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Visceral fat accumulation and insulin resistance are important factors in nonalcoholic fatty liver disease

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Background. Nonalcoholic fatty liver diseases are often associated with obesity, insulin resistance, and excessive visceral fat accumulation. The aims of this study were (1) to evaluate the relationship between the severity of fatty liver and visceral fat accumulation in nonalcoholic fatty liver diseases, and (2) to investigate the relationships of fatty liver with biochemical data and insulin resistance. ***Methods.*** One hundred twenty-nine subjects (63 women) with fatty liver diagnosed by ultrasonography were enrolled. Subjects positive for hepatitis B virus, hepatitis C virus, or autoimmune antibodies and those whose alcohol intake was over 20 g/day were excluded. The visceral fat area at the umbilical level and the liver–spleen ratio were evaluated by computed tomography. ***Results.*** The severity of fatty liver evaluated by ultrasonography showed a significant positive relationship with the visceral fat area and waist circumstance (fatty liver severity: mild, 92.0 ± 30.9 cm^2; moderate, 122.1 ± 32.6 cm^2; severe, 161.0 ± 48.4 cm^2; $P < 0.0001$). The visceral fat area and liver–spleen ratio were negatively correlated ($r = -0.605$, $P < 0.0001$). The severity of fatty liver showed strong positive relationships with serum aspartate aminotransferase, alanine aminotransferase, fasting plasma glucose, fasting plasma insulin, and insulin resistance. The severity of fatty liver was positively related to the visceral fat area in 49 nonobese subjects (body mass index <25). ***Conclusions.*** The severity of fatty liver was positively correlated with visceral fat accumulation and insulin resistance in both obese and nonobese subjects, suggesting that hepatic fat infiltration in nonalcoholic fatty liver disease may be influenced by visceral fat accumulation regardless of body mass index.

Key words: nonalcoholic fatty liver disease, insulin resistance, visceral fat, metabolic syndrome, ultrasonography

Introduction

Nonalcoholic fatty liver disease (NAFLD) has been increasing in Western countries as well as in Japan, because of the increasing prevalence of obesity, type 2 diabetes mellitus, and metabolic syndrome.[1,2] Several reports have suggested that simple fatty liver, the most common chronic liver disease, is a clinical condition that is a predecessor of nonalcoholic steatohepatitis (NASH), which sometimes progresses to liver cirrhosis and hepatocellular carcinoma.[3,4] In addition, NAFLD is considered to be one of the phenotypes of metabolic syndrome, which is characterized by obesity with visceral fat accumulation, diabetes mellitus, hyperlipidemia, and hypertension.[5] Other studies have indicated that serum triglycerides, free fatty acid, leptin, and tumor necrosis factor (TNF)-α from adipocytes in the visceral fat participate in the development of metabolic syndrome, including insulin resistance.[6,7] Accumulation of visceral fat is a more important risk factor for metabolic syndrome than subcutaneous fat, owing to its steatogenesis and production of various cytokines.[8,9] Judging from these results, accumulation of visceral fat might play a significant role in progression of fatty liver diseases, although few studies suggest a relationship between the severity of steatosis in NAFLD and accumulation of visceral fat.

The visceral fat area evaluated by abdominal computed tomography (CT) at the umbilical level is correlated with the visceral fat volume. Previous studies have reported that the accumulation of risk factors for metabolic syndrome is concomitant with an increase in the visceral fat area of more than 100 cm^2.[10,11] The clinical

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characteristics of NAFLD, usually without any symptoms, are slight elevation of serum aminotransferase, hyperglycemia, and insulin resistance with obesity.[2,12–14] The diagnosis of NAFLD is evaluated by several methods, including liver biopsy, as well as noninvasive radiological modalities, such as CT, magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and ultrasonography.[15,16] Liver biopsy is the gold standard for evaluation of steatosis and inflammation and fibrosis, including diagnosis of NASH, although it is sometimes invasive because of incidental peritoneal bleeding.

