J. Endocrinol. Invest. 30: 104-110, 2007

Ultrasonographic evaluation of liver volume and the metabolic syndrome in obese women

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ABSTRACT. Non-alcoholic fatty liver disease is a common finding in obese subjects, and increasing evidence has been provided suggesting that it represents the hepatic component of the metabolic syndrome. The aim of this study was to evaluate whether the extent of liver enlargement is related to the severity of the metabolic syndrome in obese women. The relationship between ultrasound-measured hepatic left lobe volume (HLLV) and various features of the metabolic syndrome was evaluated in 85 obese women. The mean±SD value of HLLV in obese women was 431±214 ml (range 46-1019 ml) while it was 187±31 ml (range 143-258 ml) in lean subjects. In a multiple logistic regression analysis, ultrasound-measured intra-abdominal fat was the only anthropometric measure independently associated with HLLV. A strong positive association was found between HLLV and serum liver enzymes, triglycerides, glucose, insulin, uric acid, C reactive protein, systolic and diastolic blood pressure, while a negative correlation was observed between HLLV and HDL cholesterol. The values of HLLV corresponding to the cut-off values of various risk factors for the diagnosis of the metabolic syndrome were calculated, yielding a mean value of 465 ml. In conclusion, ultrasound measurement of HLLV represents a simple, reliable and low-cost tool for the evaluation of liver involvement in the metabolic syndrome. The strong association between liver enlargement and various cardiovascular risk factors associated with insulin resistance supports the role of liver steatosis as an important link among the many facets of the metabolic syndrome in human obesity.
(J. Endocrinol. Invest. 30: 104-110, 2007)
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INTRODUCTION

The metabolic syndrome represents a clustering of risk factors for cardiovascular diseases, and it is considered the most alarming health issue related to the epidemic explosion of obesity (1-3). Visceral adiposity and insulin resistance are viewed as the key factors in the development of this condition, but the clinical spectrum and phenotypic expression of the syndrome are the results of the interaction between various genetic and environmental influences (4). Several definitions have been proposed for the metabolic syndrome, reflecting the uncertainty on the underlying pathological process and the various factors to be included in the definition. Furthermore, the exact links among various components of the syndrome and the precise pathogenic routes of increased cardiovascular morbidity have been only partially disclosed, and involve metabolic, hormonal, pro-thrombotic and pro-inflammatory factors (5-7). Fatty infiltration of liver is frequently observed in patients with the metabolic syndrome (8-10). Increasing evidence has also been provided suggesting that fat accumulation in the liver is closely correlated with hepatic insulin resistance and various features of the syndrome (11-13). The extent of liver involvement in subjects with the metabolic syndrome can be evaluated by imaging methodologies, but only liver biopsy can accurately establish the severity of the disease (14, 15). The aim of this study was to develop an ultrasound technique that allowed us to determine the relationship between hepatic volume and various features of the metabolic syndrome in obese women.

Key-words: Obesity, non-alcoholic fatty liver disease, metabolic syndrome, liver volume, ultrasonography.

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Accepted July 28, 2006.

MATERIALS AND METHODS

Sixty-six pre-menopausal and 19 post-menopausal unrelated Caucasian women with body mass index (BMI) of >35 kg/m^2, who

