Hepatitis C Virus Infection and Metabolic Syndrome—A Community-based Study in an Endemic Area of Taiwan

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Metabolic syndrome (MS) is a complicated disorder associated with a high risk of future development of micro- and macrovascular complications. The extrahepatic manifestations of hepatitis C virus (HCV) infection can include multiple metabolic abnormalities. However, the extent, severity, and characteristics of MS in HCV-infected patients have rarely been investigated in community-based settings. This study aimed to determine the difference in prevalence and distribution of the components of MS between HCV-infected patients and healthy controls. Multipurpose mass screening of adults was conducted in an HCV-endemic area of Southern Taiwan. Clinical profiles in terms of anthropometric data and MS components, as well as viral hepatitis markers, were assessed. Two hundred and thirty-seven adults (94 males; mean age, 55.5 ± 10.8 years) were recruited. The prevalence of anti-HCV seropositivity was 39.2% (93/237). The prevalence of MS was higher in the HCV-infected individuals (24.7%, 23/93) than in the control, uninfected subjects (13.2%, 19/144, $p = 0.02$). In terms of MS components, HCV-infected subjects had a higher prevalence of high waist circumference (51.6% *vs.* 25.7%, $p < 0.001$) and hypertension (58.1% *vs.* 36.8%, $p = 0.001$) than controls. Multivariate logistic regression analysis demonstrated that anti-HCV positivity was significantly associated with MS (odds ratio, 6.4; 95% confidence interval, 1.82–22.84; $p = 0.004$). HCV infection was associated with a higher prevalence of MS. Determination of MS in patients with HCV infection could therefore be indicated.

Key Words: hepatitis C virus, insulin resistance, metabolic syndrome
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Metabolic syndrome (MS) is a complicated disorder comprising clinical features including obesity, hyperglycemia, hypertension, dyslipidemia, and insulin resistance (IR). Atherosclerosis and type 2 diabetes mellitus (DM), as major consequences of MS, are critical, global health issues [1]. Current evidence suggests that the atherosclerotic process is regulated by intervening inflammatory mechanisms. IR, a key feature in the pathogenesis of MS, has been increasingly recognized as playing a key role in the inflammatory processes.

Hepatitis C virus (HCV) infection is another important global health issue. Approximately 170 million people suffer from HCV infection and it is one of the most important worldwide causes of cirrhosis and hepatocellular carcinoma. A number of metabolic

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disturbances have been shown to be directly and indirectly associated with HCV infection. An association between HCV infection and lipid metabolism has been consistently reported [2–4]. Lower total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels are commonly seen in patients with chronic HCV infection (CHC), compared with normal subjects. Hepatic steatosis is a common histologic feature of CHC and is observed in 30–70% of patients [5,6]. Many factors are known to increase the risk of hepatic steatosis, including DM, hyperlipidemia, and obesity [7]. In addition to its hepatotropic characteristic, HCV infection is associated with the pathogenesis of IR, though the underlying biological mechanisms are diverse and multifactorial. Both experimental and clinical studies have shown that IR often emerges at a young age or during the early stages of histologic liver changes [8,9]. Furthermore, emerging lines of clinical evidence have revealed that several metabolic disturbances, such as obesity, IR, and hepatic steatosis, are significant risk factors for decreased treatment response to combined pegylated interferon and ribavirin antiviral therapy in CHC patients [6,10–12]. IR and its related inflammatory processes thus appear to contribute not only to MS, but also to the metabolic disturbances associated with HCV infection. However, the characteristic features of MS in CHC patients have not been fully elucidated. Previous studies addressing the association between HCV infection and MS were mainly hospital-based and the extent, severity, and characteristics of MS in HCV-infected patients, compared with non-HCV subjects, have rarely been investigated in community-based settings.

This study aimed to determine the difference in the prevalence and distribution of MS between HCV-infected patients and healthy controls in an HCV-endemic area.

