Partial Protection from Metabolic Syndrome in Chronic Hepatitis C Elderly Subjects Due to Lower Triglyceride Level

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ABSTRACT

Background: *In Taiwan, persons over 65 years old have higher prevalence of hepatitis C. Among these patients, around 50% have non-alcoholic fatty liver disease (NAFLD). Since cardiovascular diseases and diabetes are main causes of death in this age group, in this cross-sectional study, we tried to evaluate the effects of NAFLD and hepatitis C on the risk of metabolic syndrome (MetS).*

Methods: *In total, 25 116 subjects over 65 years old who presented for routine health check-ups were enrolled. From the results of seropositivity for hepatitis C and abnormal echogenicity, they were classified into four groups: normal (N), subjects with only hepatitis C (C), subjects with only abnormal echogenicity (E) and subjects with both hepatitis C and abnormal echogenicity (CE).*

Results: *Subjects in both groups E and CE had higher abnormal MetS components than group C. Among all five components, triglyceride (TG) was the one having the highest odds ratio (OR) in determining the incidence of MetS in groups C and E. Finally, compared to group N, both groups E and CE had significantly higher OR for having MetS. However, after adjusting for confounding factors, only the significance between groups E and N remained. In other words, higher MetS was noted in group E compared to group N and there was no difference in incidence of MetS between group CE and group N.*

Conclusions: *Chronic hepatitis C is a protective factor against having MetS and this effect might be due to lower TG level in the elderly. Further studies are warranted for the underlying mechanisms.*

Keywords: Hepatitis C, metabolic syndrome, non-alcoholic fatty liver disease

Protección Parcial del Síndrome Metabólico en Sujetos Ancianos con Hepatitis C Crónica Debido al Bajo Nivel de Triglicéridos

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RESUMEN

Antecedentes: *En Taiwán, las personas mayores de 65 años tienen mayor prevalencia de hepatitis C. De estos pacientes, aproximadamente el 50% padece la enfermedad del hígado graso no alcohólico (HGNA). Puesto que la diabetes y las enfermedades cardiovasculares son la principal causa de muerte en este grupo etario, en este estudio transversal tratamos de evaluar los efectos de la EHGNA y la hepatitis C sobre el riesgo de síndrome metabólico (SMet).*

Métodos: *En total, se inscribieron 25116 sujetos mayores de 65 años que se presentaron para hacerse chequeos de salud rutinarios. A partir de los resultados de seropositividad para la hepatitis C y la ecogenicidad anormal, estos fueron clasificados en cuatro grupos: sujetos normales (N), sujetos sólo con hepatitis C (C), sujetos sólo con ecogenicidad anormal (E), y sujetos con hepatitis C y ecogenicidad anormal (CE).*

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Resultados: *Los sujetos en los grupos E y CE tuvieron componentes de SMet anormales más altos que los del grupo C. De los cinco componentes, el triglicérido (TG) fue el que tuvo el cociente de probabilidades (OR) más alto a la hora de determinar la incidencia de SMet en los grupos C y E. Finalmente, en comparación con el grupo N, tanto el grupo E como el CE tuvieron OR significativamente mayores por poseer SMet. Sin embargo, después del ajuste de los factores de confusión, solamente permaneció la significación entre los grupos E y N. En otras palabras, se observaron SMet más altos en el grupo E en comparación con el grupo N, y no hubo diferencias de incidencia entre el grupo CE y el grupo N.*
Conclusiones: *La hepatitis C crónica es un factor protector frente al SMet, y este efecto podría deberse al bajo nivel de TG en los ancianos. Se requieren otros estudios en relación con los mecanismos subyacentes.*

Palabras claves: Hepatitis C, síndrome metabólico, hígado graso no alcohólico

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INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of death in both developed and developing countries. Moreover, its incidence has been increasing recently. Thus, how to identify subjects with high CVD risk becomes an important issue. Under this circumstance, the concept of metabolic syndrome (MetS) occurred. It was first described by Reaven (1) in 1988. Although many different definitions have been suggested since then, the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) proposed the most popular and practical criteria for MetS (2). In short, it contains hyperglycaemia, central obesity, hypertension and dyslipidaemia (3).

