INTERNAL MEDICINE

Association of Visceral Obesity with High Viral Load and Histological Findings in Elderly Patients with Genotype 1 Chronic Hepatitis C

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Abstract

Objective Genotype 1 chronic hepatitis C (G1CHC) is generally accompanied by metabolic disturbances related to visceral obesity, such as insulin resistance, steatosis, or dyslipidemia. Because these abnormalities negatively influence the clinical course of G1CHC, we sought to clarify the effect of visceral obesity on the pathophysiology of G1CHC.

Methods We evaluated 180G1CHC patients for the presence of visceral obesity on the basis of computed tomography findings. Multivariate analysis was performed to estimate the relationship between visceral obesity and demographic, viral, and biochemical characteristics of patients. The associations of visceral obesity with histological findings and serum adipokine levels were also analyzed.

Results Multiple logistic regression analysis revealed that visceral obesity was independently associated with metabolic syndrome, platelet count, high-density lipoprotein level, and serum viral load in elderly patients (≥65 years). Multiple linear regression analysis confirmed the association between visceral obesity and high viral load. However, visceral obesity was not correlated with viral load in non-elderly patients (<65 years). Histological data (160 patients) demonstrated the significant association between visceral obesity and steatosis. Furthermore, patients with visceral obesity showed increase in the severity of fibrosis with advancing age. However, age-associated fibrosis progression was not evident in patients without visceral obesity. The serum adiponectin level was significantly low in patients with visceral obesity, whereas those of leptin, tumor necrosis factor-α, and interleukin-6 were not affected significantly.

Conclusion Visceral obesity was associated with high viral load and histological damage in elderly patients with reduced adiponectin levels.

Key words: chronic hepatitis C, visceral obesity, viral load, steatosis, fibrosis, adiponectin

Introduction

Infection with hepatitis C virus (HCV) is a major cause of chronic liver disease, with almost 170 million persons being affected worldwide (1). Chronic HCV infection is responsible for a range of diseases, including minimal to severe chronic hepatitis, cirrhosis, and hepatocellular carcinoma (2, 3). Several studies reported thus far have focused on the factors influencing the heterogeneous clinical course of HCV infection.

A cluster of insulin resistance (IR)-associated metabolic risk factors, such as obesity, dyslipidemia, glucose intolerance, hypertension, and hepatic steatosis, is called the metabolic syndrome. Patients with genotype 1 chronic hepatitis C (G1CHC) generally present with these metabolic factors, especially steatosis and IR (4-6). The detrimental effect of these metabolic risk factors on the course of HCV infection

is increasingly being recognized. Both IR and hepatic steatosis are associated with the histological grade of portal inflammation and progression of liver fibrosis (6-8). Poor response to interferon-based antiviral therapy is observed in patients with these metabolic risk factors (9, 10). In addition, our recent report revealed that hypertriglyceridemia and glucose intolerance, both of which are components of the metabolic syndrome, had a significant correlation with high serum HCV viral load in patients with G1CHC (11).

Obesity, which is characterized by the excessive deposition of adipose tissue, is closely correlated to the metabolic syndrome. Especially, growing attention has been paid to particular patterns of adipose tissue distribution. Individuals with a selective excess of intra-abdominal or visceral adipose tissue are at a substantially higher risk of developing IR and other features of the metabolic syndrome than those without. Visceral adipose tissue has been reported to act as an endocrine organ that secretes a large number of bioactive substances regulating metabolism and inflammatory and immune responses, and excess visceral adipose tissue accumulation induces metabolic disturbances, which are induced by the dysregulation of bioactive molecules derived from adipose tissue (12-14). Therefore, visceral obesity is recognized not only as a marker of a dysmetabolic profile but also as a causal factor of IR. In the light of the clinical importance of metabolic factors in patients with G1CHC, it would be interesting to study the role of visceral obesity in the pathogenesis of genotype 1 HCV infection.

In this study, we evaluated patients for the presence of visceral obesity by measuring visceral fat area (VFA) on abdominal computed tomography (CT) and attempted to clarify the correlation between visceral obesity and the biochemical, viral, and histological characteristics of patients with G1CHC. We stratified the patients by age because insulin sensitivity is known to decrease with aging, while the prevalence of metabolic syndrome and type 2 diabetes mellitus, both of which involve IR, increases with advancing age (15-17).

