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ORIGINAL ARTICLE

Metabolic profiles in patients with chronic hepatitis C: a case–control study

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Abstract
Background The clinical implications of metabolic profiles in patients with chronic hepatitis C remain controversial. To study the association of metabolic abnormalities with chronic hepatitis C, we conducted a case–control study with special emphasis on serum lipid pattern, fasting blood glucose, and adiponectin.
Methods We enrolled 500 patients with chronic hepatitis C and 536 sex and age-matched controls. Unadjusted and adjusted associations of demographic and metabolic variables were estimated.
Results Chronic hepatitis C patients had higher alanine aminotransferase (ALT) and high-density lipoprotein-cholesterol levels, but lower total cholesterol (TC), triglyceride (TG), and low-density lipoprotein-cholesterol levels than controls. Stratifying ALT level according to its upper limit of normal, HCV infection was associated with younger age, female gender, and higher TC levels in chronic hepatitis C patients with normal ALT levels, but with lower TC and lower TG levels in those with abnormal ALT levels. By using multiple linear regression analyses for subjects with available adiponectin data, presence of HCV infection was independently associated with higher serum adiponectin levels.
Conclusions Metabolic profiles of chronic hepatitis C patients are affected by age, gender, serum adiponectin, and ALT levels. Further longitudinal studies are needed to clarify the complex interplay between HCV infection and metabolic profiles.

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Abbreviations

HCV	Hepatitis C virus
ALT	Alanine aminotransferase
TG	Triglyceride
TC	Total cholesterol
HDL	High-density lipoprotein-cholesterol
LDL	Low-density lipoprotein-cholesterol
ULN	Upper limit of normal
ADN	Adiponectin

Introduction

The liver plays a pivotal role in nutrient and hormone metabolism; therefore, several metabolic abnormalities are common in liver disease. Hepatitis C virus (HCV) is a major causative agent of chronic hepatitis, liver cirrhosis, end-stage liver disease, and hepatocellular carcinoma worldwide [1]. However, clinical manifestations of HCV infection are heterogeneous and factors affecting liver disease progression remain to be fully elucidated.

Recently, there is increasing interest in the impact of chronic HCV infection on metabolic abnormalities, including glucose, lipid, cytokines, insulin resistance, and adipokines. Although a body of experimental data from in vitro cell cultures and in vivo transgenic mice support the existence of interaction between HCV and host metabolic factors, the results from clinical and epidemiological studies remained controversial [2–16]. The inconsistencies may be due to small sample size, the selection of patients only from hospitals or limited to hepatitis patients with cirrhosis, with diabetes, or to post-liver-transplant. Although large population-based studies have been performed [17–19], the results still lack consistency and are limited to some metabolic factors.

Adiponectin, an adipokine, has been implicated in the pathogenesis of type 2 diabetes mellitus and nonalcoholic fatty liver disease (NAFLD), and appears to have many favorable effects on glucose and lipid metabolism [20, 21]. It is positively correlated with insulin sensitivity and is decreased in obese and type 2 diabetic patients [22]. Adiponectin also antagonizes tumor necrosis factor-alpha (TNF-α) and modulates inflammatory responses [23]. In addition, adiponectin might have hepatic cytoprotective properties such as improving hepatic steatosis and injury in animal models of NAFLD [23]. Our recent data further showed that adiponectin may correlate with hepatitis C viral factors at both serum and liver tissue levels [24, 25].

To examine the influence of adiponectin, glucose and lipid metabolism on chronic hepatitis C patients, we therefore conducted a large case–control study with 500 HCV-infected index patients and 536 sex- and age-matched controls.

Patients and methods

Study population

HCV infected cases

There were more than 1,000 HCV-infected patients followed at National Taiwan University Hospital (NTUH), a tertiary medical center in Taiwan. Among them, a total of 533 patients aged 15 years or older diagnosed with chronic HCV infection who were regularly followed at the gastroenterology clinics of this hospital between 1999 and 2005 were consecutively included. After excluding the patients who had incomplete data or without informed consent, finally there were 500 patients enrolled into this study. Chronic HCV infection was defined as positivity of anti-HCV and serum HCV RNA for more than 6 months. All of them were infected with HCV genotype 1 or 2, and were negative for hepatitis B surface antigen or HIV antibody, naïve to antiviral treatment, and none had a known history or serological evidence of autoimmune liver disease, inheritable disorders such as hemochromatosis or Wilson's disease, renal insufficiency, a history of excess alcohol intake (daily alcohol consumption greater than 20 g) or drug abuse and a record of diabetes mellitus or dyslipidemia.