A previous study reported that ultrasonography, the most simple and cost-effective method among the radiological modalities, is useful for qualitative and quantitative evaluation of fatty liver in NAFLD.[15] The aims of the current prospective study were: (1) to evaluate the relationship between the severity of fatty liver in NAFLD assessed by ultrasonography and CT and the visceral fat area measured by CT, and (2) to investigate the relationships among the visceral fat area, liver function examined by liver enzymes, and insulin resistance.

Patients and methods

Study population

All 949 patients who visited Eguchi Hospital with elevated serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) between January 2004 and September 2004 underwent an ultrasonography examination for the diagnosis of fatty liver. Fat infiltration in liver was evaluated by two experienced body-imaging medical doctors (Y.E. and N.O.), who were blind to each subject's clinical and laboratory findings, according to the protocol described in the next section. In the current study, subjects with other liver diseases, including chronic viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, primary biliary cirrhosis, and drug-induced liver disease, were excluded. Subjects whose alcohol intake was over 20 g/day were also excluded. Finally, 129 outpatients with NAFLD without any other liver disease were enrolled in the study. These subjects underwent abdominal CT after informed consent was obtained.

Ultrasonography protocol

A 4-MHz transducer (LOGIQ 7; GE Healthcare, Waukesha, WI, USA) was used to observe sagittal and transverse views of the left lobe of the liver and the spleen, subcostal views of the right lobe of the liver and the right kidney, and intracostal views of the right lobe of the liver, the portal vein (right branch), and the hepatic vein (right and middle branches). The echogenic intensity of fat accumulation in the liver was graded semiquantitatively as follows, according to the criteria of Saadeh et al.:[15] normal, normal echogenicity; mild, slight diffuse increase in bright homogeneous echoes (i.e., "bright liver") in the liver parenchyma with normal visualization of the diaphragm and portal and hepatic vein borders and normal hepatorenal contrast of echogenicity; moderate, diffuse increase in bright echoes in the liver parenchyma with slightly impaired visualization of the peripheral portal and hepatic vein borders (i.e., "vascular blurring"); and severe, marked increase in bright echoes at a shallow depth with deep attenuation and impaired visualization of the diaphragm and marked vascular blurring.

CT protocol

Unenhanced spiral acquisition through the liver was obtained during a breath-hold at 5.0 mm collimation, 15.0 mm/rotation table speed (HQ mode, pitch 1:3), 120 kV (p), and auto mA (Light speed QXi; GE Healthcare). Images were reconstructed in 10-mm increments.

Clinical and laboratory assessments

Venous blood samples were taken from all subjects before 9:00 a.m. after a 12-h overnight fast to determine the serum levels of AST (IU/l), ALT (IU/l), total cholesterol (T-CHO; mg/dl), triglycerides (TG; mg/dl), plasma glucose (PG; mg/dl), and plasma insulin (μU/ml). Plasma insulin was determined using an enzyme immunoassay (Dainabot, Tokyo, Japan). All subjects were subjected to a 75-g oral glucose tolerance test (75 g-OGTT), and type 2 diabetes mellitus was diagnosed based on the World Health Organization criteria.[17] Insulin resistance was calculated by the homeostasis model (HOMA-IR) using the following formula: HOMA-IR = fasting insulin (μU/ml) × PG (mg/dl)/405.[18] Patients whose fasting plasma glucose level was higher than 140 mg/dl were not included in this evaluation. The body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. For the diagnosis of metabolic syndrome, we referred to the third report by the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III), which constitutes the updated guidelines of the National Cholesterol Education Program (NCEP).[19] Since most Japanese are smaller than Western people, we defined obesity using the following waist circumferences reported by the Japan Society for the Study of Obesity: >85 cm in men and >90 cm in women.[20]