Materials and Methods

Patients

We prospectively assessed 180 consecutive patients with G1CHC who visited the Department of Gastroenterology and Hepatology at Juntendo University Shizuoka Hospital, Shizuoka, Japan, between February 2006 and April 2011. Eligibility was defined by the detection of serum HCV-RNA of genotype 1. Exclusion criteria were (a) positivity for hepatitis B surface antigen; (b) presence of liver disease caused by mixed etiologies, including alcohol intake greater than 30 g/day, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, and Wilson's disease; (c) evidence of hepatocellular carcinoma by ultrasonography or CT; and (d) histology of liver transplantation.

The study protocol was approved by the Ethical Commit-

tee of Juntendo University Shizuoka Hospital and was in accordance with the Helsinki Declaration. Written informed consent was obtained from all the patients participating in the study.

Clinical and laboratory examinations

All patients underwent abdominal CT scan for the evaluation of visceral obesity (18). VFA was measured at the umbilical level and calculated using the Fat Scan® software (N2 System Osaka Japan). Visceral obesity was defined as VFA ≥130 cm^2 for male patients and VFA ≥90 cm^2 for female patients, as defined previously (19). All clinical, anthropometric, and laboratory data were collected at the time of obtaining the abdominal CT scan. The patients were classified into 2 groups according to their age: non-elderly (<65 years) and elderly (≥65 years) according to the previous report (17).

Fasting blood samples were obtained from all subjects, and the following laboratory parameters were measured using commercially available assays: blood cell count; serum levels of aspartate transaminase (ALT), total cholesterol, and high-density lipoprotein (HDL); plasma triglyceride (TG); and blood levels of glucose, insulin, hemoglobin A1c, and alpha-fetoprotein (AFP). The level of low-density lipoprotein (LDL) was calculated using the Friedewald formula: [LDL (mg/dL)] = [total cholesterol]-[HDL]-([TG] ÷5). If the plasma TG level exceeded 400 mg/dL, LDL was measured directly. IR was determined using the homeostasis model assessment (HOMA-IR) method. The following equation was used: HOMA-IR = fasting insulin (μIU/mL) × fasting glucose (mg/dL) ×0.05551÷22.5 and was defined as HOMA-IR >2.7. Serum HCV viral load was quantified by quantitative reverse transcription polymerase chain reaction performed using the COBAS TaqMan HCV Test (Roche Diagnostics, Branchburg). The HCV genotype was determined by polymerase chain reaction with the HCV Genotype Primer Kit (Institute of Immunology Co., Ltd., Tokyo, Japan) and classified according to Simmonds' classification system. Serum levels of adiponectin, leptin, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) were determined in thawed serum samples after storage at -20° and measured in a commercial laboratory (SRL Inc. Tokyo, Japan).

Body mass index (BMI) was calculated by dividing the body weight (kg) by the square of the height (m^2). Metabolic syndrome was diagnosed according to criteria defined by The Japanese Society of Internal Medicine (JIM) (20). According to the JIM, metabolic syndrome is diagnosed if the patient has central obesity (measured by ethnicity-specific thresholds for waist circumference for a population of Japanese origin: ≥90 cm in male patients and ≥80 cm in female patients) and any 2 of the following 3 components: (a) plasma TG of ≥150 mg/dL (1.7 mmol/L) and/or serum HDL cholesterol level of <40 mg/dL (<1.03 mmol/L) for both men and women, or taking lipid-lowering medications (b) systolic blood pressure of ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, or receiving antihypertensive medications; and (c) fasting plasma glucose level of ≥110 mg/dL

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(6.1 mmol/L) or treatment with oral hypoglycemic medications or insulin. The diagnosis of arterial hypertension was based on the following criteria: systolic blood pressure of ≥ 140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg or use of blood pressure-lowering agents. The diagnosis of type 2 diabetes was based on the World Health Organization criteria (21). In the cases of previously diagnosed type 2 diabetes, current therapy with insulin or oral hypoglycemic agent was documented.

