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Hepatic steatosis rather than visceral adiposity is more closely associated with insulin resistance in the early stage of obesity

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Abstract

The aim of the present study was to investigate the specific relationship between hepatic steatosis and insulin resistance in the early stage of obesity. Among general health examinees who received an ultrasound scanning, 131 subjects without fatty liver (non-FL group) and 142 subjects with fatty liver (FL group) were selected so that both groups were matched for age, sex, body mass index, and % body fat. The FL group was then subdivided into 2 groups according to the severity of steatosis by ultrasound. Insulin resistance was assessed by homeostasis model assessment for insulin resistance, serum high-molecular-weight (HMW) adiponectin, and insulin-like growth factor binding protein 1 concentrations. Unexpectedly, the non-FL group showed higher waist circumference than the FL group. Nevertheless, homeostasis model assessment for insulin resistance as well as conventional insulin resistance indexes such as serum insulin, free fatty acid, and triglyceride levels demonstrated a stepwise increase, and HMW adiponectin and insulin-like growth factor binding protein 1 demonstrated a stepwise decrease with increasing degree of hepatic steatosis. Overall, insulin resistance markers correlated with obesity indexes, but only HMW adiponectin no longer showed any meaningful correlation in the presence of fatty liver. The prevalence of BP, fasting serum glucose, and high-density lipoprotein cholesterol above or below cutoff points and subjects having 2 or more metabolic syndrome components were higher in the moderate to severe FL group compared to the non-FL group. In conclusion, these results in nondiabetic and relatively normal–body mass index subjects suggest that hepatic steatosis is independently associated with insulin resistance regardless of extrahepatic adiposity and might be the earliest event in pathogenesis of the metabolic syndrome.

1. Introduction

Previous studies established that visceral fat accumulation is a major contributor to the development of insulin resistance and the metabolic syndrome (MetS) [1,2]. To date, however, the relative importance of fatty liver, which usually coexists with visceral adiposity, remains elusive. Emerging evidences support that fatty liver plays an essential role in the pathogenesis of insulin resistance [3-5]. Therefore, the purpose of this study was to examine whether a close relationship exists between liver steatosis and insulin resistance independent of obesity. To explore this, we recruited a substantial number of nondiabetic subjects and those with almost normal body mass index (BMI). Insulin resistance was assessed by homeostasis model assessment for insulin resistance (HOMA-IR), serum high-molecular-weight (HMW) adiponectin, and insulin-like growth factor binding protein 1 (IGFBP-1). We compared these biomarkers between the 2 groups that were comparable with respect to age, sex, BMI, and % body fat (%BF), with one group having fatty liver and the other not. In addition, to clarify whether an association exists between the magnitude of steatosis present in the liver and the insulin resistance parameters, subjects with fatty liver were subdivided into 2 groups, the mild degree of fatty liver and the other, that is, the moderate to severe degree of fatty liver according to the ultrasound (US) findings. We also compared the crude prevalence of the MetS components between the groups.

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2. Subjects and methods

2.1. Subjects

A total of 568 apparently healthy middle-aged people were enrolled in our health checkup program during February to March 2006. Of these participants, 536 received an US scan of the abdomen as a part of the examinations and 153 (28.5%) subjects were diagnosed with fatty liver, the prevalence being similar to our previous study [6]. After excluding 11 markedly obese subjects (BMI ≥35 kg/m^2), the remaining 142 subjects were allocated to fatty liver (FL) group. Most of them had nonalcoholic fatty liver disease (NAFLD) according to the western country's criteria of alcohol intake of less than 20 g/d. Of 142 subjects, 52 were diagnosed with mild hepatic steatosis (mild FL group) and the remaining 90 subjects with moderate to severe steatosis (moderate to severe FL group). Among people who had no fatty liver on US, 131 subjects (non-FL group) were selected mainly based on BMI to match for FL group. As a result, both groups were comparable with respect to age, sex, BMI, % BF, but not waist circumference (WC). A third group consisted of 60 normal controls (NC group), who had neither fatty liver nor abnormalities in all parameters defined as follows: BMI <25 kg/m^2, %BF ≤23 % (men) or ≤ 27% (women), WC <85cm (men) or <80cm (women), blood pressure <130 mm Hg systolic and <85 mm Hg diastolic, fasting serum glucose (FSG) <6.11 mmol/L, triglyceride (TG) <1.68 mmol/L, and high-density lipoprotein cholesterol (HDL-C) ≥1.03 mmol/L (men) or ≥1.29 mmol/L (women). The cutoff points 85 cm for WC of men and 6.11 mmol/L for FSG used in this study are derived from the current Japanese criteria for the diagnosis of the MetS. Clinical characteristics of the subjects in each group are shown in Table 1. No subject had evidence of viral hepatitis, autoimmune hepatitis, and liver cirrhosis nor were any being treated with drugs known to affect glucose, lipid, or hepatic metabolism at the time of the study.