Interestingly, besides these so called 'traditional criteria', other risk factors such as uric acid or elevated liver enzyme had also been discovered and proved to be related to CVD and could be regarded as the 'non-traditional risk' for MetS (4, 5). For instance, Younossi and McCullough showed that non-alcoholic fatty liver disease (NAFLD), ranging from simple steatosis to non-alcoholic steatohepatitis, is recognized as the hepatic manifestation of MetS and is an important cause of liver-related morbidity and mortality (6). At the same time, southeast Asia is endemic for chronic hepatitis C and, not like NAFLD, the relationship between MetS is still controversial (7–9). Interestingly and importantly, it should be noted that around 50% of the subjects with hepatitis C have NAFLD (10). Based on these facts, the question arises whether subjects with both chronic hepatitis C and NAFLD would have higher risks for CVD than those with either one of them.

Ageing of the population is a common phenomenon in many developed countries. Therefore, geriatric medicine becomes an important issue for healthcare providers and related government departments nowadays. More than 10% of inhabitants are over 65 years old in Taiwan now. Due to lack of modern concepts of prevention 40 years ago, they have higher prevalence of hepatitis C. In this study, we enrolled subjects with and without hepatitis C to evaluate the effects of NAFLD and hepatitis C on the risk of MetS.

SUBJECTS AND METHODS

We enrolled subjects aged over 65 years old who underwent routine health check-ups at the MJ Health Screening Center in Taiwan. MJ Health Screening Centers are private clinics located throughout Taiwan that provide regular health examinations to individuals. The study protocol was approved by the Institutional Review Board of MJ Health Screening Center with informed consents signed by each subject enrolled. Originally, 43 730 subjects were randomly selected between 1999 and 2008. The following exclusion steps were performed to fit study purposes.

- 1584 subjects were excluded due to missing data of MetS components, liver function test, hepatitis B core antibody, hepatitis B surface antigen or hepatitis C virus antibody.
- 8931 subjects were excluded who had history of diabetes, hypertension, hyperlipidaemia, CVD, and those taking medications for these diseases or medications known to affect components of MetS.
- 3247 subjects were excluded due to chronic hepatitis B infection.
- 4852 were excluded due to a history of excessive alcohol consumption more than 20 grams per day in men and 10 grams per day in women; those with liver fibrosis, cirrhosis and acute hepatitis were also excluded from this study.

Finally, 25 116 subjects were eligible for analysis. According to hepatitis C virus antibody and abnormally increased echogenicity, they were further divided into four groups as follows: N (normal), C (hepatitis C), E (abnormal echogenicity) and CE [both hepatitis C and abnormal echogenicity] (Table 1). The definition of the abnormal echogenicity will be explained in the following 'liver sonogram' section.

Data collection

Participants visited the clinic at 8 am after at least a 10-hour fast. Information about medical history, lifestyle, alcohol intake, smoking and physical exercise was obtained through an

Table 1: Grouping of subjects according to hepatitis C and abnormal liver echogenicity

	Hepatitis C antibody (-)	Hepatitis C antibody (+)
Normal liver echogenicity	Group N (normal)	Group C (hepatitis C)
Abnormal liver echogenicity	Group E (Echogenicity)	Group CE (both)

interview with senior nursing staff. A complete physical examination was conducted, and waist circumference (WC) was taken at the midway point between the inferior margin of the last rib and the crest of the ilium, in a horizontal plane. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by nursing staff using a computerized automercury sphygmomanometer on the right arm of the participants, who had rested for five minutes in a sitting position. A venous blood sample was collected for biochemistry study. Plasma was separated from blood within one hour and stored at -70 ˚C and analysed for fasting plasma glucose (FPG) and lipid profiles. The FPG was detected using a glucose oxidase method (YSI 203 glucose analyser, Scientific Division, Yellow Springs Instruments, Yellow Springs, OH). Total cholesterol and triglycerides (TG) were measured using the dry, multilayer analytical slide method in the Fuji Dri-Chem 3000 analyser (Fuji Photo Film, Minato-Ku, Tokyo, Japan). Serum high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) concentration were analysed using an enzymatic cholesterol assay following dextran sulfate precipitation. Aspartate aminotransferase and alanine aminotransferase were analysed by ultraviolet (UV) with P5P method (ARCHITECT c System, Abbott, US). Hepatitis C antibody, hepatitis B surface antigen and hepatitis B core antibody were analysed by chemiluminescent microparticle immunoassay (ARCHITECT i System, Abbott, US).