Histological evaluation

One hundred sixty of the 180 patients underwent ultrasound-guided percutaneous liver biopsy within 4 weeks of the abdominal CT scan. Liver biopsy specimens were embedded in paraffin and stained with hematoxylin-eosin, Azan-Mallory, and reticulin silver impregnation. The specimens were evaluated by an experienced pathologist who was blind to the clinical data of the patients. Histological evaluation was based on the METAVIR criteria reported previously (22). Hepatic fibrosis was defined as follows: F0, no fibrosis; F1, periportal fibrous expansion; F2, portal fibrous widening with bridging fibrosis; F3, bridging fibrosis with lobular distortion; and F4, liver cirrhosis. On the basis of the degree of lymphocyte infiltration and hepatocyte necrosis, inflammation was classified with scores A0 to A3, with higher scores indicating more severe inflammation. Steatosis in the biopsy specimens was quantitatively assessed by computer-assisted morphometric image analysis. The average percentage of the total area of macrovesicular fat droplets to the liver parenchyma was measured in 2 independent fields at 100× magnification, by using the Lumina Vision 2.4 Bio-imaging software (Mitani Corporation, Tokyo, Japan).

Statistical analysis

Continuous variables were summarized as median (range) values, and categorical variables, as frequency and percentage. Mann-Whitney U test and chi-square test were used as appropriate. Multiple logistic regression analysis was used to identify factors that were independently associated with visceral obesity. As candidate factors, we selected gender, BMI, type 2 diabetes, arterial hypertension, metabolic syndrome, platelet count; levels of blood AFP, plasma TG, serum HDL, serum hemoglobin A1c; IR, and HCV viral load. Multiple linear regression analysis was performed to assess the relationship of serum HCV viral load with the demographic and biochemical characteristics of the patients. As candidate factors, we selected gender, serum ALT level, platelet count, blood AFP, plasma TG, serum HDL, blood hemoglobin A1c, IR, and visceral obesity. The Spearman's rank correlation coefficient was used to analyze the correlation between 2 variables. All analyses were conducted using IBM SPSS version 19 (IBM SPSS, Chicago, IL, USA), and p value below 0.05 was considered to be statistically significant.

Results

Characteristics of patients

The clinical, anthropometric, and laboratory data of the patients enrolled in this study are summarized in Table 1. The 180 patients (91 male and 89 female) had a median age 60 years (range, 20-85 years). The prevalence of arterial hypertension, type 2 diabetes mellitus, and metabolic syndrome were 51.4%, 13.3%, and 16.8%, respectively. The median VFA of all patients was 66.9 cm^2 (range, 2.4-298.6 cm^2), with 41 of 180 patients (23%) having visceral obesity.

According to their age, 101 of 180 patients (56%) were classified as non-elderly (<65 years) and 79 patients (44%), as elderly (≥65 years). Comparison of the variables of non-elderly and elderly patients showed that the latter had a higher prevalence of arterial hypertension (p=0.002), lower platelet count (p=0.003), and higher blood AFP levels (p=0.003). No significant difference was noted between elderly and non-elderly patients in VFA or prevalence of visceral obesity.

Factors associated with visceral obesity

Data from the 180 patients were analyzed by logistic regression analysis to examine the correlation between visceral obesity and the demographic and biochemical variables stratified by patient age (Table 2). For non-elderly patients, BMI (p<0.001), presence of metabolic syndrome (p<0.001), plasma TG level (p=0.018), and IR (p=0.046) were associated with visceral obesity in univariate analysis. Multivariate analysis revealed that BMI (p=0.011) and presence of metabolic syndrome (p=0.003) were significantly associated with visceral obesity. For elderly patients, univariate analysis showed that BMI (p=0.03), metabolic syndrome (p=0.001), platelet count (p=0.03), plasma TG level (p=0.009), IR (p=0.03), and HCV viral load (p=0.008) were associated with visceral obesity. Multivariate analysis revealed that the presence of metabolic syndrome (p=0.007), platelet count (p=0.020), serum HDL level (p=0.048), and HCV viral load (p=0.027) were independently associated with visceral obesity.

Factors associated with HCV viral load

Because visceral obesity was associated with HCV viral load in elderly patients, further examination was performed to confirm this association by stepwise linear regression analysis (Table 3). In the case of elderly patients, univariate analysis showed that serum viral load was significantly correlated only with visceral obesity (p=0.004), while multivariate analysis revealed that HDL (p=0.038) and visceral obesity (p=0.004) were independently associated with the serum viral load. In the case of non-elderly patients, both univariate and multivariate analyses showed that only plasma TG level was a significant factor associated with the serum viral load (p=0.009). No significant correlation was observed between HCV viral load and visceral obesity in the case of