2.2. Waist circumference, %BF, and US examination

Waist circumference was measured at the level of the umbilicus in standing position by one physician (TW). Body fat mass was estimated by bioelectric impedance using a TBF-410 (Tanita, Tokyo, Japan). The US scan was performed by trained technicians using the Ultrasound Equipment Model SSA-250A (Toshiba, Tokyo, Japan). Fatty liver was diagnosed based on 4 ultrasonographic criteria [7]: (1) a diffuse hyperechoic echotexture ("bright liver"), (2) increased echotexture compared to the kidneys, (3) vascular blurring, and (4) deep attenuation. The mild degree of fatty liver and the other, namely, the moderate to severe degree of fatty liver, were distinguished based on the strength of echogenicity.

Table 1
Clinical characteristics of subjects in the NC, non-FL, mild FL, and moderate to severe (moderate≦) FL groups

	NC	Non-FL	FL	
			Mild	Moderate≦
n (% male)	60 (48.3)	131 (77.1)	52 (75.0)	90 (74.4)
Age (y)	47.3 ± 11.5	52 ± 9.8	53.2 ± 9.4	52.4 ± 9.1
BMI (kg/m^2)	20.4 ± 1.8	24.9 ± 2.1	24.3 ± 2.6	24.7 ± 2.4
Body fat (%)	20.5 ± 4.5	26.3 ± 5.8	25.6 ± 5.7	26.8 ± 5.6
WC (cm)	74.6 ± 6.1	88.6 ± 4.1	84.9 ± 6.6[a] ***	85.8 ± 5.4[a] ***
SBP (mm Hg)	112.2 ± 11.8	128.6 ± 16.6	132.6 ± 18.4	133.4 ± 16.4[a] *
DBP (mm Hg)	64.7 ± 7.4	75.7 ± 9.9	78.1 ± 10.7	79.4 ± 9.6[a] **
TC (mmol/L)	4.72 ± 0.63	5.27 ± 0.85	5.42 ± 0.90	5.03 ± 1.30
TG (mmol/L)	0.87 ± 0.28	1.28 ± 0.67	1.39 ± 0.60	1.48 ± 0.62[a] *
HDL-C (mmol/L)	1.69 ± 0.37	1.44 ± 0.36	1.46 ± 0.46	1.31 ± 0.33[a] **
FSG (mmol/L)	5.10 ± 0.38	5.56 ± 1.02	5.64 ± 1.12	6.10 ± 1.62[a] **,[b] *
HbA_{1c} (%)	5.18 ± 0.25	5.38 ± 0.59	5.44 ± 0.53	5.70 ± 1.09[a] **
UA (mmol/L)	0.28 ± 0.07	0.33 ± 0.09	0.34 ± 0.08	0.36 ± 0.08
AST (IU/L)	26.1 ± 5.0	29.2 ± 6.9	29.8 ± 7.3	36.0 ± 17.2[a] *,[b] *
ALT (IU/L)	20.3 ± 7.2	25.3 ± 11.7	28.8 ± 15.5	38.8 ± 21.0[a] ***,[b] **
γ-GTP (IU/L)	19.2 ± 9.8	36.5 ± 28.0	39.0 ± 36.6	46.6 ± 37.7[a] *
FFA (mmol/L)	0.36 ± 0.16	0.46 ± 0.19	0.52 ± 0.22	0.54 ± 0.20[a] **
IRI (μU/L)	4.5 ± 1.9	6.9 ± 3.8	7.3 ± 3.4	9.5 ± 4.8[a] ***,[b] **
hs-CRP (mg/dL)	0.17 ± 0.13	0.21 ± 0.17	0.21 ± 0.13	0.23 ± 0.17[c] *