Patients and Methods

Patient selection

Tzukuan Township is located in southern Taiwan and is a hyper-endemic area for HCV infection, in both adults and adolescents. Our previous studies demonstrated that the prevalence of anti-HCV seropositivity (anti-HCV+) in Tzukuan Township reached 41.6% among adult residents, with an annual incidence of 4.5%. Moreover, about 90% of hepatocellular carcinoma cases in this township were HCV-related [9,13–15]. Based on occupational and geographic data, seven villages along the southwest coast were classified as maritime, while the other eight were non-maritime. Our previous study showed that the prevalence of HCV infection was markedly higher in the maritime area, compared with the non-maritime area. A multipurpose health surveillance study was conducted in three hyper-endemic maritime villages in March 2007. A total of 396 adults participated in this study on a voluntary basis. After excluding those who refused examination (55, 13.9%), those who failed to complete the study (50, 12.6%), those who were very elderly (46, 11.6%), and those who had received prior antiviral therapy (8, 2.0%), a total of 237 adults constituted the study population.

Study design

All subjects underwent a 12-hour overnight fast before blood tests. Blood was analyzed for anti-HCV antibody, fasting plasma glucose (FPG), TC, HDL-C, LDL-C, TG, and alanine aminotransferase (ALT) levels. Anthropometric data including body weight, height, and blood pressure were measured using standardized techniques. Research staff administered a questionnaire covering medical history, drug history, possible parenteral risk history, and family history. Verbal or written informed consent for interviews, anthropometric measurements, blood sampling, and medical record reviews were obtained from patients prior to enrolment. The study was approved by the ethics committee of Kaohsiung Medical University Hospital.

Definition of MS

MS was defined based on the updated National Cholesterol Education Program Adult Treatment Panel III criteria for Asian-Americans, modified by the criteria of obesity proposed for Asians by the Steering Committee of the Regional Office for the Western Pacific Region of WHO [1,16]. This requires the presence of at least three of the following components: (1) waist circumference >90 cm in men or >80 cm in women; (2) TG >150 mg/dL; (3) HDL-C <40 mg/dL in men or <50 mg/dL in women; (4) blood pressure $>130/85$ mmHg or current use of antihypertensive medications; (5) FPG >100 mg/dL or use of oral antidiabetic agents or insulin.

Laboratory analyses

Hepatitis B surface antigen and anti-HCV antibody were detected using a third-generation, commercially available enzyme-linked immunosorbent assay kit (AxSYM 3.0; Abbott Laboratories, Chicago, IL, USA). Detection of serum HCV RNA was performed using a standardized automated qualitative reverse transcription-polymerase chain reaction assay (COBAS AMPLICOR Hepatitis C Virus Test, version 2.0; Roche, Branchburg, NJ, USA). The detection limit was 50 IU/mL. HCV genotypes 1a, 1b, 2a, 2b, and 3a were determined by the Okamoto method [17]. FPG, TC, TG, and ALT levels were measured using a multichannel autoanalyzer (Hitachi Inc., Tokyo, Japan). Fasting serum insulin levels were measured by radioimmunoassay (Diagnostic Products, Los Angeles, CA, USA).

IR and β-cell function were calculated based on FPG and insulin levels, according to the homeostasis model assessment (HOMA) method [18]. The formulae for the HOMA model are as follows: β-cell function (HOMA-%B) = fasting insulin level (μU/mL) × 360/[FPG (mg/dL) − 63]; IR (HOMA-IR) = FPG (mg/dL) × fasting insulin level (μU/mL)/405.

Statistical analysis

Frequencies were compared between groups using the χ^2 test with Yates's correction for categorical variables and Student's *t* test for continuous variables. Results were expressed as mean ± standard deviation. A *p* value <0.05 was considered statistically significant. Univariate and multivariate logistic regression analyses were conducted to explore the factors that were independently associated with MS. The strength of association was presented as odds ratio (OR) with 95% confidence intervals (CI) and *p* values. Quality control procedures, database processing and analyses were performed using the SPSS 12.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

A total of 237 sex- and age-matched subjects (93 anti-HCV+ and 144 anti-HCV−) were recruited and their basic demographic characteristics are shown in Table 1. Fifty-six anti-HCV+ subjects (60.2%) were positive for HCV RNA (36 of genotype 1, 17 of genotype 2, and 3 of unclassified genotype infection). Forty-two subjects (17.7%) fulfilled the criteria for MS. The prevalence of anti-HCV+ was 39.2% (93/237). The anti-HCV+ subjects had a higher prevalence of hypertension, and higher waist circumference, ALT levels, insulin levels, HOMA-IR, and HOMA-%B than the anti-HCV− subjects. The TC and LDL-C levels