Table 1. Patient Characteristics

	All patients (N = 180)	Non-elderly (N = 101)	Elderly (N = 79)	p value
Age, years	60 (20–85)	56 (20–64)	70 (65–85)	
Male gender, N (%)	91(49.4)	59 (58.4)	32 (40.5)	0.017 ‡
BMI, kg/m^2	23.2 (14.1–36.8)	23.7 (18.1–36.8)	22.5 (14.1–35.3)	0.10 †
Visceral fat area, cm^2	66.9 (2.4–298.6)	69.3 (8.5–298.6)	62.6 (2.36–279.9)	0.27 †
Metabolic syndrome, N (%)	31 (16.8)	18 (17.5)	12 (15.2)	0.68 ‡
Arterial hypertension, N (%)	94 (51.4)	42 (40.8)	50 (64.1)	0.002 ‡
Type 2 diabetes, N (%)	24 (13.3)	10 (9.8)	14 (18.2)	0.10 ‡
Past history of interferon therapy, N (%)	14 (7.8)	8 (7.9)	6 (7.6)	0.94‡
Viral load, log IU/mL	6.4 (3.9–7.8)	6.4 (3.9–7.8)	6.4 (4.6–7.7)	0.65 †
ALT, IU/L	58 (14–470)	53 (16–470)	60 (14–235)	0.56 †
Platelet count, ×10^3/μL	16.1 (4.0–85.9)	17.8 (4.0–85.9)	14.7 (6.8–33.8)	0.003 †
AFP, ng/mL	7 (1–307)	6 (1–142)	8 (2–307)	0.003 †
Total cholesterol, mg/dL	170 (110–251)	171 (110–251)	167 (113–246)	0.37 †
HDL, mg/dL	55 (27–123)	54 (27–123)	58 (31–104)	0.12 †
TG, mg/dL	89 (30-379)	96.5 (30–379)	88 (32–278)	0.10 †
LDL, mg/dL	92 (33–172)	92.5 (33–172)	89 (36–169)	0.37 †
Blood glucose, mg/dL	101 (69–235)	100 (70–235)	103 (69–226)	0.33 †
HbA1c, %	5.1 (3.8–8.3)	5.0 (3.8–8.3)	5.1 (3.8–7.9)	0.11 †
IR, N (%)	55 (43.7)	35 (50)	20 (35.7)	0.11 †

Date are shown as median (range)

p values are for comparison between non-elderly patients and elderly patients.

BMI: body mass index, ALT: alanine transaminase, AFP: alpha-fetoprotein, HDL: high-density lipoprotein, TG: triglyceride,

LDL: low-density lipoprotein, HbA1c: hemoglobin A1c, IR: insulin resistance

† Mann-Whitney U test.

‡ Chi-square test

Table 2. Univariate and Multivariate Analyses of Factors Associated with Visceral Obesity

	Non-elderly				Elderly			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Male gender	0.46 (0.17–1.29)	0.14			0.62 (0.22–1.72)	0.36		
BMI, kg/m^2	1.39 (1.19–1.62)	<0.001	1.30 (1.06–1.60)	0.011	1.22 (1.02–1.46)	0.03		
Type 2 diabetes	0.90 (0.18–4.58)	0.90			1.28 (0.35–1.28)	0.71		
Arterial hypertension	1.82 (0.71–4.63)	0.21			1.97(0.63–6.17)	0.24		
Metabolic syndrome	10.6 (3.38–33.05)	<0.001	9.69 (2.12–44.38)	0.003	10.18 (2.61–39.80)	0.001	11.53 (1.96–68.05)	0.007
History of IFN therapy	4.17(0.07–0.52)	0.06			3.56(0.66-19.38)	0.14		
ALT, IU/mL	1.00 (1.00–1.01)	0.21			1.00 (0.99–1.01)	0.63		
Platelet ×10^3/μL	1.01 (0.96–1.06)	0.71			1.11(1.01–1.22)	0.03	1.19 (1.02–1.38)	0.020
AFP, ng/mL	0.96 (0.90–1.04)	0.31			1.01 (0.99–1.02)	0.32		
TG, mg/dL	1.01 (1.00–1.02)	0.018			1.02 (1.01–1.03)	0.009		
HDL, mg/dL	0.98 (0.95–1.02)	0.30			0.98 (0.94–1.01)	0.15	0.95 (0.91–1.00)	0.048
HbA1c, %	1.28 (0.73–2.25)	0.40			1.12 (0.59–2.14)	0.73		
IR	3.11 (1.02–9.45)	0.046			3.43 (1.12–10.50)	0.03		
Log 10 HCV RNA	0.92 (0.50–1.72)	0.80			6.05 (1.51–22.70)	0.008	8.28 (1.28–53.65)	0.027

Logistic regression analysis was used in the univariate and multivariate analyses.