Non-HCV controls

A total of 536 sex and age-matched non-HCV controls were selected from the database of the Health Management Center in National Taiwan University Hospital, and more than 10,000 subjects received regular physical check-up at this Health Management Center each year.

We excluded subjects positive for hepatitis B surface antigen (HBsAg) or anti-HCV, and those with a known history of diabetes mellitus or dyslipidemia. Random selection without replacement was used to ensure that no non-HCV control was assigned more than once.

Informed consent was obtained from each patient and control at the time of drawing blood. The NTUH ethics committee approved the study protocol conforming to the ethical guidelines of the 1975 Declaration of Helsinki.

Laboratory assays

Venous blood samples were collected in the morning after 12 h fasting and measured by standard laboratory

techniques. Hepatitis B surface antigen and anti-HCV were assayed with commercial kits (Abbott Laboratories, North Chicago, IL, USA). Plasma glucose, serum AST, ALT, total cholesterol, triglyceride, low-density lipoprotein-cholesterol, and high-density lipoprotein-cholesterol were measured by an autoanalyzer (Hitachi 7250, Special; Hitachi, Tokyo, Japan). The remnant serum samples were stored at −80°C to test the adiponectin level. Because not all of the cases and controls had enough stored samples for testing, only 668 subjects (210 HCV patients and 458 non-HCV controls) had adiponectin data. Serum adiponectin level was determined by an ELISA assay (Human Adiponectin ELISA Kit, B-Bridge International, Inc., CA, USA) according to the manufacturer's instructions.

Serum RNA was extracted by using a commercial kit (QIAamp RNA Blood Mini Kit; Qiagen Inc., Valencia, CA, USA). HCV RNA was assayed by a real-time polymerase chain reaction (PCR) assay, with the detection limit of 1,000 copies/ml (i.e. 370.37 IU/ml) [26, 27]. Genotyping of HCV was performed by reverse transcriptase-PCR with type-specific primers [28, 29]. The detection limit of type-specific primers genotyping method is 100 copies/ml (i.e. 37 IU/ml). All samples were tested in duplicate. Serum samples from anti-HCV-positive patients with undetectable HCV RNA by real-time PCR assay were re-checked by the qualitative type-specific primers genotyping method.

Metabolic and demographic features

We collected information on sex, age, body weight, body height, body mass index, adiponectin, fasting blood glucose, triglyceride (TG), total cholesterol (TC), alanine aminotransferase (ALT), high-density lipoprotein-cholesterol (HDL), and low-density lipoprotein-cholesterol (LDL).

Fasting plasma glucose (FPG) levels ≧100 mg/dl (5.6 mmol/l) but <126 mg/dl (7.0 mmol/l) was considered as impaired fasting glucose (IFG) according to the latest American Diabetes Association criteria [30]. Upper limit of normal (ULN) of serum ALT level was set at 30 U/l for men and 20 U/l for women [31, 32].

Statistical analysis

Demographic features and metabolic factors were compared between chronic hepatitis C patients and non-HCV control using chi-square test for categorical variables and *t*-test for continuous variables. Odds ratio (OR) and 95% confidence interval (CI) as well as *P*-values were estimated for each variable by logistic regression. Stepwise approaches were performed to examine the association between fasting blood glucose, triglyceride, adiponectin, total cholesterol, ALT levels, and risk of HCV infection, after adjusting for sex, age, and body mass index. Parameters of metabolic profiles and the presence of HCV infection were estimated by multiple linear regression analysis. ANOVA was used to examine the relationship between HCV infection and various metabolic profiles. All analyses were performed with Stata statistical software (version 8.0, Stata Corp., College Station, TX, USA) and all tests were 2-sided and $P < 0.05$ was considered statistically significant.

Results

Demographic features

Serum ALT and HDL were significantly higher in chronic hepatitis C patients compared with controls. In contrast, serum TC, TG, and LDL levels were significantly lower in chronic hepatitis C patients than controls (Table 1).

It is known that patients with advanced liver diseases have hyperinsulinemia and impaired glucose tolerance. In order to know the severity of liver dysfunction in the cases of present study, we also collected available data from the medical records of enrolled CHC cases. About 461 cases had available platelet (PLT) data (Table 2). If we use the Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) more than 1 as a cutoff level of significant fibrosis, about 51% enrolled cases might have significant fibrosis or cirrhosis.