Data are expressed as means ± SD. a vs non-FL; b vs mild FL; c vs NC. Moderate≦ indicates moderate to severe; TC, total cholesterol; HbA_{1c}, hemoglobin A_{1c}; UA, uric acid; AST, asparate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; FFA, free fatty acid; IRI, immunoreactive insulin; hs-CRP, high-sensitive C-reactive protein.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

Table 2
Insulin resistance markers in NC, non-FL, mild FL, and moderate to severe FL groups

	NC (60)	Non-FL (131)	FL (142)	
			Mild (52)	Moderate ≦(90)
HMV adiponectin (μg/mL)				
Male	5.08 ± 2.01	3.88 ± 2.07	3.42 ± 1.75	2.41 ± 1.43[a] ***,[b] **
Female	9.27 ± 5.05	6.07 ± 2.55	5.72 ± 3.43	4.10 ± 1.42[a] ***,[b] ***
IGFBP-1 (ng/mL)	30.2 ± 13.4	18.2 ± 11.9	15.4 ± 15.2	12.5 ± 7.4[a] ***
HOMA-IR	1.03 ± 0.44	1.75 ± 1.10	1.83 ± 0.90	2.51 ± 1.25[a] ***,[b] ***

Data are expressed as means ± SD. a vs non-FL; b vs mild FL.
** $P < .01$.
*** $P < .001$.

2.3. Biological measurements

After an overnight fast, blood samples were drawn and serum samples for the measurement of insulin, adiponectin, and IGFBP-1 were stored at −30°C until assayed. High-molecular-weight adiponectin concentrations were determined by a 2-step sandwich ELIA using monoclonal antibodies against recombinant human adiponectin (Fujirebio, Tokyo, Japan). Cross-reactivity with lower molecular forms was negligible in this assay. The recovery rate was almost 100%, and the intra- and interassay coefficients of variation were 3.8% and 6.5%, respectively. Insulin-like growth factor binding protein 1 concentrations were measured by a 2-site immunoradiometric assay using the Total IGFBP-1 DSL-7800 Kit (Diagnostic Systems Laboratories, Webster, TX). The minimal detection limit was 0.33 ng/mL, and the intra- and interassay coefficients of variation were 4.2% and 4.4%, respectively.

2.4. Statistical analysis

Statistical significance between the 2 groups was analyzed by an unpaired t test or Wilcoxon test, appropriately. Simple correlation analyses were performed using Spearman correlation coefficient. Prevalence was assessed by χ^2 analysis. All data are mean ± SD, and statistical significance was defined as $P < .05$.