BMI: body mass index, ALT: alanine transaminase, AFP: alpha-fetoprotein, HDL: high-density lipoprotein, TG: triglyceride, HbA1c: hemoglobin A1c, IR: insulin resistance

non-elderly patients.

Figure 1 shows the distribution of HCV viral load in terms of visceral obesity. In the non-elderly group, 22 patients (22%) had visceral obesity, while 79 patients (78%) did not, and their median HCV viral load were 6.4 logU/mL (range, 3.9-7.7 logU/mL) and 6.5 logU/mL (range, 4.2-7.8 logU/mL), respectively. The difference between the 2 subgroups of patients was not statistically significant. In the elderly group, 19 patients (24%) had visceral obesity, while 60 patients (76%) did not, and the median HCV viral loads

Table 3. Univariate and Multivariate Analyses of Factors Associated with HCV Viral Load

Variables	Non-elderly				Elderly			
	Univariate		Multivariate		Univariate		Multivariate	
	coefficient	p value	coefficient	p value	coefficient	p value	coefficient	p value
Male gender	-0.154	0.12			0.147	0.20		
History of IFN therapy	0.032	0.76			0.086	0.46		
ALT, IU/L	0.022	0.82			-0.020	0.86		
Platelet, $\times 10^3$/μL	-0.143	0.15			0.177	0.12		
AFP, ng/mL	-0.047	0.64			0.055	0.64		
TG, mg/dL	0.241	0.015	0.291	0.009	0.107	0.36		
HDL, mg/dL	-0.187	0.07			0.182	0.13	0.256	0.038
HbA1c, %	0.119	0.25			0.192	0.10		
IR	0.129	0.24			0.158	0.60		
Visceral obesity	-0.024	0.81			0.328	0.004	0.363	0.004

Stepwise linear regression analysis was used for the univariate and multivariate analyses.

IFN: interferon, ALT: alanine transaminase, AFP: alpha-fetoprotein, TG: triglyceride, HDL: high-density lipoprotein, HbA1c: hemoglobin A1c, IR: insulin resistance
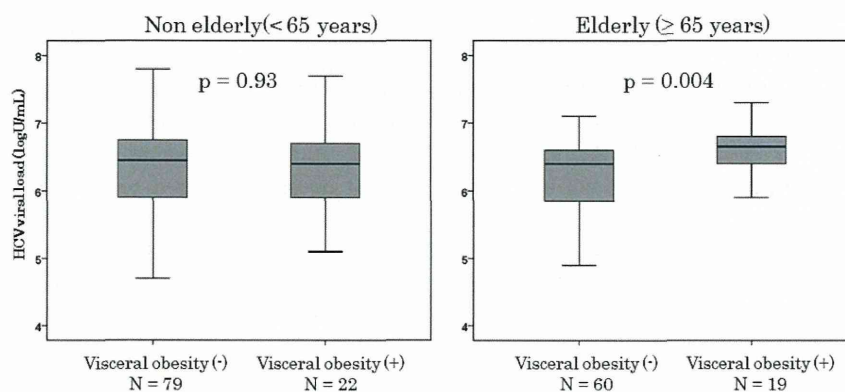

Figure 1.   Comparison of serum viral load between patients without visceral obesity and those with visceral obesity stratified by age. Mann-Whitney *U* test was used for statistical analysis.

were significantly different, at 6.7 logU/mL (range, 5.4-7.7 logU/mL) and 6.4 logU/mL (range, 4.6-7.1 logU/mL), respectively (p=0.004).

Visceral obesity and histological findings

We next investigated the relationship between visceral obesity and histological findings in patients with G1CHC (Table 4). Histological data were available for 160 of the 180 patients (89%). A total of 77 patients had mild hepatic fibrosis (F0-1), and 83 patients had severe hepatic fibrosis (F2-4). Severe necroinflammatory change (A2-A3) was observed in 120 of the160 patients (75%). Median percentage of steatosis was 2.6% (range, 0-21%). A comparison of patients with or without visceral obesity revealed no significant difference between them in the prevalence of severe hepatic fibrosis and severe necroinflammatory change. On the other hand, the percentage of steatosis was significantly higher in patients with visceral obesity than in those without (3.8% vs. 2.2%, p=0.036). In addition, the percentage of steatosis was significantly correlated with HCV viral load (r=0.214, p=0.003).