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turned to the obesity center of our department for evaluation in expectation of bariatric surgery, were included in the study. None of the patients was taking hypoglycemic, hypolipemic or hypouricemic agents. Additional exclusion criteria were: self-reported alcohol consumption >20 g daily, use of illicit drugs or hepatotoxic medications, viral hepatitis as assessed by conventional serum markers, pregnancy or breast feeding within the 12-month period before enrollment. Two women were taking oral contraceptive agents. Clinical, hematological and instrumental examinations of each patient were performed following the Italian guidelines for obesity, and each patient was treated according to appropriate protocols for her condition. Anthropometric measures were determined after an overnight fast. Body weight was measured to the nearest kilogram, and body height and abdominal circumference were determined to the nearest centimeter. Blood pressure on admission was recorded with a large cuff while the patient was recumbent. Twelve patients were taking anti-hypertensive drugs. Subject characteristics are shown in Table 1. Venous blood samples were obtained after an overnight fast for measurement of serum glucose, triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), C-reactive protein (CRP) and insulin. The homeostasis model of insulin resistance (HOMA) was calculated based on fasting serum glucose and insulin concentrations (16). Ultrasound examination was performed by a single expert operator with the patient in supine position, with state-of-the art equipment (Technos, Esaote Biomedica, Genoa, Italy) and either convex (2.5-5 MHz) or linear (7,5 MHz) probes. The ellipsoid formula (width x height x length x 0.52) was applied to calculate the hepatic left lobe volume (HLLV). The height (longitudinal diameter) of the lobe was obtained by an epigastric-longitudinal scan, considering the distance between the diaphragm and the lower margin of the left lobe. When the distance was larger than the field of view of the scan, measurement was performed by two contiguous scans of the lobe. The length of the lobe (lateral-lateral diameter) was calculated on the axial scan by drawing a line between the round ligament and the lateral margin of the hepatic lobe. Thickness was obtained on both the axial and the longitudinal scans, measuring the distance between the anterior and the posterior borders of the liver. When measures did not coincide, the mean value was calculated. Ultrasound measurement of HLLV was also performed in 15 normal-weight female volunteers without known hepatic diseases, as controls. Thickness of the abdominal sc fat was taken 1 cm over the transversal umbilical vein, by measuring the distance between the skin and the external face of the muscular fascia, while intra-abdominal fat thickness was defined as the distance between the internal face of the same muscle and the anterior wall of the aorta (17). To validate our ultrasound procedure HLLV measured sonografically was compared with that measured by magnetic resonance (MR) in 11 obese women undergoing abdominal MR examination because of diagnostic purposes. MR examination was performed by 1.5 equipment (MRExcite 1.5T, GE/Medical Systems Milwaukee, WI) with a Fast Spoiled Gradient-Echo T1-weighted sequence on the axial scans (TR/TE 100/1.4 ms, FA 70°, thickness 5 mm, matrix 320-256 x 192, NEX 1, scan time 20-30 sec). The left lobe and the total liver volumes were calculated by semiautomatic segmentation on an independent workstation, with dedicated software, using the sum of areas technique. The region-of-interest was drawn manually on each axial scan. The system automatically determined the boundaries around a class of similar voxel intensity values, and calculated the volume of the segmented region. A highly significant correlation was demonstrated between ultrasound and MR measured HLLV ($p<0.0001$, R=0.946). Furthermore, there was a strong association between HLLV measured by ultrasound and the total volume of liver (Fig. 1).

Table 1 - *Characteristic of the study group.*

	Mean±SD	Range
Age (yr)	40.9±11.8	20-67
Height (cm)	160.8±5.9	149-178
Weight (kg)	117.7±21.4	82.5-174
BMI (kg/m^2)	45.4±7.4	35.1-65.7
Waist (cm)	125.3±14.8	100-170

BMI: body mass index.

RESULTS

The mean±SD value of HLLV in obese women was 431±214 ml (range 46-1019 ml) while it was 187±31 ml (range 143-258 ml) in the normal weight group. The following results refer exclusively to obese women. A highly significant positive association was observed between HLLV and BMI, weight and intra-abdominal fat, while the correlation with abdominal circumference was much weaker (Table 2). However, in a multiple logistic regression analysis, intra-abdominal fat was the only anthropometric measure independently associated with HLLV (Fig. 2). No significant association was observed between HLLV and sc fat. We then analyzed the relationship between HLLV and serum concentrations of liver enzymes. A

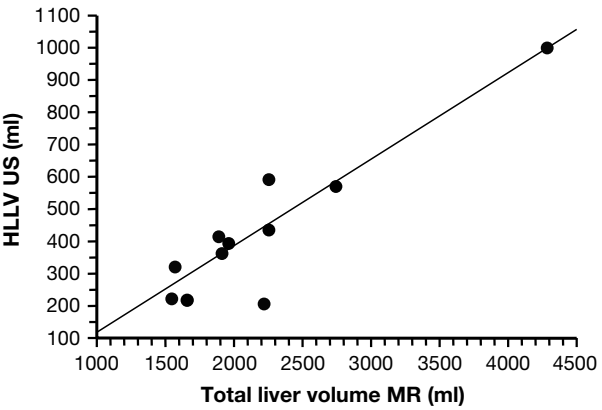

Fig. 1 - *Correlation between hepatic left lobe volume measured by ultrasound (HLLV US) and total liver volume measured by magnetic resonance (MR). A highly significant positive association was demonstrated* ($p<0.0001$, *R=0.912).*