Table 1. Characteristics of patients

	Overall (n = 129)	Men (n = 66)	Women (n = 63)
Age (years)	58.5 ± 11.9	55.9 ± 13.0	61.1 ± 10.1
Height (cm)	158.5 ± 9.1	164.3 ± 7.2	152.4 ± 6.5
Weight (kg)	65.5 ± 12.1	70.9 ± 12.2	59.9 ± 9.1
Body mass index (kg/m^2)	25.9 ± 3.1	26.1 ± 3.2	25.7 ± 3.0
Waist circumference (cm)	95.6 ± 10.1	94.1 ± 9.4	97.0 ± 10.6
Diabetes mellitus (yes:no)	48:81	31:35	30:33
Hyperlipidemia (yes:no)	66:63	38:28	36:27
Fatty liver (mild:moderate:severe)	42:45:42	14:23:29	28:22:13
VFA (cm^2)	129.3 ± 53.4	149.7 ± 56.9	107.9 ± 39.8
SFA (cm^2)	193.9 ± 84.4	155.5 ± 77.4	232.3 ± 73.8
AST (IU/l)	37 ± 32	38 ± 29	37 ± 36
ALT (IU/l)	41 ± 29	45 ± 29	37 ± 28
ALP (IU/l)	248 ± 111	242 ± 104	254 ± 118
T-CHO (mg/dl)	213 ± 41	211 ± 34	215 ± 48
TG (mg/dl)	143 ± 87	159 ± 104	129 ± 68
FPG (mg/dl)	118 ± 39	119 ± 37	116 ± 41
Insulin (μg/ml)	11.7 ± 7.3	12.2 ± 7.8	10.9 ± 6.5
HOMA-IR	3.6 ± 2.5	3.8 ± 2.7	3.5 ± 2.1

Data are expressed as means ± SD or number of subjects. The Spearman's correlation coefficient was used to correlate continuous variables. A χ-squared test was used for nominal variables
VFA, viscsral fat area; SFA, subcutaneous fat area; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; T-CHO, total cholesterol; TG, triglycerides; FPG, fasting plasma glucose; HOMA-IR, homeostasis model = fasting insulin (μU/ml) × plasma glucose (mg/dl)/405

Radiological assessment

All 129 subjects were subjected to abdominal CT in the morning after a 12-h overnight fast. The CT numbers (in Hounsfield units) were measured at 3 points each in the liver and spleen, and the mean numbers were used to determine the liver–spleen ratio.[15] In addition, the subcutaneous and intra-abdominal visceral fat areas (in cm^2) were measured at the umbilical level and calculated using a computer software program (Fat Scan; N2 System, Osaka, Japan).[10]

Statistical analysis

Continuous variables were summarized as means ± SD. Differences according to sex were compared using the Fisher exact test if the outcome variable was categorical (e.g., presence/absence of diabetes mellitus or hyperglycemia) or the χ-squared test (e.g., grading of fatty liver). Pearson's correlation coefficient analysis was used to compare the liver–spleen ratio and the visceral fat area and variables. Kruskal-Wallis analysis followed by Scheffe's post hoc test and a Spearman's correlation coefficient analysis was used to test for relationships between the severity of fatty liver and the visceral or subcutaneous fat areas, biochemical data, and BMI. All analyses were carried out using the SAS program (SAS Institute, Cary, NC, USA). Differences were considered significant if the probability of the difference occurring by chance was less than 5% ($P < 0.05$).

Results

Patient characteristics

The classification of the 949 members of the study population receiving ultrasonography on the basis of elevated serum AST and/or ALT is shown in Fig. 1. In total, 129 subjects with fat infiltration in the liver evaluated by ultrasonography without any other liver disease were included in the study. Table 2 shows the background characteristics of the 129 subjects. Their mean age was 59 ± 12 years (range, 26–80 years); 66 (51%) subjects were male; the mean BMI was 25.9 ± 3.1 kg/m^2 (range, 19.9–35.2 kg/m^2); type 2 diabetes mellitus was present in 48 (37%) subjects; hyperlipidemia was found in 66 (51%) subjects; the overall visceral fat area was 129.3 ± 53.4 cm^2 (range, 20.6–389.6 cm^2), and fat area was 149.7 ± 56.9 cm^2 (range, 80.0–389.6 cm^2) in men and 107.9 ± 39.8 cm^2 (range, 20.6–266.9 cm^2) in women.