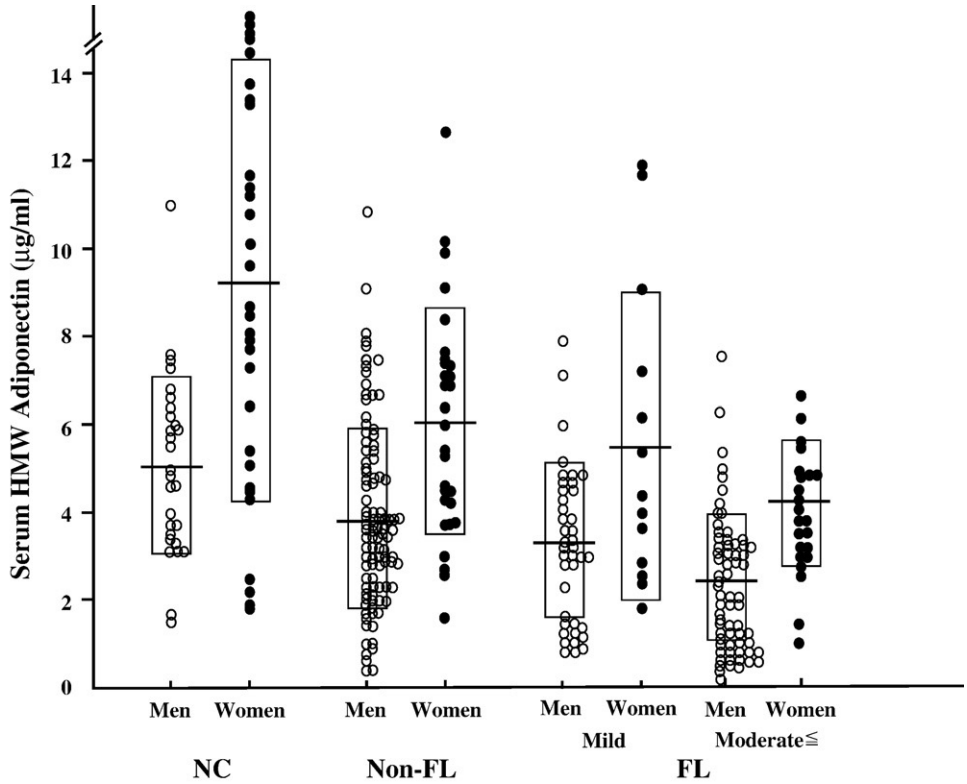

Fig. 1. Serum HMW adiponectin concentrations in NC, non-FL, mild FL, and moderate to severe fatty liver (moderate ≦ FL) groups, each separately by sex. The horizontal bar and box represent mean ± SD. In both sexes, the mean values were significantly different between NC and non-FL groups ($P < .001$) and between non-FL or mild FL and moderate to severe FL groups ($P < .001$).

3. Results

3.1. Clinical characteristics of NC, non-FL, mild FL, and moderate to severe FL groups

The anthropometric and metabolic characteristics of each group were shown in Table 1. There was no difference in the mean values for age, BMI, %BF, or in sex distribution between non-FL and FL groups as intended. Unexpectedly, WC was significantly higher in the non-FL than in both FL groups, not only in pooled data of both sexes (Table 1) but also in each sex (88.6 ± 4.2 vs 86.0 ± 5.5 cm, $P < .001$ for men; 88.7 ± 3.6 vs 83.8 ± 6.8 cm, $P < .001$ for women). The proportion of subjects with WC ≥85 cm for men or ≥80 cm for women was also higher in the non-FL than in the FL group (88.5% vs 62.7%, $P < .001$). Nevertheless, systolic blood pressure (SBP) and diastolic blood pressure (DBP), fasting serum insulin, glucose, hemoglobin A_{1c}, TG, free fatty acid, aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase levels were significantly higher and HDL-C was significantly lower in the moderate to severe FL group than in the non-FL group, whereas uric acid, total cholesterol, and high-sensitive CRP were not different between them (Table 1). In particular, as shown in Table 2, HOMA-IR increased from NC (1.03 ± 0.44) to non-FL (1.75 ± 1.10, $P < .001$) and mild FL (1.83 ± 0.90) and further to moderate to severe FL group (2.51 ± 1.25, $P < .001$ vs non-FL and mild FL). The raw values of serum HMW adiponectin were plotted separately by sex in each group (Fig. 1), showing higher values in women than in men in all groups. Serum HMW adiponectin decreased from NC