Table 1. Basic characteristics of anti-HCV-seropositive and -negative subjects*

Variables	All subjects (*n* = 237)	Anti-HCV		*p*
		Positive (*n* = 93)	Negative (*n* = 144)	
Age (yr)	55.5 ± 10.8	57.1 ± 9.0	54.5 ± 11.7	NS
Male	94 (39.7)	33 (35.5)	61 (42.4)	NS
Hypertension	107 (45.1)	54 (58.1)	53 (36.8)	0.001
BMI (kg/m^2)	24.9 ± 3.7	25.4 ± 3.5	24.6 ± 3.9	NS
Waist circumference (cm)	80.2 ± 11.0	82.5 ± 10.5	78.7 ± 11.1	0.01
ALT (U/L)	26.6 ± 26.6	36.3 ± 36.2	20.3 ± 15.0	<0.001
FPG (mg/dL)	101.6 ± 40.8	105.3 ± 48.3	95.9 ± 24.3	NS
TC (mg/dL)	183.8 ± 32.9	176.1 ± 33.3	188.8 ± 31.7	<0.01
HDL-cholesterol	58.1 ± 15.0	56.1 ± 13.3	59.4 ± 15.9	NS
LDL-cholesterol	120.6 ± 34.3	113.1 ± 35.6	125.4 ± 32.7	0.01
Triglycerides (mg/dL)	110.0 ± 64.6	102.9 ± 54.8	114.6 ± 69.9	NS
Uric acid (mg/dL)	6.0 ± 1.5	6.2 ± 1.6	5.8 ± 1.5	NS
Insulin (μU/mL)	10.3 ± 7.6	12.5 ± 9.7	8.8 ± 5.3	0.001
HOMA-IR	1.8 ± 0.1	2.2 ± 0.3	1.6 ± 0.2	0.02
HOMA-%B	103.2 ± 7.3	128.2 ± 13.4	87.1 ± 8.1	0.01
Metabolic syndrome	42 (17.7)	23 (24.7)	19 (13.2)	0.02

*Data presented as mean ± standard deviation or *n* (%). HCV = hepatitis C virus; BMI = body mass index; ALT = alanine aminotransferase; FPG = fasting plasma glucose; TC = total cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; HOMA = homeostasis model assessment; IR = insulin resistance; %B = β-cell function.

were significantly lower in the anti-HCV+ subjects compared with the anti-HCV− subjects. Overall, the anti-HCV+ subjects had a higher prevalence of MS (24.7%, 23/93) than the anti-HCV− subjects (13.2%, 19/144, $p = 0.02$).

The prevalences of high waist circumference (51.6% *vs.* 25.7%, $p < 0.001$) and hypertension (58.1% *vs*. 36.8%, $p = 0.001$) were significantly higher in anti-HCV+ subjects compared with anti-HCV− subjects (Figure). There were no significant differences between anti-HCV+ and anti-HCV− subjects in terms of high TG levels (21.5% *vs*. 19.4%, $p = 0.7$), low HDL-C levels (19.4% *vs*. 18.1%, $p = 0.8$), and DM (22.6% *vs*. 29.9%, $p = 0.2$).

Regarding the age-specific distribution of MS, the prevalence of MS among anti-HCV+ subjects aged 40–60 years was higher (25.5%, 14/55) than that of controls (10.6%, 10/94; $p = 0.02$). For those aged ≥60 years, the prevalence was not higher in anti-HCV+ subjects (25.7%, 9/35) compared with controls (18.9%, 7/37; $p = 0.5$).

Multivariate logistic regression analyses were conducted to clarify the independent factors associated with MS. Variables included age, sex, body mass index (BMI), ALT, creatinine, uric acid, FPG, HDL-C levels, and the presence of hypertension and IR. Anti-HCV+ was significantly associated with MS (OR, 6.4; 95% CI, 1.82–22.84; $p = 0.004$) as well as with hypertension, BMI, and HDL-C (Table 2).