Table 2 - *Results of simple regression analyses between hepatic left lobe volume (HLLV) or intra-abdominal fat and various clinical and biochemical parameters.*

	HLLV		Intra-abdominal fat	
Parameters	*p*-value	R	*p*-value	R
BMI	0.0003	0.384	<0.0001	0.544
Weight	0.0016	0.337	<0.0001	0.513
Waist circumference	0.0383	0.273	0.0006	0.439
Age	Not significant		0.0256	0.242
Intra-abdominal fat	<0.0001	0.572		
ALP	0.0003	0.38	0.032	0.234
AST log	<0.0001	0.42	0.0015	0.34
ALT log	<0.0001	0.434	0.0298	0.236
GGT log	<0.0001	0.483	0.0009	0.354
Triglycerides	<0.0001	0.485	0.1216	0.169
HDL cholesterol	<0.0001	–0.583	0.0009	–0.43
Serum fasting glucose	<0.0001	0.483	0.012	0.27
Serum fasting insulin	0.0032	0.33	0.0009	0.37
HOMA index	0.0007	0.377	0.0002	0.41
SBP	0.0079	0.308	Not significant	
DBP	0.006	0.319	Not significant	
Uric acid	<0.0001	0.549	<0.0001	0.436
CRP	0.0007	0.508	0.0062	0.421

BMI: body mass index; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; HOMA: homeostasis model assessment; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C-reactive protein; GGT: γ-glutamyltranferase (GGT).

strong positive association was found with GGT, ALT, AST and ALP (Fig. 3). For all these parameters, the association with HLLV was stronger than that observed with intra-abdominal fat (Table 2). When looking at serum indexes of lipid metabolism, a positive association with triglycerides and a negative association with HDL-cholesterol were observed (Fig. 4), while no relationship was detected between HLLV and total cholesterol or LDL-cholesterol. As for liver enzymes, the relationship between serum lipids and HLLV was stronger than that observed between serum lipids and intra-abdominal fat (Table 2). Serum glucose, serum insulin and HOMA were also positively associated with HLLV, and the results of statistical analysis were close to those observed when the same parameters were related to intra-abdominal fat (Table 2). Finally, a positive association was observed between HLLV and systolic blood pressure, diastolic blood pressure, serum uric acid and CRP. Among these, only uric acid and CRP were significantly associated with intra-abdominal fat, though statistically weaker values were found with respect to HLLV (Table 2). Using the linear regression formulas, the values of HLLV corresponding to the cut-off values of various risk factors for the diagnosis of the metabolic syndrome, as proposed by the National Cholesterol Education

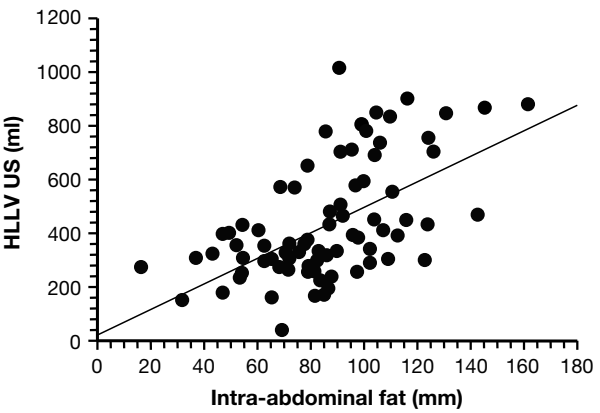

Fig. 2 - *Correlation between hepatic left lobe volume (HLLV) and intra-abdominal fat (p<0.0001, R=0.572). US: ultrasound.*