Fatty liver evaluation by CT and ultrasonography

As shown in Fig. 2, the liver–spleen ratio and the visceral fat area for the abdominal plain CT were significantly negatively correlated (r = –0.605, $P < 0.0001$). The liver–spleen ratio assessed by CT was inversely related to the severity of fat infiltration in the liver evaluated with ultrasonography ($P < 0.0001$) (Fig. 3). This result indicates that the ultrasonography

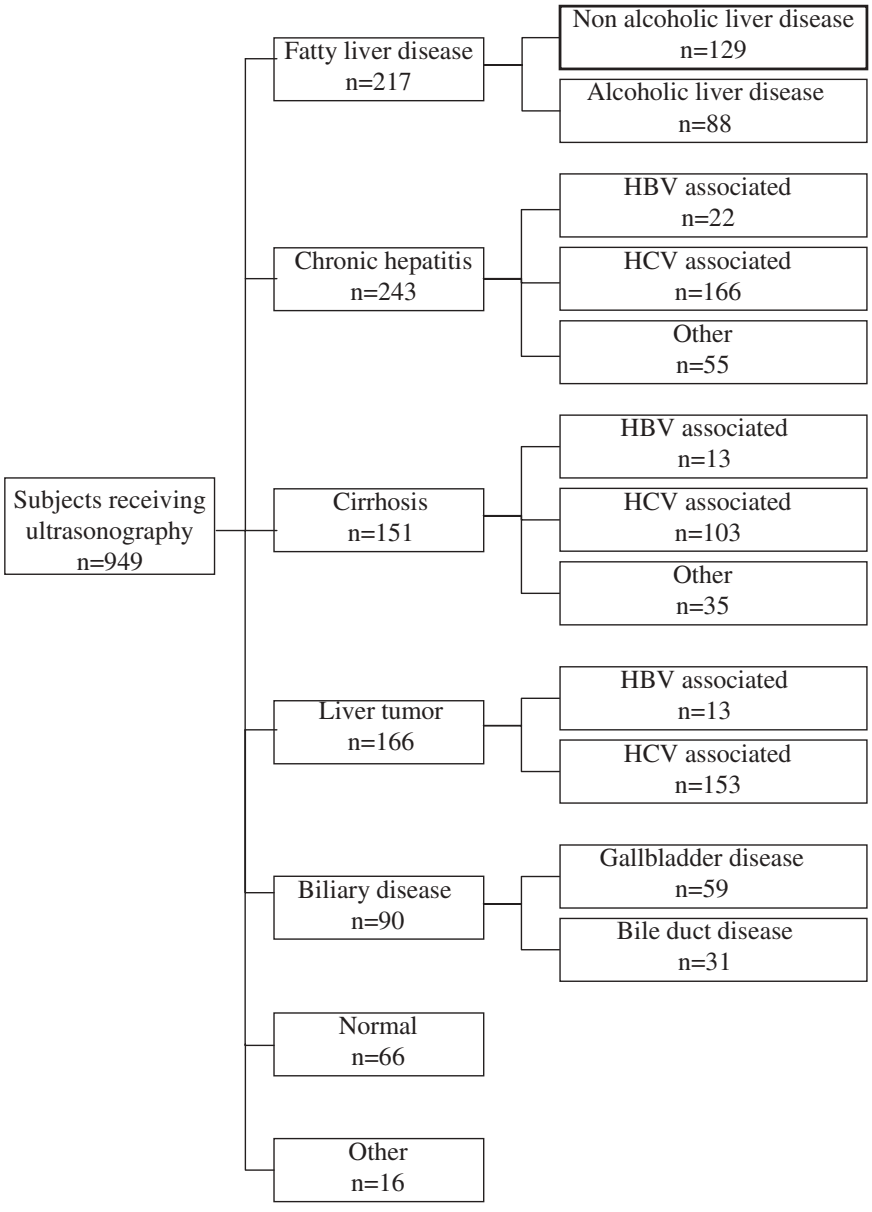

Fig. 1. Classification of the 949 subjects in the study population who received ultrasonography based on elevated serum aspartate aminotransferase and/or alanine aminotransferase. *HBV*, hepatitis B virus; *HCV*, hepatitis C virus

Table 2. Associations between ultrasonography grading of fatty liver and variables

	Mild (n = 42)	Moderate (n = 45)	Severe (n = 42)	P value
Weight (kg)	61.7 ± 10.1	67.9 ± 10.7	71.1 ± 10.8	0.01
Body mass index (kg/m^2)	24.7 ± 3.1	26.1 ± 2.5	27.4 ± 3.0	0.01