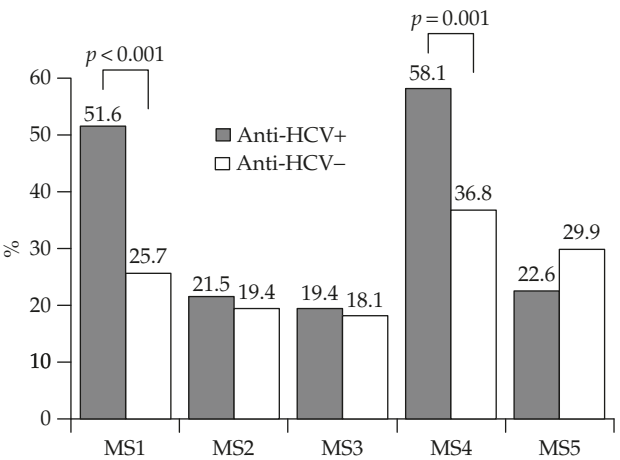

Figure. *Distribution of metabolic syndrome components in relation to anti-hepatitis C virus (HCV) seropositivity. MS1 = waist circumferences > 90 cm in men or > 80 cm in women; MS2 = triglyceride level > 150 mg/dL; MS3 = high-density lipoprotein cholesterol < 40 mg/dL in men or < 50 mg/dL in women; MS4 = blood pressure > 130/85 mmHg or current use of antihypertensive medications; MS5 = type 2 diabetes or use of oral antidiabetic agents or insulin.*

Discussion

The unique HCV hyper-endemic geographic background of the current case-control study allowed us to examine the association between HCV infection and MS. Our data demonstrated that HCV infection was associated with an increased prevalence of MS, compared with that in non-HCV-infected subjects. High waist circumference and hypertension were the common features of MS in subjects with HCV infection. We also demonstrated that anti-HCV+ subjects had a higher prevalence of IR than anti-HCV− subjects. IR plays a key role in the emergence of MS, and our data may thus further suggest that HCV infection contributes to the risk of developing MS.

Subjects with MS generally have higher rates of IR and are therefore also at increased risk of developing type 2 DM, as well as future micro- and macrovascular complications [19,20]. Previous reports have indicated that metabolic abnormalities, including liver steatosis, obesity and DM, can worsen the course of CHC [21,22]. In addition, CHC has a direct steatogenic effect on liver cells and may be involved in the

Table 2. Multivariate logistic regression analyses of variables associated with metabolic syndrome

Variables*		OR	95% CI	*p*
Hypertension	Positive = 1, Negative = 0	31.8	6.49–155.84	< 0.001
Anti-HCV+	Positive = 1, Negative = 0	6.4	1.82–22.84	0.004
BMI (kg/m^2)	Per 1 kg/m^2 increase	1.3	1.09–1.51	0.002
HDL-C (mg/dL)	Per 1 mg/dL increase	0.9	0.88–0.98	0.009

*Variables included age, sex, body mass index (BMI), aminotransferase, creatinine, uric acid, fasting plasma glucose, high-density lipoprotein cholesterol (HDL-C) levels, and the presence of hypertension and insulin resistance. For the continuous variables, OR represents one unit increase in the value of the variable tested. OR = odds ratio; CI = confidence interval; HCV = hepatitis C virus.

development of type 2 DM [22–24]. However, the correlation between MS and HCV infection has rarely been investigated in clinical settings. We demonstrated that subjects with HCV infection were at increased risk of developing MS. This suggests that patients with HCV infection should be evaluated for the presence of MS, while lifestyle changes directed at increasing physical activity, optimal weight maintenance, and diet composition should be emphasized.