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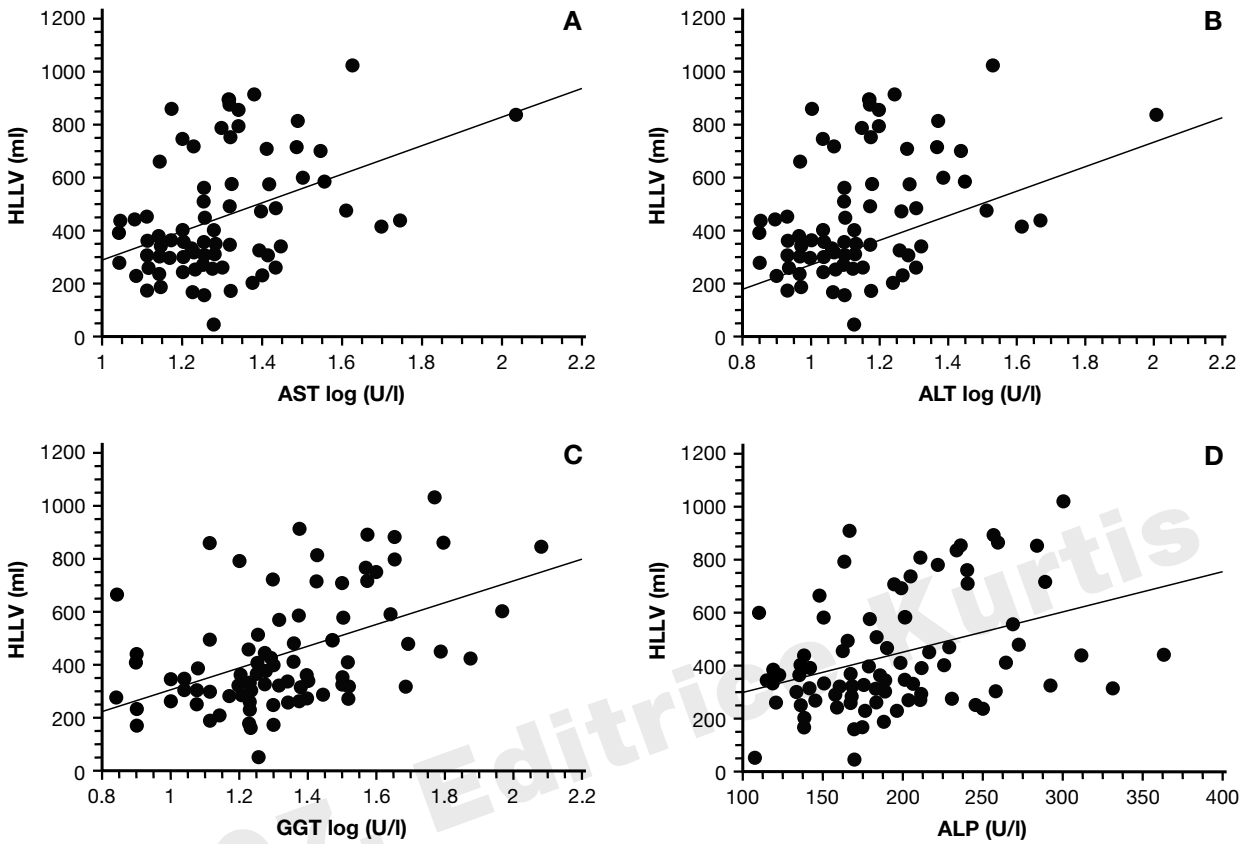

Fig. 3 - *Correlations between hepatic left lobe volume (HLLV) and serum concentration of liver enzymes. A strong positive association was found between HLLV and aspartate aminotransferase (AST) (panel A), alanine aminotransferase (ALT) (panel B), γ-glutamyltranferase (GGT) (panel C) and alkaline phosphatase (ALP) (panel D). For* p *and R values see Table 2.*

Program Adult Treatment Panel III (ATP III) (18) or the International Diabetes Federation (IDF) (19), were calculated. The formula could not be applied to abdominal circumference since all women had values far above the proposed cut-off values. Results of these analyses are shown in Table 3, and indicate a mean value of 465 ml (450 ml according to the criteria of the International Diabetes Federation) as the threshold volume matching the outbreak of the syndrome.

DISCUSSION

Liver enlargement due to a diffuse accumulation of triglycerides in hepatocytes is a common finding in obese subjects (20, 21). The term Nonalcoholic Fatty Liver Disease (NAFLD) has been introduced to indicate a clinicopathologic syndrome that encompasses a broad spectrum of hepatic lesions, ranging from simple steatosis to necroinflammatory lesions and fibrosis, which closely resemble those induced by alcohol (20, 22). NAFLD is the result of a multi-factorial process, and there is increasing evidence that it represents the hepatic component of the metabolic syndrome (8, 9, 13, 23). The metabolic syndrome in NAFLD patients increases the likelihood of severe disease, and mortality among NAFLD patients is higher than the general population (24). Abdominal obesity is more commonly associated with the metabolic syndrome than peripheral obesity, but whether visceral fat is the cause of the metabolic syndrome or the result of a common pathogenic abnormality is still a matter of debate (11, 25). Waist circumference is routinely employed to estimate the degree of visceral adiposity (26). However, this may not be reliable in severe obesity, when the excess of sc fat may lead to an overestimation of intra-abdominal fat deposits. Imaging techniques such as computed tomography (CT) and MR have been employed to obtain precise measures of intra-abdominal fat and liver volume (27, 28). They may also yield alterations suggesting liver steatosis (29). However, they are sophisticated techniques unlikely to be accessible