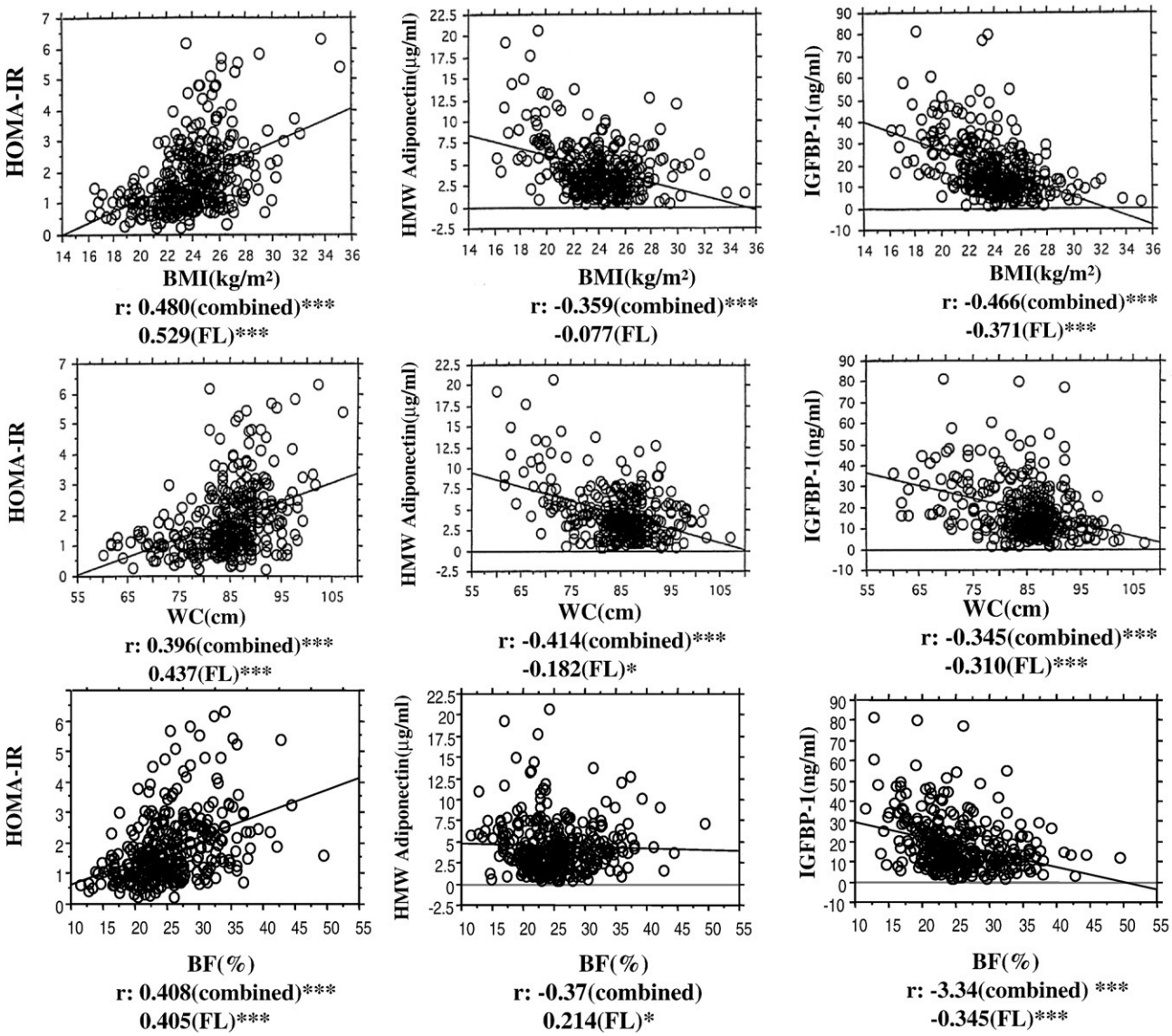

Fig. 2. Correlations between insulin resistance markers (HOMA-IR, HMW adiponectin, IGFBP-1) and obesity indexes (BMI, WC, %BF). The regression line is derived from the combined data of the 4 groups. Coefficient of correlation (r value) is given in each combined group and FL group. *$P < .05$; ***$P < .001$.

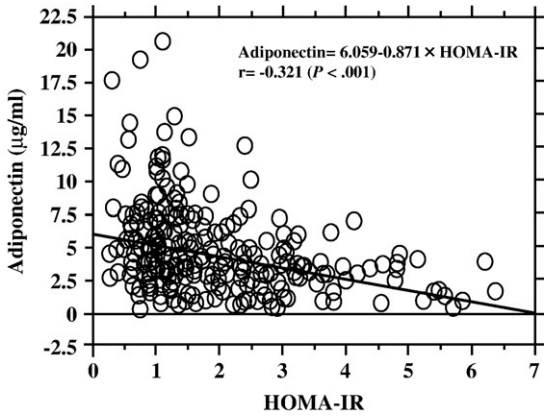

Fig. 3. Correlation between HMW adiponectin and HOMA-IR in combined data.

(5.08 ± 2.01 μg/mL for men and 9.27 ± 5.05 μg/mL for women) to non-FL (3.88 ± 2.07 and 6.07 ± 2.55μg/mL, respectively; both $P < .001$) and mild FL (3.42 ± 1.75 and 5.72 ± 3.43 μg/mL, respectively) and further to moderate to severe FL (2.41 ± 1.43 and 4.10 ± 1.42 μg/mL, respectively [both $P < .01$], vs non-FL and mild FL).