The precise biological mechanisms whereby HCV infection leads to MS are not fully understood. HCV may induce a Th1 lymphocyte immune-mediated response, leading to activation of the tumor necrosis factor (TNF)-α system and elevation of interleukin-6 levels. Meanwhile, HCV directly causes liver steatosis. A combination of these events may result in the development of liver fibrosis. TNF-α system activation, liver steatosis, and fibrosis in turn contribute to the development of IR, which plays a pivotal role in the development of MS [25]. HCV-induced inflammatory changes may subsequently lead to increased oxidative stress and peroxidation, which evoke higher systemic inflammatory responses. Our results therefore imply that, in addition to the direct hepatotropic effects of HCV infection, MS should be considered as a possible extrahepatic manifestation of HCV [24,26–28].

The current study demonstrated that anti-HCV+ subjects had significantly lower TC and LDL-C levels and lower HDL-C and TG levels than anti-HCV– subjects. These data are in agreement with those from previous experimental and clinical studies that addressed the association between HCV infection and lipid metabolism [3,29]. HCV infection was shown to be associated with significantly lower cholesterol (TC, HDL-C and LDL-C) and TG levels compared with normal subjects [2,3] and a recent study demonstrated that TC, LDL-C and TG levels increased after successful eradication of HCV genotype-1 infection with antiviral therapy [30]. Although our study failed to show significant differences in TG and HDL-C levels between anti-HCV+ and anti-HCV– subjects, further long-term studies aimed at assessing the changing features of MS after antiviral therapy are warranted. In addition, the relative risk of atherosclerotic cardiovascular disease in patients with MS and HCV infection, compared with non-HCV subjects, deserves further investigation.

The increasing burden of obesity is the driving force behind the rising prevalence of MS. Body fat distribution, particularly excess abdominal fat, plays an important role in the etiology of MS [1]. Regardless of the relative contributions of visceral fat and abdominal subcutaneous fat to IR, abdominal (or upper-body) obesity correlates more strongly with IR and MS than does lower-body obesity [31]. Our previous study also demonstrated that the discrepancy in prevalence of MS between CHC patients and controls was inversely related to age, suggesting that HCV infection may contribute to the subtle development of glucose abnormalities at a younger age [9]. Intriguingly, the current study showed that anti-HCV+ subjects had a significantly higher mean waist circumference than anti-HCV– subjects. This may somehow reflect the common observation that IR is a general feature of HCV infection. However, the cross-sectional nature of the current study and incomplete coverage of all genotypes did not allow us to reach a definite conclusion on this issue. A large collaborative study comparing patients with different HCV genotypesis needed to further clarify any relationship between genotype and predisposition to or protection from MS. A well-designed longitudinal follow-up study is also warranted to further clarify if HCV infection predisposes to the development of upper-body obesity.

In conclusion, we demonstrated that HCV infection was associated with an increased prevalence of MS. High waist circumference and presence of hypertension were the common features of MS in patients with HCV infection. Our data indicate a possible link between HCV infection and MS and suggest that assessment of MS in patients with HCV infection may therefore be warranted.

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C 型肝炎感染與代謝症候群 — 一個台灣 C 型肝炎高盛行地區之社區研究

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代謝症候群是一個複雜的疾病且具有發生小血管及大血管併發症之高風險。C 型肝炎感染在肝外的表現常見許多代謝上的異常，然而卻極少有社區流行病學的研究來探討 C 型肝炎病人代謝症候群的發生率、嚴重性及特徵。本研究的目的在於探討 C 型肝炎病人及健康對照組之間代謝症候群構成因素的發生率及分布。本研究在一南部 C 型肝炎高盛行地區共收集 237 位成年人 (94 位男性，平均年齡 55.5 ± 10.8 歲)，其中 C 型肝炎抗體陽性發生率為 39.2% (93/237)。93 位 C 型肝炎感染病人 (24.7%，23/93) 相較於健康對照組 (13.2%，19/144，$p = 0.02$) 有較高的代謝症候群發生率。在代謝症候群構成因素方面，高腰圍 (51.6% *vs.* 25.7%，$p < 0.001$) 及高血壓 (58.1% *vs.* 36.8%，$p = 0.001$) C 型肝炎病患相較健康對照組有較高的發生率。本研究顯示 C 型肝炎病患有較高的代謝症候群發生率，因此可建議其接受代謝症候群之篩檢。

關鍵詞：C 型肝炎，胰島素耐受性，代謝症候群
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