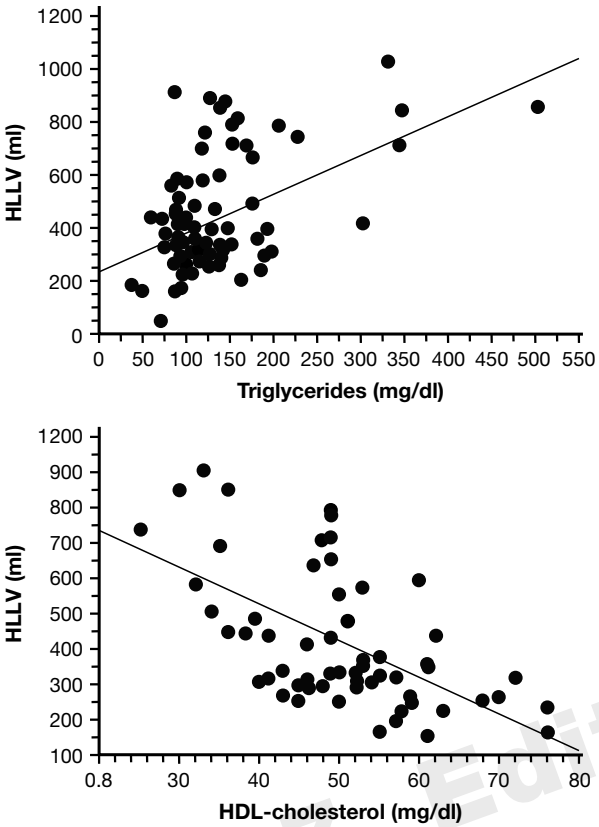

Fig. 4 - *Correlations between hepatic left lobe volume (HLLV) and serum indexes of lipid metabolism. A positive correlation between HLLV and triglycerides and a negative correlation between HLLV and HDL-cholesterol were observed. For* p *and R values see Table 2. Values of serum HDL-cholesterol were available in 56 subjects.*

Table 3 - *Hepatic left lobe volume (HLLV) values corresponding to the cut-off values of risk factors for the diagnosis of the metabolic syndrome, as proposed by the Adult Treatment Panel III (ATP III) or the International Diabetes Federation (IDF), calculated using the linear regression formulas.*

Risk factors for the metabolic syndrome	HLLV (ml)
Triglycerides (≥150 mg/dl)	452
HDL cholesterol (≤50 mg/dl)	422
Glucose ATP III (≥110 mg/dl)	549
Glucose IDF criteria (≥100 mg/dl)	478
SBP (≥130 mmHg)	443
DBP (≥85 mmHg)	457
Mean±SD (ATP III)	465±49
Mean±SD (IDF)	450±20