Serum IGFBP-1 levels were not different between sexes. They decreased in parallel with adiponectin from NC (30.2 ± 13.4 ng/mL) to non-FL (18.2 ± 11.9 ng/mL $P < .001$), mild FL (15.4 ± 15.2 ng/mL), and further to moderate to severe FL groups (12.5 ± 7.4 ng/mL [$P < .001$] vs non-FL).

3.2. Correlations among parameters

There were significant correlations between obesity indexes (BMI, WC, %BF) and putative hepatic insulin resistance markers (HOMA-IR, HMW adiponectin, IGFBP-1) in pooled data from 4 groups (Fig. 2). However, HMW adiponectin no longer showed a meaningful correlation in the presence of fatty liver (r value: 0.077 with BMI; 0.182 with WC; 0.214 with %BF in both FL groups). HMW adiponectin correlated with HOMA-IR ($r = -0.321$, $P < .001$, Fig. 3) and more strongly with IGFBP-1 ($r = 0.405$, $P < .001$, Fig. 4). Insulin-like growth factor binding protein 1 correlated with HOMA-IR ($r = -0.387$, $P < 0.001$) and with insulin ($r = -0.234$, $P < .005$) as expected (data not shown). Alanine aminotransferase correlated with neither HMW adiponectin nor IGFBP-1.

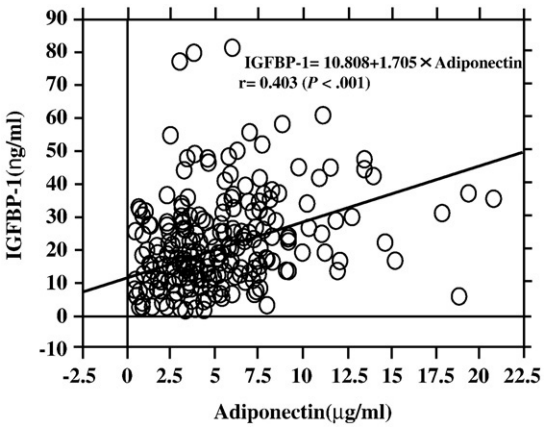

Fig. 4. Correlation between IGFBP-1 and HMW adiponectin in combined data.

Table 3
Prevalence of individual components of the MetS and elevated hepatic enzymes

	Non-FL (131)	FL (142)		P[a]
		Mild (52)	Moderate ≦ (90)	
SBP ≧130 mm Hg	61 (46.6%)	28 (53.8%)	55 (61.1%)	<.05
DBP ≧85 mm Hg	24 (18.3%)	9 (17.3%)	28 (31.1%)	<.05
FSG ≧6.11 mmol/L	18 (13.7%)	8 (15.4%)	27 (30.0%)	<.01
TG ≧1.68 mmol/L	25 (19.1%)	12 (23.1%)	26 (28.9%)	NS
HDL-C <1.03 mmol/L (men), <1.29 mmol/L (women)	19 (14.5%)	8 (15.4%)	23 (25.6%)	<.05
UA ≧0.42 mmol/L (men), ≧0.36 mmol/L (women)	25 (19.1%)	9 (17.3%)	26 (28.9%)	NS
ALT ≧50 IU/L	7 (5.3%)	5 (9.6%)	20 (22.2%)	<.001
AST ≧ 50 IU/L	2 (1.5%)	2 (3.8%)	10 (11.1%)	<.002
γ-GTP ≧80 IU/L	14 (10.7%)	7 (13.5%)	15 (16.7%)	NS

[a] Statistical significance between non-FL and moderate ≦ FL groups by χ^2 test. NS indicates not significant. Other Abbreviations are the same as in Table 1.

3.3. Prevalence of individual components of the MetS and its aggregation in the non-FL, mild, and moderate to severe FL groups

The positive rate of SBP, DBP, FSG, and HDL-C above or below the individual cutoff points indicated in Table 3 was higher in the moderate to severe FL group compared to the non-FL group. Subjects having 2 or more MetS components were more common in this group than in the non-FL group (40.0% vs 25.8%, $\chi^2 = 5.025$; $P < .05$).

