ghrelin, gastric inhibitory peptide, glucagon-like peptide-1, interleukin-6, tumor necrosis factor-α (TNFα), leptin, adiponectin, adipsin, and visfatin were measured by Luminex xMAP Technology on a BioRad Multiplex Suspension Array System (BioRad, Hemel Hempstead, Herts), according to the manufacturer's instructions. We also calculated the leptin/adiponectin (L/A) ratio.

The study population was divided into two groups: MHO individuals, i.e., subjects who were "insulin sensitive" and had no more than one risk factor (hypertension or dyslipidemia); and "at-risk" individuals, i.e., subjects who were "insulin-resistant" with or without other risk factors, namely, hypertension, dyslipidemia, and hyperglycemia. A homeostasis model assessment index (HI) lower or greater than 1.95 defined insulin sensitivity or resistance, respectively (6,12).

Statistics

Data are reported as mean ± s.d. or the 95% CI. Angular transformation (arcsin of the square root) of the L/A ratio was applied before statistical analyses. The unpaired Student's *t*-test, the Mann–Whitney test or the χ^2-test were used for between-group comparisons, as appropriate. Differences were considered statistically significant at a P level <0.05. Binomial logistic regression analysis was used to investigate the association between the biochemical and clinical characteristics and the "at-risk" condition, as previously defined. The odds ratio relative to clinically meaningful differences for the continuous variables are reported. To explore the possibility of missing a potential association due to the loss of information consequent to the introduction of the binary categorization of the HI in the logistic analysis, a multiple linear regression analysis was performed using the continuous HI as dependent variable for the same set of independent variables used in the logistic regression analysis. Both forward and backward procedures were used for model selection and gave concordant results. Statistical analyses were carried out with the SPSS package for Windows (ver. 17; SPSS, Chicago, IL).

RESULTS

A family history of obesity was recorded in 31.5% individuals, of concomitant obesity + hypertension + diabetes in 53% and hypertension alone in 6.2%. Thirty-four individuals (21.3%) were classified "MHO". There were no significant differences between "at-risk" and MHO individuals regarding sex, smoking habit, and family history of obesity. Only 6.3% of insulin-resistant "at-risk" individuals were also hyperglycemic. Mild hypertransaminasemia was also present in 52/160 (32.3%) of the study population: 37.3% of the "at-risk" group and 11.8% of the MHO group ($P = 0.004$). Hypertension (mean systolic blood pressure/diastolic blood pressure >133/89 mm Hg) was present in 11% of our "at-risk" patients; moreover, these patients also had a higher mean L/A ratio and HI values (hypertensive vs. normotensive patients, L/A ratio: 0.46 vs. 0.35, $P = 0.038$; HI: 5.3 vs. 3.9, $P = 0.002$). However, all our hypertensive obese patients belonged to the "at-risk" group.

Levels of GGT (women, $P = 0.001$) and of urea ($P = 0.027$) were higher in the "at-risk" than in the MHO group. The FLI was higher in the "at-risk" group (94.4), as expected, given the liver involvement, than in the MHO group (86.7) ($P < 0.0001$). **Table 1** shows the mean serum levels of adipokines and hormones measured in MHO and "at-risk" individuals together with the other physical and biochemical parameters measured in this study. The "at-risk" individuals had, at univariate analysis, higher mean levels of BMI ($P < 0.0001$), leptin ($P = 0.039$, men) and L/A ratio ($P = 0.003$), and lower mean levels of visfatin ($P = 0.026$) than the MHO group.

The variables used in the logistic model to assess their association with the "at-risk" phenotype in our obese population are indicated in **Table 1** (variables "[b]" labelled). The final model showed a Nagelkerke $R^2 = 0.19$, and only two variables were retained as significant: the L/A ratio (odds ratio/95% CI = 1.44/1.07–1.94), and the serum concentration of triglycerides (odds ratio/95% CI = 1.87/1.19–2.94). The final multiple linear regression model resulted in the addition of gender to the other significant factors, i.e., the L/A ratio and serum triglycerides. The overall adjusted R^2 was equal to 0.195, indicating that both the logistic and the multiple linear models are, in practice, equivalent.