Metabolic profiles in HCV infection

To further clarify the association between HCV infection and metabolic profiles, categorized metabolic data were included in multiple linear regression models after adjustment for age, sex, and body mass index. We found that the presence of HCV infection was positively associated with the categorized ALT levels, but negatively associated with categorized TG levels and TC levels (Table 3).

ALT level and metabolic profiles in chronic HCV infection

Because chronic inflammation is known to be correlated with metabolic homeostasis, and ALT serves as a surrogate marker of hepatocytes injury, we thus attempted to clarify the modifying effect of ALT on metabolic profiles in chronic hepatitis C patients. We stratified ALT level

Table 1 Comparison of clinical and metabolic characteristics between HCV patients and non-HCV controls

Characteristics	HCV patients ($N = 500$)	Non-HCV controls ($N = 536$)	P-value
Age (years)	52.77 ± 0.56	52.61 ± 0.56	0.84
Male (%)	279 (55.8)	312 (58.2)	0.43
Body mass index (kg/m^2)	25.91 ± 0.95	25.18 ± 0.17	0.43
Fasting blood glucose (mg/dl)	102.05 ± 1.46	100.45 ± 1.41	0.43
ALT (U/l)	103.75 ± 5.42	29.54 ± 1.42	<0.01
Triglyceride (mg/dl)	112.53 ± 2.87	138.92 ± 5.53	<0.01
Total cholesterol (mg/dl)	184.20 ± 1.87	195.45 ± 1.49	<0.01
LDL (mg/dl)	116.87 ± 1.89	124.54 ± 1.48	<0.01
HDL (mg/dl)	47.99 ± 0.68	46.20 ± 0.53	0.04

Data are shown by mean ± standard error

Abbreviations: ALT, alanine aminotransferase; LDL, low-density lipoprotein-cholesterol; HDL, high-density lipoprotein-cholesterol

Table 2 The characteristics of 461 HCV patients with available PLT data

Characteristics	N (%)	Mean ± SE	95% CI
PLT (K/μl)	461	171.3 ± 2.7	166.0–176.5
Albumin (g/dl)	401	4.2 ± 0.0	4.2–4.2
T-bilirubin (mg/dl)	417	0.9 ± 0.0	0.8–1.0
D-bilirubin (mg/dl)	394	0.2 ± 0.0	0.2–0.3
AST (U/l)	456	87.6 ± 3.4	81.0–94.2
APRI	459	1.5 ± 1.1	1.4–1.7
APRI ≦ 0.5	97 (21.1)		
0.5 < APRI ≦ 1	128 (27.9)		
1.0 < APRI ≦ 1.5	93 (20.3)		
1.5 < APRI ≦ 2	39 (8.5)		
APRI > 2	102 (22.2)		

Data are shown by mean ± standard error (mean ± SE)

N represents the number of enrollers with available PLT data in each character. The values in the parentheses represent the proportion of enrollers with available data to the total enrollers of each group

Abbreviations: AST, aspartate aminotransferase; PLT, platelet count; T-bilirubin, total bilirubin; D-bilirubin, direct bilirubin; APRI, Aspartate Aminotransferase-to-Platelet Ratio Index

according to its upper limit of normal (ULN) (30 U/l for men and 20 U/l for women) into two subgroups, and examined the differences of the metabolic profiles between HCV patients and matched controls. In the subgroup with ALT level less than or equal to ULN, HCV infection was independently associated with younger age, female gender, and higher TC levels. However, in the subgroup with ALT levels greater than ULN, HCV infection was independently associated with lower TC and lower TG levels (Table 4). To clarify the impact of hyperglycemia and dyslipidemia on the modifying effect of ALT in CHC patients, we also analyzed our data after excluding the persons with fasting glucose levels ≥110 mg/dl, triglyceride ≥150 mg/dl, or total cholesterol ≥200 mg/dl (according to the suggestion

Table 3 Parameter estimates gained from separate multiple linear regression identifying categorized metabolic data associated with the presence of HCV infection

	Parameter estimate	Standard error	P-value
Fasting blood glucose (mg/dl)[a]			
<80	Reference		
80–120	−0.09	0.08	0.25
120–200	−0.04	0.09	0.70
>200	−0.06	0.14	0.65
ALT (U/l)[b]			
<20	Reference		
20–40	0.07	0.03	0.03
40–80	0.45	0.04	<0.01
80–160	0.73	0.04	<0.01
160–400	0.83	0.05	<0.01
>400	0.75	0.13	<0.01
Triglyceride (mg/dl)[c]			
<150	Reference		
150–300	−0.07	0.04	0.07
>300	−0.24	0.08	<0.01
Total cholesterol (mg/dl)[d]			
<220	Reference		
≧220	−0.09	0.04	0.02