Waist circumference (cm)	92.1 ± 10.2	98.1 ± 9.0	101.2 ± 8.0	0.01
Metabolic syndrome (%)	11 (26)	14 (31)	18 (43)	N.S.
AST (IU/l)	24.6 ± 11.2	35.2 ± 19.4	40.6 ± 30.0	0.01
ALT (IU/l)	24.1 ± 14.7	45.2 ± 29.8	53.9 ± 37.3	0.01
ALP (IU/l)	231.6 ± 80.6	252.7 ± 75.0	233.4 ± 85.2	N.S.
T-CHO (mg/dl)	213.4 ± 42.6	214.2 ± 39.1	214.8 ± 45.2	N.S.
TG (mg/dl)	123.9 ± 73.2	153.4 ± 94.5	161.4 ± 112.2	0.05
FPG (mg/dl)	106.4 ± 30.7	114.1 ± 29.2	110.8 ± 22.6	0.01
Insulin (μg/ml)	8.7 ± 7.9	9.3 ± 4.0	13.2 ± 8.7	0.01
HOMA-IR	1.26 ± 2.10	1.84 ± 1.80	2.82 ± 2.87	0.01

Data are expressed as means ± SD or number of subjects. The Spearman's correlation coefficient was used to correlate continuous variables. A χ-squared test was used for nominal variables
N.S., not significant

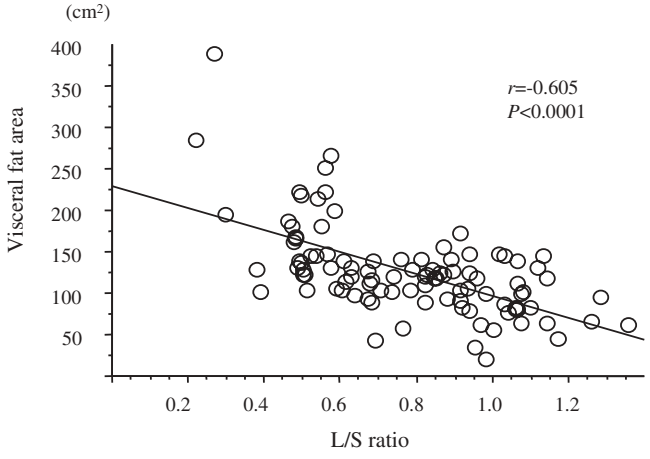

Fig. 2. The relationship between the liver–spleen ratio (*L/S ratio*) and the visceral fat area evaluated by abdominal plain computed tomography shows a significant negative correlation ($r = –0.605$, $P < 0.0001$)