for routine management of obese subjects and, due to technical limitations, they may not be available for the most severely obese patients. Ultrasonography represents an easy and reliable tool for the estimation of visceral adiposity through measurement of visceral fat thickness (17). Ultrasonography may also provide semiquantitative information on the degree of liver steatosis (30, 31), and it has been employed for the estimation of liver volume (27). The left lateral segment of the liver can be easily visualized in its entirety by ultrasound examination that has been employed for its measurement in patients scheduled for liver transplantation (32). In this study we present an easy, safe, repeatable and low-cost technique that allows a precise determination of HLLV during routine abdominal ultrasound examination in obese subjects, thus providing a measure of hepatic enlargement. The relationship between HLLV values and several anthropometric and serologic parameters that may be altered in obese subjects was evaluated, aimed at better understanding the connections between hepatic steatosis and various features of the metabolic syndrome. Our data confirmed a strong association between hepatic volume and visceral fat (28), and are in agreement with recent findings indicating that hepatic triglyceride content is closely related with central obesity (33), while a poorer association was observed with body weight or BMI. Free fatty acids from abdominal fat depots are traditionally viewed as the main source of hepatic fat. Alternatively, visceral fat accumulation and hepatic steatosis may be the results of the same pathogenic mechanism. Indeed, the origin of fatty acids stored in liver includes several potential sources, and recent evidence indicates that both serum fatty acids (including diet-derived fatty acids) and *de novo* lipogenesis contribute to the accumulation of hepatic fat (34, 35). The extent of fatty liver infiltration depends, on one hand, on the rate of hepatic triglycerides synthesis. On the other hand, it is regulated by the rate at which liver is able to secrete them into the bloodstream as triglyceride-rich VLDL. When triglyceride synthesis exceeds triglyceride secretion, lipid accumulation occurs. Therefore, any factor affecting triglyceride synthesis and/or secretion may influence the hepatic fat content. That being stated, our data are not in contrast with previous studies (11) showing that hepatic fat content was independent of BMI and either visceral or sc fat in normal weight and moderately overweight subjects. Indeed, in that weight range, factors other than substrate availability are likely to influence the rate of triglyceride synthesis and metabolism in liver, including genetic, nutritional, behavioral, toxic, hormonal, age and gender-related factors. At variance, in our study group including only severely obese subjects,

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the abundance of substrate and the severity of insulin-resistance seem to play a major role in increasing the rate of triglyceride synthesis and in promoting their accumulation in liver. Supporting this view, a strong association was observed between HLLV and serum glucose, insulin and HOMA, thus confirming the pathogenic link observed between insulin resistance and hepatic steatosis (8, 9, 13, 36). Serum levels of liver enzymes may be increased as a consequence of liver steatosis but their predictive value to establish the severity of liver damage is poor (37). An association between serum levels of liver enzymes and insulin resistance has been recently demonstrated in obese subjects (38, 39). In our study, HLLV was highly related to serum concentrations of various hepatic enzymes, suggesting that elevation of serum liver enzymes is proportional to liver enlargement. Beside insulin resistance, a strong relationship was demonstrated between HLLV and various parameters related to the metabolic syndrome. For most of them the association with HLLV was stronger than that observed with visceral fat. Of particular interest in this context, serum triglycerides and HDL cholesterol appeared mainly related to hepatic volume, suggesting that the dyslipidemic components of the metabolic syndrome are the features linked most closely with hepatic dysfunction. The triad of hyperglycemia, hypertension and hyperuricemia was described several decades ago, and the possibility that serum uric acid may contribute to the pathogenesis of hypertension has been recently reviewed (40). Our study, showing a positive relationship between hepatic volume, serum uric acid and blood pressure, suggests that hepatosteatosis may be involved in the pathogenesis of these abnormalities. Several studies have demonstrated a correlation between inflammation and the various manifestations of the metabolic syndrome, including insulin resistance, hypertension, dyslipidemia, endothelial dysfunction and a pro-coagulant state (6, 7, 41). Obesity is associated with increased serum levels of CRP (42), but the precise mechanisms leading to increased levels of this protein have not been fully elucidated, yet. Recently, an increase in CRP has been shown to be an independent risk factor for NAFLD (43). The results of our study, showing a clear association between liver volume and serum CRP, point to hepatosetatosis as a further link between obesity and the pro-inflammatory state of the metabolic syndrome. Finally, very close numbers were obtained when cut-off values of various risk factors for the diagnosis of the metabolic syndrome were used to calculate a cut-off value for HLLV, suggesting that liver enlargement accompanies the development of various features of the metabolic syndrome in obese women.

In conclusion, ultrasound measurement of HLLV represents a reliable, simple and low-cost tool for the evaluation of liver enlargement in obese women. A strong relationship between liver enlargement and various cardiovascular risk factors associated with insulin resistance has been demonstrated, supporting the view that liver steatosis should be included among the many facets of the metabolic syndrome in human obesity.

ACKNOWLEDGMENTS

This work was supported by: Ministero dell'Istruzione, dell'Università e della Ricerca Scientifica, programmi di ricerca cofinanziati 2002 "Obesity: Phenotype characterization and relationship with pathogenesis"; Centro di Eccellenza AmbiSEN "Effects of environmental chemical agents on the endocrine and nervous systems"; Ministero della Salute, programma speciale di sperimentazione 2002 "Istituzione osservatorio epidemiologico permanente per valutazione, prevenzione e cura dell'obesità e dei disturbi del comportamento alimentare".

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