Note: Multiple linear regression models using the presence of HCV infection as the dependent variable and age, sex, and body mass index as independent variables. Categorized fasting blood glucose, ALT, triglyceride, and total cholesterol levels were separately added as independent variables

[a] Categorizing fasting blood glucose to 4 groups and using fasting blood glucose <80 mg/dl as reference group

[b] Categorizing ALT to 5 groups and using ALT <40 U/l as reference group

[c] Categorizing serum triglyceride to 3 groups and using serum triglyceride <150 mg/dl as reference group

[d] Categorizing serum total cholesterol to 2 groups and using serum total cholesterol <220 mg/dl as reference group

Table 4 Multiple logistic regression analysis stratified by upper limit of normal ALT levels to examine the odds of HCV patients versus non-HCV controls

	ALT ≦ ULN[a] ($N = 417$)		ALT > ULN ($N = 532$)	
	Adjusted OR	95% CI	Adjusted OR	95% CI
Age (years)	0.96*	0.94–0.99	1.01	0.99–1.02
Sex (male vs. female)	0.13*	0.07–0.27	1.08	0.71–1.64
Body mass index (kg/m^2)	1.08**	0.99–1.18	1.00	0.99–1.01
Total cholesterol (mg/dl)	1.01*	1.00–1.02	0.99*	0.98–0.99
Fasting blood glucose (mg/dl)	1.00	0.99–1.01	1.01	1.00–1.01
Triglyceride (mg/dl)	1.00	1.00–1.00	0.99*	0.99–0.99

OR, odds ratio; CI, confidence interval

The models adjusted for age, sex, body mass index, adiponectin, fasting blood glucose, triglyceride, and total cholesterol

[a] Upper limit of normal (ULN) of serum ALT level is 30 U/l for men and 20 U/l for women

* $P < 0.05$

** $P < 0.1$

of ATPIII). The results are similar to those shown in Table 4.

Adiponectin and metabolic profiles in chronic HCV infection

A total of 668 subjects (210 HCV patients and 458 non-HCV controls) had available adiponectin data, and were subjected to further subgroup analysis. By using multiple linear regression models, HCV infection was positively correlated with serum adiponectin levels (Table 5).

During stepwise addition of adiponectin and ALT levels into the regression models, we found TC and TG levels were affected by adiponectin. The negative association between TG/TC levels and HCV infection disappeared when adiponectin was added to the model. In addition, the negative association between TC levels and HCV infection also disappeared after ALT was added into the model, implying a possible interaction between TC and ALT levels.

Table 5 Parameter estimates gained from multiple linear regression identifying factors associated with the presence of HCV infection in 668 enrollers with available adiponectin data

	Parameter estimate	Standard error	*P*-value
Age (years)	−0.00	0.00	0.10
Sex (male vs. female)	−0.20	0.04	<0.01
Body mass index (kg/m^2)	0.01	0.00	0.06
Adiponectin (μg/ml)[a]			
<4	Reference		
4–8	0.09	0.04	0.04
>8	0.09	0.05	0.04

Note: Multiple linear regression models using the presence of HCV infection as the dependent variable and age, sex, body mass index, and stratified adiponectin levels as independent variables

[a] Categorizing serum adiponectin level to 3 groups and using serum adiponectin <4 μg/ml as reference group

Discussion

In this study, we enrolled greater than 1,000 subjects, including 500 cases and 536 matched controls. This large sample size ensured that we could reliably analyze-related parameters. Our findings showed the existence of a close link between HCV infection and metabolic abnormalities. We found that HCV infection was positively correlated with serum adiponectin level, which was different from previously reports on subjects with non-alcoholic steatohepatitis (NASH) [20, 33].

Our data displayed that HCV infection was associated with lower TG, TC, LDL, and higher HDL levels, which confirmed and extended previous studies [10]. Of particular note is that we found adiponectin to be highly correlated with TC and TG profiles. Several lines of evidence have indicated that HCV or its viral components are able to induce derangements of host lipid metabolism, possibly via interfering with the expression of peroxisome proliferator-activated receptor α, retinoid receptor α, and multidrug resistance 3 genes [34, 35]. These genes are not only related to lipid metabolism, but also related to the functions of adiponectin [36]. Nevertheless, most previous data were based on systems overexpressing various HCV proteins in cell cultures or transgenic mouse models. Our observations on human subjects therefore provided strong support to these experimental results.