Because the natural history of hepatic fibrosis progression

is age dependent (23), we further analyzed the correlation between patients' age and the fibrosis stage (Fig. 2). The analysis revealed a significant correlation between these factors in patients with visceral obesity (r=0.355, p=0.021), but not in those without visceral obesity. Furthermore, among patients with visceral obesity, severe fibrosis was observed in 8 of 22 non-elderly patients and 14 of 20 elderly patients. The prevalence of severe hepatic fibrosis was significantly higher in elderly patients than in non-elderly patients (70.0% vs. 36.4%, p=0.029), which is indicative of age-dependent progression of fibrosis. On the other hand, in patients without visceral obesity, the prevalence of severe fibrosis of elderly patients and non-elderly patients was 26 of 47 (55.3%) and 35 of 71 (49.3%), respectively, showing no significant difference between the 2 age groups.

Visceral obesity and adipokines

Adipose tissue releases a variety of proinflammatory and anti-inflammatory cytokines, including the adipokines: adiponectin, leptin, TNF-α, and IL-6, and excess accumulation of visceral adipose tissue is associated with adipokine dysregulation, which has adverse metabolic conse-

Table 4. Visceral Obesity and Histological Findings

	Visceral obesity (-)	Visceral obesity (+)	p value
Stage of fibrosis			
F 0 / 1 / 2 / 3 / 4	1 / 56 / 30 / 23 / 8	0 / 20 / 11 / 8 / 3	0.985 †
Grade of inflammation			
A 0 / 1 / 2 / 3	0 / 28 / 84 / 5	0 / 9 / 31 / 2	0.943 ††
Steatosis, (%)*	2.2 (0–21)	3.8 (0–18.4)	0.036 ‡

†Cramer's measure of association

††Chi-square test

‡Mann-Whitney *U* test.

*Date are shown as median (range)

quences (13, 14). In this point of view, we compared the serum levels of adiponectin, leptin, TNF-α, and IL-6 between G1CHC patients with and without visceral obesity (Fig. 3). Serum adipokine levels were evaluated in 159 of 180 patients. The median levels of adiponectin in patients without visceral obesity and those with visceral obesity were 13.7 ng/mL (range, 3.9-96.2 ng/mL) and 9.35 ng/mL (range, 1.9-31.6 ng/mL), respectively. Patients with visceral obesity showed significantly lower serum levels of adiponectin than those without visceral obesity (p=0.012). On the other hand, serum levels of leptin, TNF-α, and IL-6 did not show any significant difference between patients with and those without visceral obesity. A significant association was also noted between serum adiponectin level and HCV viral load (r= -0.182, p=0.023).

Discussion

Serum HCV viral load is clinically important because it has been identified as one of the most substantial factors that predict the outcome of interferon-based anti-virus treatment. For instance, among patients treated with 48 weeks of pegylated interferon and ribavirin, those with genotype 1 and a high viral load (>2×10⁶ copies/mL) showed a sustained virologic response rate of 46%, while those with genotype 1 and a low viral load (<2×10⁶ copies/mL) showed a rate was 61% (24). Interestingly, the serum viral load is persistently stable over prolonged periods in untreated patients with chronic hepatitis C (25, 26). However, differences in the serum viral load between individuals vary widely even among patients with identical genotypes. The interpersonal difference in serum viral load was noted to be greater than 6 logU/mL in our study (11). These observations suggest that interpersonal differences in the serum viral load might be affected by environmental predispositions, such as host demographic and biochemical characteristics. Several recent reports have confirmed the correlation between high serum viral load and hypertriglyceridemia or glucose intolerance in patients with G1CHC (11, 27, 28). However, the reasons for the correlation between these biochemical disturbances and HCV viral load have not yet been established.