Definition of metabolic syndrome

In the current study, MetS was regarded as a risk factor for future CVD. We used the following ATP III (2) criteria to define MetS, which were WC ≥ 90 cm and ≥ 80 cm for Taiwanese men and women, respectively, TG ≥ 150 mg/dL, HDL-C < 40 mg/dL in men and < 50 mg/dL in women, SBP ≥ 130 mmHg or DBP ≥ 85 mmHg and FPG ≥ 100 mg/dL. Subjects with more than three components were defined as having MetS.

Liver sonogram

An abdominal sonogram was performed and the results were interpreted for every participant by two well-experienced radiologists using a high-resolution B-mode scanner (SSA-240A, Toshiba Corporation, Tokyo, Japan). The radiologists had regular conferences to discuss all the radiological results to reduce bias from different readers. The normal liver echogenicity was labelled as "0" and increasing echogenicity was labelled as "1" based on liver-kidney echo discrepancy and loss of echoes from the walls of the portal veins (11). Liver cyst, mass or cirrhosis were all excluded by the radiologist.

Statistical analysis

The data were analysed with SPSS version 18.0 (SPSS, Chicago, IL, USA). All data were tested for normal distribution with Kolmogorov-Smirnov test and for homogeneity of variances with Levene's test. Continuous variables are expressed as mean ± SEM. The *t*-test was used to evaluate the differences between groups. When comparing the differences between three groups, one-way ANOVA was used. For *post hoc* comparison, the Bonferroni test was applied. To test for the percentage of MetS in different groups, Chi-squared analysis was performed for categorical variables. The odds ratio (OR) was calculated to compare the possibility of having MetS in different groups. To observe the correlation between different parameters, univariate and multivariate logistic regression were used. All statistical tests were two-sided and considered statistically significant when $p < 0.05$.

RESULTS

According to the aforementioned grouping criteria, the demographic data and MetS components of the four groups are shown in Table 2. There were no significant differences in demographic data and MetS components between N and C group other than TC and LDL-C which were found to be lower in C group. Not surprisingly, subjects in both E and CE groups had higher BP, WC, BMI, FPG, TG, LDL-C and lower HDL-C than the C group. Finally, when comparing E and CE groups, CE group had lower TG, TC, HDL-C and LDL-C than the E group.

The prevalence of MetS in each group is shown in the Figure. Both E and CE groups had significantly higher prevalence of MetS than N and C groups. It should be mentioned that the prevalence of MetS between E and CE groups, and N and C groups had no significant difference.

In order to know which component had the most profound effect on the occurrence of MetS in either subjects who have chronic hepatitis C (including both group C and CE group; Table 3a) or NAFLD (including both group E and CE group; Table 3b), multiple logistic regression was performed. It was noted, consistently, that TG had the highest odds ratio of having MetS. More importantly, they are independently related to the occurrence of MetS.

Finally, the OR was calculated before and after age, BMI and LDL-C were adjusted (Table 4). Compared to group N, both groups CE and E all had significantly higher OR for having MetS. Of note, the OR of group E was higher than that of group CE. After adjustment, only group E still remained significant. At the same time, the strength of the OR decreased from 4.07 to 2.24 in men and 3.25 to 1.11 in women.

Table 2: Demographic data of normal (N), pure non-alcoholic fatty liver disease (E), pure hepatitis C (C) and combined non-alcoholic fatty liver disease with hepatitis C (CE) groups