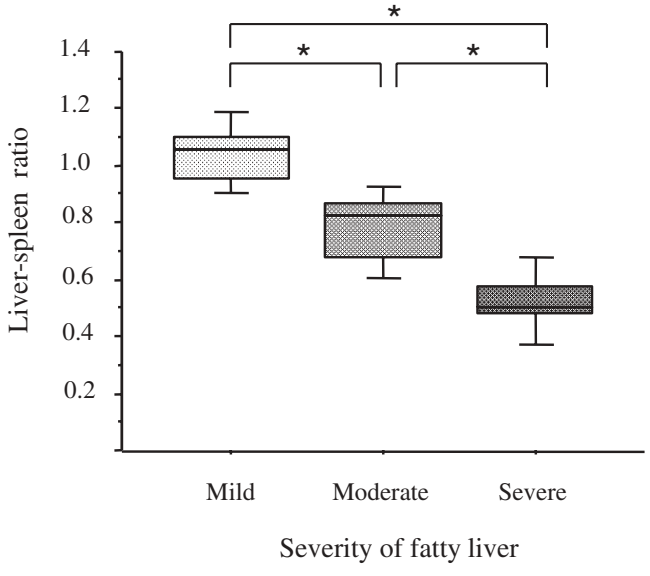

Fig. 3. The liver–spleen ratios in the three groups of fatty liver evaluated semiquantitatively by ultrasonography. Among the three groups, the liver–spleen ratio assessed by computed tomography for fatty liver is the inverse of fatty liver severity evaluated by ultrasonography. Values were expressed as means ± SD. The comparisons between groups were made using one-way analysis of variance with Scheffe's post hoc test. *$P < 0.01$

examination is adequate to classify the severity of fatty liver in this study.

Associations between grading of fatty liver and fat areas and laboratory findings

The severity of fatty liver evaluated by ultrasonography was related to the visceral fat area at the umbilical level ($P < 0.01$, Fig. 4A), but not to the subcutaneous fat area (Fig. 4B). Even in nonobese subjects, the severity of fatty liver evaluated by ultrasonography was significantly correlated with the visceral fat area (Fig. 4C; $P < 0.01$), indicating that accumulated visceral fat in nonobese subjects could be detected by ultrasonography. This relationship was not observed between fatty liver and the subcutaneous fat area (Fig. 4D). Among the 49 nonobese subjects (BMI < 25 kg/m^2) with fatty liver, 19 subjects had mild fatty liver, 15 moderate fatty liver, and 14 severe fatty liver. As shown in Table 2, BMI and waist circumference increased with the severity of fatty liver ($P < 0.0001$). Among biochemical parameters, increases in serum AST and ALT were related to the severity of fatty liver, whereas other factors, including ALP, T-CHO, and TG, remained unaffected. Both the PG and plasma insulin levels and HOMA-IR were strongly correlated with the severity of fatty liver evaluated by ultrasonography. The ratio of metabolic syndrome in fatty liver increased with the severity of fatty liver, but did not differ significantly among the three groups: 26% in mild fatty liver, 31% in moderate fatty liver, and 43% in severe fatty liver. Regarding the relationship between the liver–spleen ratio and laboratory parameters, a Pearson's correlation coefficient analysis revealed a correlation only with ALT ($r = –0.4$, $P < 0.01$) without any correlation with other factors, including AST, plasma glucose, plasma insulin, and HOMA-IR (Table 3).

Discussion

The results of the current study demonstrated that the severity of fatty liver in NAFLD assessed by ultrasonography and the liver–spleen ratio calculated by CT are closely correlated with the visceral fat accumulation evaluated by CT. CT-evaluated visceral fat accumulation was correlated with the waist circumference in this study, indicating that the waist circumference is a good marker for visceral fat accumulation, as previously demonstrated.[21] A previous study indicated that visceral fat accumulation is one of the important risk factors for metabolic syndrome, including diabetes mellitus with insulin resistance, hyperlipidemia, and hypertension,[7] while the current results indicate that risk factors for metabolic syndrome can be estimated by ultrasonographic imaging of fatty liver. In fact, the severity of fatty liver was positively related to HOMA-IR, an index for insulin resistance.