Dyslipidemia and glucose intolerance are frequent find-

ings in patients with metabolic syndrome. It is generally accepted that excess accumulation of visceral adipose tissue plays an essential role in the development of this multiple risk factor syndrome (14). Therefore, the correlation between hypertriglyceridemia or glucose intolerance and HCV viral load suggests the involvement of visceral obesity in the interpersonal differences of serum viral load in patients with G1CHC. Thus far, many studies have shown the correlation between visceral obesity and glucose intolerance or between metabolic syndrome and insulin resistance or adiponectin level. However, only a few reports have indicated a correlation between visceral obesity and HCV viral load. Only one previous study showed the correlation between HCV viral load and visceral adiposity index, which is a surrogate marker of visceral adiposity (29). In the present study, by using CT to evaluate patients for the presence of visceral adiposity, we demonstrated the close correlation between visceral obesity and high serum viral load in elderly patients with G1CHC. It is unclear why the association between visceral obesity and viral load was observed only in elderly patients in our study. In general, the prevalence of metabolic syndrome increases in advancing age (15, 16). This finding suggests that elderly persons are more seriously affected by visceral obesity compared to non-elderly persons. In addition, recent large-scale Japanese cohort studies have revealed that the proportion of patients with substitution at amino acid 70 of the HCV core protein tend to increase with advancing age (30, 31). These observations suggest that some age-related viral factors are involved in the association between visceral obesity and HCV viral load only in the case of elderly patients.

Further, reports indicate that HCV infection per se is associated with host insulin resistance, independent of the visceral fat area (32). However, the correlation between HOMA-IR and HCV viral load was not found to be significant, both in this study and in a previous one (29). The reason for this discrepancy remains unclear. One of the differences among these studies was the eligible criteria of the patients. The former study excluded obese and diabetic patients, while the latter ones did not. In general, obesity itself causes insulin resistance, even in the absence of HCV infection. HOMA-IR can-not accurately reflect the degree of insulin resistance in individuals whose β-cells are unable to secrete sufficient insulin to overcome existing insulin resistance, for example, in patients with uncontrolled diabetes. Considering these findings together, we believe that the study cohort in the present investigation would be inadequate to assess the exact correlation between HCV viral load and insulin resistance itself.

Histological analysis in this study demonstrated that visceral obesity was associated with steatosis, as reported in a previous study (33, 34). In addition, age-dependent progression of liver fibrosis was significantly noted in patients with visceral obesity; however, no difference was noted in the prevalence of severe hepatic fibrosis between non-elderly and elderly patients without visceral obesity. These results
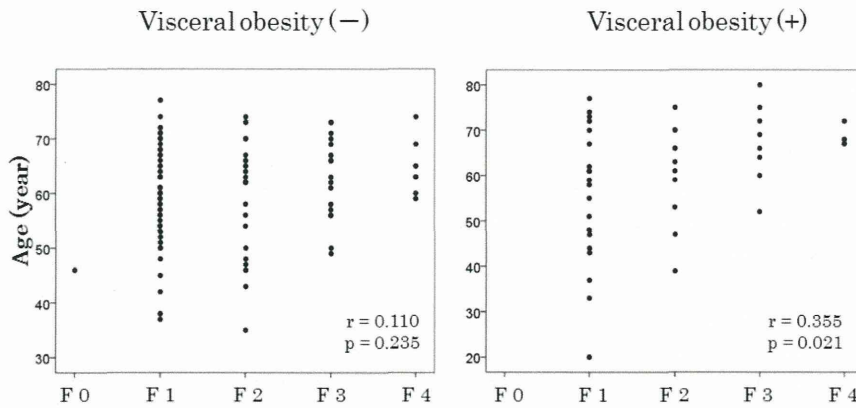
Figure 2. Comparison of age-dependent fibrosis progression between patients without visceral obesity (n=118) and those with visceral obesity (n=42). The Spearman's rank correlation coefficient was used for statistical analysis.
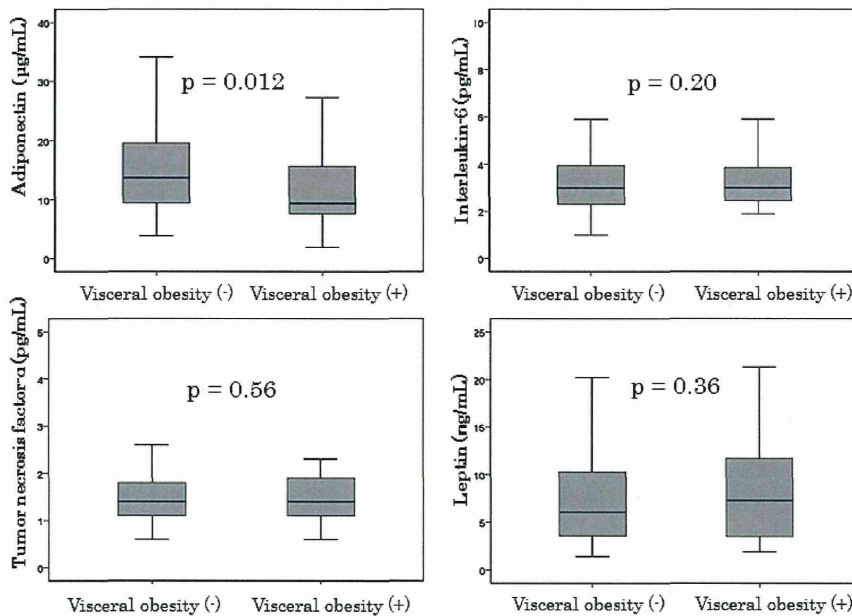