Variables	HCV (-)		HCV (+)	
	N	E	C	CE
Male				
n	**5599**	**7283**	**89**	**117**
Age (year)	70.8 ± 5.0	70.4 ± 4.8**	70.3 ± 3.9	71.1 ± 5.0
SBP (mmHg)	129.8 ± 19.8	133.1 ± 19.2*	130.1 ± 20.5	133.6 ± 19.8
DBP (mmHg)	73.8 ± 11.3	76.1 ± 11.4*	72.8 ± 12.1**	76.2 ± 11.7*††
WC (cm)	80.1 ± 7.9	86.7 ± 8.4*	80.1 ± 8.2*	84.3 ± 8.3*
BMI (Kg/m^2)	20.3 ± 94.9	23.6 ± 58.9*	22.3 ± 2.9	23.5 ± 2.8
FPG (mg/dL)	101.0 ± 16.6	107.1 ± 25.0*	102.7 ± 15.2	108.7 ± 25.2*
TG (mg/dL)	99.9 ± 46.6	132.8 ± 66.3*	91.6 ± 49.8†	111.8 ± 55.4†
TC (mg/dL)	197.2 ± 35.1	201.5 ± 35.4*	172.0 ± 26.9*†	176.9 ± 34.2*†
HDL-C (mg/dL)	54.7 ± 14.8	49.0 ± 12.9*	50.1 ± 13.0*	45.7 ± 13.1*
LDL-C (mg/dL)	122.4 ± 31.5	125.9 ± 31.9*	103.6 ± 25.4*†	108.8 ± 32.3*†
MetS n (%)#	737 (13.16)	2780 (38.17)*	89 (13.48)	35 (29.91)*
Female				
n	**4611**	**7238**	**74**	**105**
Age (year)	69.8 ± 4.5	69.4 ± 4.2	69.2 ± 4.0	68.9 ± 4.0
SBP (mmHg)	133.8 ± 20.2	136.1 ± 19.7*	133.6 ± 24.6	138.9 ± 23.1*
DBP (mmHg)	73.3 ± 11.3	74.8 ± 11.4*	74.6 ± 12.0	77.6 ± 12.0*
WC (cm)	74.7 ± 7.3	80.6 ± 8.4*	74.0 ± 7.7*†	80.0 ± 8.4*
BMI (Kg/m^2)	22.2 ± 2.9	24.8 ± 3.3*	22.2 ± 3.0*†	24.3 ± 3.5
FPG (mg/dL)	99.8 ± 14.0	105.6 ± 24.3*	98.9 ± 20.5*†	102.7 ± 19.7
TG (mg/dlL	107.6 ± 51.7	136.8 ± 65.7*	97.2 ± 35.6*†	119.2 ± 54.1*††
TC (mg/dL)	211.7 ± 37.0	214.9 ± 37.6*	193.7 ± 33.9*†	194.8 ± 44.8*†
HDL-C (mg/dL)	63.8 ± 16.3	57.5 ± 14.7*	62.6 ± 16.8*†	53.1 ± 14.3*††
LDL-C (mg/dL)	126.4 ± 33.2	130.0 ± 33.8*	111.6 ± 30.3*†	117.9 ± 41.3††
MetS n (%)#	962 (20.86)	3341 (46.16)*	10 (13.51)†	48 (45.71)*

SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; BMI: body mass index; FPG: fasting plasma glucose; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MetS: metabolic syndrome

*$p < 0.001$, **$p < 0.05$ to N group; †$p < 0.001$, ††$p < 0.05$ to E group; #by Chi-squared test

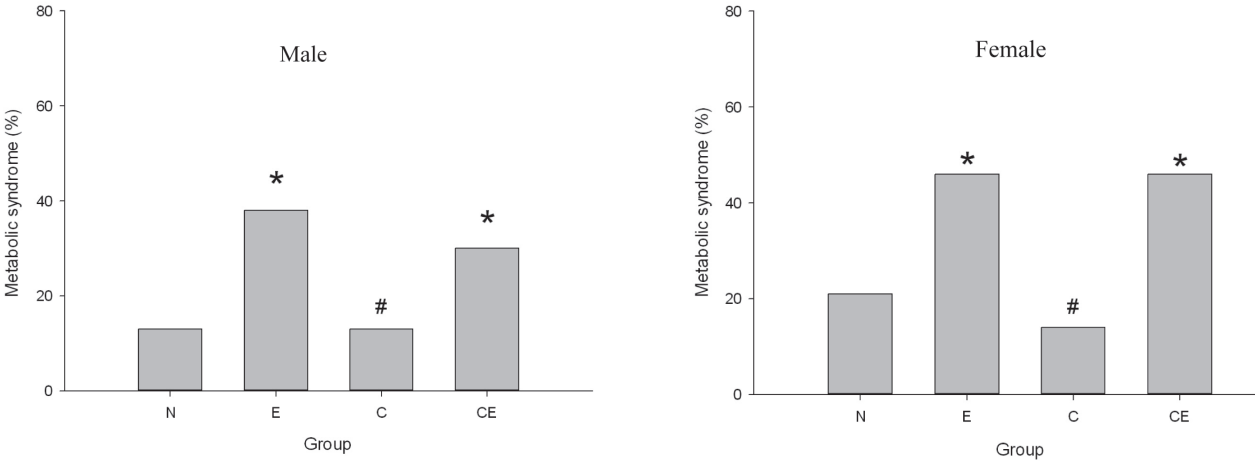

Figure: Metabolic syndrome percentage in each group, according to gender.
*$p < 0.001$ when compared with group N; #$p < 0.001$ when compared with group E