Previous studies have shown that adipocytes in the visceral fat produce adipocytokines, such as leptin, TNF-α, and adiponectin,[22] and that these adipocytokines flow directly into the liver via the portal vein.[23] Recently, these adipocytokines have been reported to

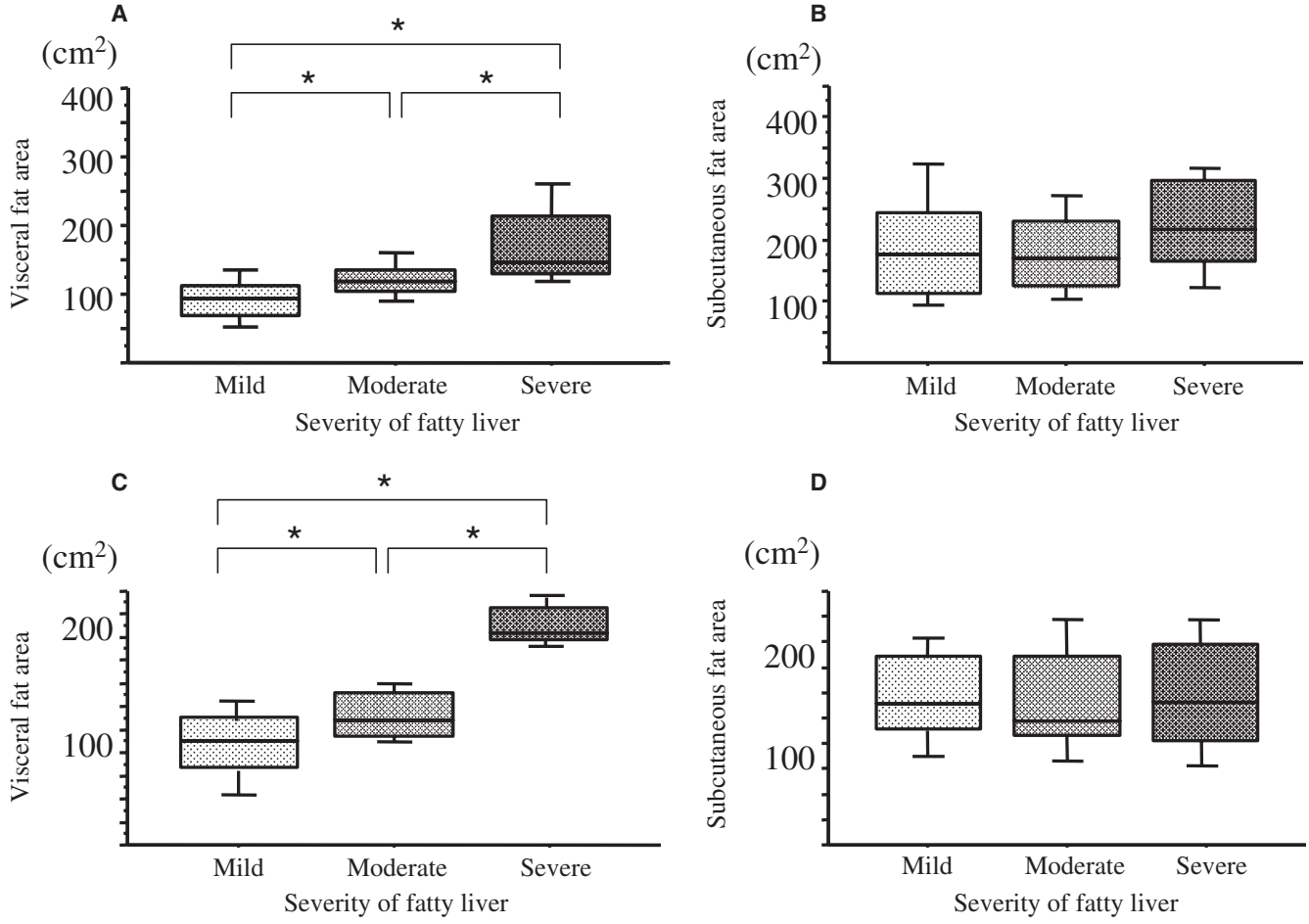

Fig. 4A–D. The fatty liver severity evaluated semiquantitatively by ultrasonography is related to the visceral fat area at the umbilical level ($P < 0.01$) (**A**), but not to the subcutaneous fat area (**B**). Among the 49 nonobese subjects (BMI < 25 kg/m^2) with fatty liver, the severity of fatty liver evaluated by ultrasonography is a significant marker for the visceral fat area ($P < 0.01$) (**C**). This relationship is not observed between fatty liver and the subcutaneous fat area (**D**). Values are expressed as means ± SD. The comparisons between groups were made using one-way analysis of variance with Scheffe's post hoc test. *$P < 0.01$s

Table 3. Relationship between liver–spleen ratio and laboratory parameters

Variable	Correlation (r)	95% CI	P value
Weight	–0.331	–0.462 to –0.186	0.01
Waist	–0.122	–0.271 to –0.033	N.S.
Body mass index	–0.163	–0.309 to –0.009	0.05
AST	–0.244	–0.384 to –0.093	0.01
ALT	–0.403	–0.525 to –0.266	0.01
ALP	0.022	–0.194 to –0.235	N.S.
T-CHO	0.041	–0.175 to –0.253	N.S.
TG	–0.094	–0.302 to –0.123	N.S.
FPG	–0.086	–0.295 to –0.131	N.S.
Insulin	–0.156	–0.358 to –0.061	N.S.
HOMA-IR	–0.164	–0.366 to –0.052	N.S.

A Pearson's correlation coefficient analysis was used to compare the liver–spleen ratio and laboratory parameters
95% CI, 95% confidence interval; N.S., not significant

have several effects on metabolism, such as induction of a second hit on NASH in simple fatty liver, and induction of insulin resistance and metabolic syndrome.[24]