Figure 3. Comparison of serum levels of adiponectin, interleukin-6, tumor necrosis factor-α and leptin between without visceral obesity (n=121) and those with visceral obesity(n=38). Mann-Whitney U test was used for statistical analysis.

indicated that visceral obesity was possibly involved in age-dependent progression of liver fibrosis. Consistent with this finding, previous studies have shown that steatosis was a major determinant of the progression of fibrosis in HCV-infected patients (7, 8). Until now, many factors have been found to influence the progression of liver fibrosis in patients with CHC, such as age, duration of infection, alcohol consumption, male gender, hepatic steatosis, and anti-viral therapeutic response. Because these factors interact in a complex manner to influence the progression of fibrosis, it is difficult to determine which one is essential. However, our results suggested that visceral obesity could influence not only the therapeutic response but also the progression of hepatic fibrosis itself. Thus, we can infer that visceral obe-

sity is one of the important factors influencing hepatic fibrosis and that it is clinically important in the management of CHC patients.

Besides serving as a passive reservoir for energy storage, adipose tissue acts as an endocrine organ that secretes various bioactive peptides, known as adipokines (12). To identify the adipokines that might play a key role in the visceral obesity-associated elevation in the serum viral load in G1 CHC patients, we compared the serum levels of adiponectin, leptin, TNF-α, and IL-6 of patients with and those without visceral obesity. Among the 4 adipokines, only adiponectin showed a statistically significant difference between those with visceral adiposity and those without, i.e., the serum adiponectin level was significantly lower in the former. Fur-

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thermore, a significant association was also observed between serum adiponectin level and HCV viral load. Importantly, a close association between the serum level of adiponectin and anti-HCV immune response was reported (35). Taken together, our findings indicate that visceral obesity might reduce the immune response to HCV via the downregulation of adiponectin, resulting in the upregulation of HCV kinetics and elevation of serum viral load in patients with G1CHC.

In conclusion, visceral obesity was found to be associated with high viral load, steatosis, and age-dependent fibrosis progression in patients with G1CHC. These results are suggestive of the detrimental impact of visceral obesity both on the natural course of HCV infection and the effect of interferon-based anti-viral therapy. Strategies aiming at correct visceral obesity might have a beneficial effect on the management of patients with G1CHC

The authors state that they have no Conflict of Interest (COI).

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Waiting list mortality of patients with primary biliary cirrhosis in the Japanese transplant allocation system

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Abstract

Background The present study aimed to evaluate etiology-based differences in the risk of waiting list mortality, and to compare the current Japanese transplant allocation system with the Child–Turcotte–Pugh (CTP) and the Model for End-Stage Liver Disease (MELD) scoring systems with regard to the risk of waiting list mortality in patients with primary biliary cirrhosis (PBC).

Methods Using data derived from all adult candidates for deceased donor liver transplantation in Japan from 1997 to 2011, we assessed factors associated with waiting list mortality by the Cox proportional hazards model. The waiting list mortality risk of PBC patients was further estimated with adjustment for each scoring system.

Results Of the 1056 patients meeting the inclusion criteria, 743 were not on the list at the end of study period; waiting list mortality was 58.1 % in this group. In multivariate analysis, increasing age and PBC were significantly associated with an increased risk of waiting list mortality. In comparison with patients with hepatitis C virus (HCV) infection, PBC patients were at 79 % increased risk and had a shorter median survival time by approximately 8 months. The relative hazard of PBC patients was statistically significant with adjustment for CTP score and medical point score, which was the priority for ranking candidates in the Japanese allocation system. However, it lost significance with adjustment for MELD score. Stratification by MELD score indicated a comparable waiting list survival time between patients with PBC and HCV.

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