DISCUSSION

The characterization of several serum adipokines and gastrointestinal hormones in the young severely obese population reported herein suggests that the serum L/A ratio, serum triglycerides, male sex, and the HI could be useful markers for the diagnosis of "at-risk" obese patients. Based on an almost complete absence of traditional risk factors for cardiovascular and metabolic diseases (1,2,6,13), a variable proportion (between 10% and 30%) of obese subjects is classified "MHO". Using an HI <1.95 as classification criterion (3), we found a prevalence of 21.3% of MHO patients in our young severely obese patients. This prevalence was similar to or lower (from 24.4% to 31.7%) than those obtained in mild and/or severe older obese subjects in other European and non-European populations (3,4,7,8,14). Besides the use of different criteria to classify MHO, these differences could be explained by the different age, female/male ratio, and classes of obesity investigated. In fact, the prevalence of uncomplicated obesity was reported to be higher in a very young (16–29 years) obese population than in other age groups, independent of BMI category (8). Our patients had been obese for at least 5 years, but the MHO group was 3 years younger than the "at-risk" group. This finding suggests that juvenile onset obesity rapidly progresses toward a more severe phenotype as observed in older obese populations (4,5,7,8,14).

Levels of the two inflammatory markers interleukin-6 and TNFα did not differ between the MHO and the "at-risk" groups in our obese population. This finding is in agreement with some reports (15,16) but not with others (6,7,17). It is possible that the discrepancy stems from the young age of the population we studied.

The young age of our patients might also explain the relatively low percentage of hypertensive subjects in our population. In a previous study of a nonobese male population of our geographical area, hypertension was associated with decreased insulin sensitivity (18). However, the L/A ratio remained significantly higher in the "at-risk" group than in the MHO group, also when hypertensive patients were excluded from the statistical analysis (0.35 vs. 0.25, $P = 0.008$). This suggests that factors other than hypertension are at play during the onset of insulin resistance in young obese subjects. Furthermore, the low high-density lipoprotein cholesterol levels in our MHO and "at-risk" subjects probably reflects the similar sedentary lifestyle of our subjects.

In agreement with a lower hepatic insulin resistance and a lower liver fat content in MHO patients observed in postmenopausal women (19), in the general population (11) and by us in a middle-aged obese population (20), the levels of FLI, an index of liver steatosis, were higher in "at-risk" individuals than in the MHO group ($P < 0.0001$). This could be due to the fact that trapping of free fatty acids is impaired in "at-risk" individuals (19). Furthermore, in overweight patients, the L/A ratio was reported to be higher in nonalcoholic steatohepatitis than in simple steatosis, irrespective of insulin resistance (21). In our study, the L/A ratio was not correlated with FLI, although the latter was significantly higher in "at-risk" than in MHO patients. This observation could be due to the lower sensitivity of FLI compared to liver biopsy, which is not routinely performed in severe obesity, in diagnosing liver steatosis (21).

In our study, the serum L/A ratio, serum triglycerides, and male sex were the most significant parameters associated with "at-risk" obesity; indeed they accounted for 19.5% of the insulin-resistant phenotype. The L/A ratio was reported to be negatively correlated with insulin sensitivity indexes in a large population of nonobese and nondiabetic individuals (22), and we previously demonstrated that this ratio contributed to the metabolic syndrome in severe obesity (20).

Brochu *et al*. found that visceral adipose tissue plays a relevant role in insulin resistance insurgence (3). We are unable to evaluate the relative effect of this tissue or of the L/A ratio on insulin resistance because we did not measure visceral adipose tissue in our population. However, the lack of a significant association between WC, a rough index of visceral adiposity, and the BMI, an index of total adiposity, with the HI in both the logistic and the multiple regression models probably indicates that, in this selected population with severe obesity, the L/A ratio is a better marker of "at-risk" obesity than either WC or BMI. This observation is supported by the fact that the association of WC and BMI with HI becomes statistically significant ($P = 0.031$ and $P = 0.042$, respectively) when the adipokines are not included in the model. Consequently, the L/A ratio-HI association that we observed is independent of both WC and BMI. The apparent discrepancy between our findings and those of Brochu *et al*. is probably due to the differences between the two examined populations, namely mean age (MHO vs. "at risk", Brochu *et al*: 58.0 vs. 58.6 years; our data: 22.6 vs. 25.8 years), gender composition, (Brochu *et al*. 100% females, in our population 65% females) and underlying physiopathologic conditions (severity of obesity and postmenopausal condition) and to different methodological aspects.

In conclusion, we demonstrate that a high serum L/A ratio and high levels of serum triglycerides may be markers of "at-risk" obesity, independent of WC and BMI, in young severely obese population.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/oby

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DISCLOSURE

The authors declared no conflict of interest.

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