It has been reported that the severity of fatty liver can be generally evaluated by the liver–spleen ratio examined with CT and/or the fat accumulation examined with ultrasonography.[25] The current results also indicate that both these methods are useful for detecting visceral fat accumulation. The advantage of ultrasonography over CT is that it is noninvasive and does not involve any exposure to radiation.[26] It is further speculated that CT has another disadvantage for the diagnosis of fatty liver, since CT imaging, as evaluated by the improved festoon bulb, makes the distinction of mild and/or moderate fatty liver from the spleen difficult.

One of the aims of this study was the detection of visceral fat accumulation in nonoverweight subjects as defined by WPRO criteria.[27] Previous reports showed that BMI as well as visceral fat accumulation were related to the development of nonalcoholic fatty liver disease.[28,29] Recent studies have demonstrated that nonoverweight subjects with BMI <23 have been diagnosed as having fatty liver with the complication of glucose intolerance and metabolic syndrome in Asian countries, including Japan.[30,31] This study indicated that fatty liver, easily detected by ultrasonography, is implicated in nonoverweight subjects with visceral fat accumulation, and that fatty liver is a good indicator for metabolic syndrome in both obese and nonobese subjects.

In conclusion, the present results showed that fatty liver evaluated by ultrasonography and CT is related to the visceral fat accumulation, which represents a risk factor for metabolic syndrome. Therefore, fatty liver detection by ultrasonography appears to be very useful for the diagnosis of metabolic syndrome. In the experienced hands of a gastroenterologist or radiologist, ultrasonography should be integral to the evaluation of liver diseases, including fatty liver. Since ultrasonography could not distinguish simple fatty liver from steatohepatitis, which was detected only by liver biopsy, further study is required to assess the relationship between pathological evaluation for the grading of fatty liver and steatohepatitis and visceral fat accumulation.

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