4. Discussion

Fat accumulation in the liver generally occurs at the same time as in visceral and subcutaneous tissues. Therefore, it is difficult to discriminate between effects of regional adiposity on insulin resistance. In the present study, we intended to specify the relationship between fatty liver and insulin resistance independent of obesity. For this purpose, we recruited a cohort of apparently healthy middle-aged nondiabetic (FSG <6.11 mmol/L) people with relatively normal BMI. The subjects were divided into 2 groups according to the presence or absence of fatty liver on US examination, and major confounders such as age, sex, BMI, and %BF were matched in both groups. It has been reported that the sensitivity and specificity of the US image for recognizing fat, as assessed on liver biopsy, are 60% to 94% and 84% to 95%, respectively [7].

Although US imaging is not very sensitive for liver steatosis, it is especially diagnostic when positive [7]. We believe that US examination is, at least, possible to discriminate between subjects with mild degree and moderate to severe degree of fatty liver based on its echogenicity. Thus, the semiquantitatively classified groups of subjects allow us to examine the impact of hepatic fat accumulation on insulin resistance and the MetS.

The main findings in the present study are that fatty liver is closely associated with insulin resistance as evidenced by HOMA-IR, IGFBP-1, and HMW adiponectin, an established very sensitive biomarker of insulin resistance [8,9], irrespective of obesity indexes (BMI, %BF, WC). The results remain unchanged when analyzed in men or women separately. Previous studies suggested that HMW adiponectin is the active form of this protein: thiazolidinedione treatment caused an increase in only the HMW form of circulating adiponectin, which correlated strikingly with improved hepatic insulin action [10] Therefore, the lower adiponectin levels in the moderate to severe FL group indicate that this group is more hepatic insulin resistant than the others. Moreover, adiponectin no longer showed any meaningful correlations with BMI, WC, and %BF in the FL group, whereas HOMA-IR and IGFBP-1 remained correlated with them. These results are in line with the recent findings by Targher et al [11] that hypoadiponectinemia closely correlated with NAFLD in obese individuals, which was only slightly weakened after adjustment for BMI and waist-to-hip ratio. We, therefore, believe that serum adiponectin level is the most sensitive reflection of hepatic steatosis. In fact, Tiikkainen et al [12] demonstrated a significant correlation between changes in adiponectin levels and liver fat content. To our knowledge, this is the first study incorporating HMW adiponectin measurements. Because WC is a measure for visceral adiposity and abdominal subcutaneous fat volume, the present results strongly argue that insulin resistance is more closely associated with fatty liver than with extrahepatic fat deposition. In this context, Seppälä-Lindroos et al [3] found no correlation between visceral fat volume (determined by magnetic resonance imaging) and liver fat content (determined by proton spectroscopy) in 30 apparently healthy men with a relatively normal weight. The degree of obesity in our subjects was modest (the mean BMI was <25 kg/m^2 in both non-FL and FL groups), suggesting that an increase in liver fat content might be the earliest event in the development of hepatic insulin resistance. Obviously, a major limitation of our study resides in the absence of quantitative estimations for both liver fat content and visceral fat accumulation. Consequently, the present results could not completely exclude the effect of intra-abdominal fat deposition.

As for the mechanism, Samuel et al [13] demonstrated that high fat feeding for 3 days in rats caused a 3-fold elevation in hepatic TG and fatty acyl-coenzyme A content without any significant alterations of muscle and visceral (mesenteric) fat content. These rats with NAFLD displayed increased gluconeogenesis and endogenous glucose production and led to hepatic insulin resistance. They showed a positive linear correlation between liver TG content and inability of insulin to suppress endogenous glucose production, which could be attributed to impaired insulin-stimulated phosphorylation of insulin receptor substrate (IRS)-1 and IRS-2 tyrosine secondary to activation of protein kinase C (PKC)-ε and Jun-NH_2-terminal kinase 1 (JNK1) by accumulation of intracellular fatty acid metabolites.

In the present study, the prevalence of positive individual MetS components such as SBP, DBP, FSG, and HDL-C was significantly higher, and their aggregation was significantly greater in the moderate to severe FL group.

In conclusion, the results of this study suggest that fatty liver disease per se, rather than its association with intra-abdominal fat accumulation, is a determining factor for insulin resistance and leads to the MetS.

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