Lipoproteins may have an intriguing interaction with HCV. Recent studies indicated that lipoprotein-associated

HCV particles may infect cells via LDL receptors [37]. HDL and scavenger receptor class B type I (SR-BI) play an active role in facilitating HCV entry but oxidized LDL (oxLDL) is a potent cell entry inhibitor [38, 39]. We also found that higher TC level had a positive correlation with HCV infection while lower TC level displayed inverse correlation (data not shown). These data suggested a possible interaction between TC and HCV infection. Our speculations were supported by recent data that higher TC and LDL levels are associated with a better therapeutic outcome of chronic hepatitis C [40].

In this study, we consistently showed HCV infection was associated with a lower TG level [18]. In the transgenic mouse model, HCV core protein appears to interfere with the hepatic assembly and secretion of ApoB containing very low-density lipoproteins (VLDL) [41]. These effects cause TG to accumulate within hepatocytes, and contribute to decreased serum triglyceride, which may explain the association between HCV infection and lower TG levels. However, considering that approximately 51% of the enrolled cases may have significant fibrosis or cirrhosis, and these patients with liver cirrhosis may have impaired lipid metabolism or malnutrition. Low serum TG level in the HCV group may not only result from HCV infection but also from liver cirrhosis.

Although both in vitro and in vivo studies revealed correlation between glucose metabolism and HCV infection, the clinical relevance of this issue remains unclear. Recently, a population-based study revealed a positive association between HCV infection and hyperglycemia [18], but the association disappeared when adjusted for age and gender. However, our analyses demonstrated that more chronic hepatitis C patients had an impaired fasting glucose compared to sex- and age-matched controls (data not shown). Before the subjects were included, we could only exclude the subjects with a known history of diabetes mellitus or dyslipidemia. All of these relevant histories were told by the subjects themselves or kept on their past medical records. In addition, we used the information told by the subjects themselves or kept on past medical records as a definition of diabetes mellitus or dyslipidemia. This means that some cases of diabetes mellitus or dyslipidemia may be enrolled into our study, and accordingly the possible association between the development of diabetes mellitus or dyslipidemia with HCV infection is weakened. Further studies are needed to solve this important issue.

As anticipated, HCV infection served as an important and independent correlate of serum ALT level. Previous studies indicated that metabolic factors influence ALT activities as well [32, 42]. However, whether ALT level affects metabolic profiles in chronic HCV infection remains unclear. We thus added ALT into the multivariate analysis models, and found an inverse association between TC with HCV infection in chronic hepatitis C patients with abnormal ALT. We also analyzed our data after excluding the persons with elevated fasting glucose, triglyceride, or total cholesterol levels to clarify the impact of hyperglycemia and dyslipidemia on the modification role of ALT in CHC patients, and we got similar results. Since ALT is a surrogate parameter of hepatocyte turnover and damage, we could infer that extent of liver injury may influence lipid and glucose metabolism and thus plays an important role in the metabolic derangement of chronic HCV infection.

Adiponectin is reported to have an inverse association with hepatic inflammation in NASH patients [23]. On the contrary, recent data revealed a positive association in chronic hepatitis C patients, and inferred that the increased adiponectin in the scenario of hepatic inflammatory activity might be secondary to the response of viral infection [43]. Our data added support to this speculation and suggested HCV might have an interaction with adiponectin.

Given the cross-sectional and case–control study design, we could not investigate the duration–response relationship between HCV infection and metabolic profiles. However, previous studies have shown a link between HCV infection and insulin resistance [44], and the presence of insulin resistance is one of the risk factors for fibrosis progression in chronic hepatitis C patients. These evidences give supports to the possible connection between HCV infection and metabolic derangements through insulin resistance. Besides, our study further indicated that HCV-related liver dysfunctions, such as ALT levels and the extent of liver injury, are important modifiers of host metabolic profiles. Further studies are needed to clarify the roles of metabolic variables in liver disease progression of chronic hepatitis C.

In summary, our results indicate that HCV infection is associated with higher alanine aminotransferase, high-density lipoprotein-cholesterol, and serum adiponectin levels, but with lower total cholesterol, triglyceride, and low-density lipoprotein-cholesterol levels. The association persists even after adjusting for sex, age, and body mass index. In addition, ALT may serve as a modifying factor affecting metabolic profiles in chronic hepatitis C patients. These findings highlight the complex pathophysiologic relationships between HCV infection and metabolic factors.

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