Table 3: Odds ratio of each metabolic syndrome component developing metabolic syndrome in different groups. A) non-alcoholic fatty liver disease (including subjects with only abnormal echogenicity (group E) and subjects with both hepatitis C plus abnormal echogenicity (group CE)) and B) chronic hepatitis C (including subjects only with hepatitis C (group C) and both hepatitis C plus abnormal echogenicity (group CE)

A) Variables	**Odds ratio (95% CI)**		***p*-value***
Male			
Waist circumference ≥ 90 cm	11.96	(10.69, 13.39)	< 0.001
Triglyceride ≥ 150 mg/dL	13.87	(12.29, 15.64)	< 0.001
LDL-C ≥ 130 mg/dL	1.10	(1.00, 1.21)	0.04
HDL-C < 40 mg/dL	8.34	(7.41, 9.39)	< 0.001
SBP ≥130 or DBP ≥ 85 mmHg	5.01	(4.48, 5.60)	< 0.001
Fasting plasma glucose ≥ 100 mg/dL	5.07	(4.53, 5.67)	< 0.001
Female			
Waist circumference ≥ 80 cm	6.09	(5.34, 6.94)	< 0.001
Triglyceride ≥150 mg/dL	14.32	(12.52, 16.37)	< 0.001
LDL-C ≥ 130 mg/dL	0.99	(0.90, 1.10)	0.874
HDL-C < 50 mg/dL	11.53	(10.15, 13.09)	< 0.001
SBP ≥ 130 or DBP ≥ 85 mmHg	4.58	(4.08, 5.14)	< 0.001
Fasting plasma glucose ≥ 100 mg/dL	6.42	(5.74, 7.19)	< 0.001
B) Variables	**Odds ratio (95% CI)**		***p*-value***
Male			
Waist circumference ≥ 90 cm	7.68	(2.70, 21.85)	< 0.001
Triglyceride ≥ 150 mg/dL	23.81	(7.27, 78.03)	< 0.001
LDL-C ≥ 130 mg/dL	1.50	(0.68, 3.34)	0.315
HDL-C < 40 mg/dL	15.81	(6.50, 38.48)	< 0.001
SBP ≥130 or DBP ≥ 85 mmHg	3.62	(1.56, 8.39)	0.003
Fasting plasma glucose ≥ 100 mg/dL	35.72	(7.51, 169.97)	< 0.001
Female			
Waist circumference ≥ 80 cm	7.61	(2.88, 20.10)	< 0.001
Triglyceride ≥ 150 mg/dL	36.77	(9.37, 144.32)	< 0.001
LDL-C ≥ 130 mg/dL	1.01	(0.46, 2.24)	0.972
HDL-C < 50 mg/dL	9.26	(4.03, 21.28)	< 0.001
SBP ≥130 or DBP ≥ 85 mmHg	9.21	(3.44, 24.65)	< 0.001
Fasting plasma glucose ≥ 100 mg/dL	8.01	(3.60, 17.81)	< 0.001

HDL-C: high-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; CI: confidence interval; **p*-value was adjusted for age, gender and body mass index (BMI)

Table 4: Odds ratio of having metabolic syndrome in each group

Group	**OR (95% CI) Crude**		**Adjusted**	
Male				
N	Reference		Reference	
E	4.07	(3.72, 4.46)*	2.24	(2.09, 2.51)*
C	1.03	(0.56, 1.90)	0.78	(0.41, 1.75)
CE	2.82	(1.88, 4.21)*	1.34	(0.88, 2.32)
Female				
N	Reference		Reference	
E	3.25	(2.99, 3.54)*	1.11	(1.08, 1.23)*
C	0.59	(0.30, 1.16)	0.52	(0.26, 1.31)
CE	3.19	(2.16, 4.72)*	1.15	(0.79, 2.10)

N: normal subjects; E: subjects with abnormal echogenicity; C: subjects with hepatitis C; CE: subjects with both hepatitis C and abnormal echogenicity; OR: odds ratio; CI: confidence interval
Adjusted by age, body mass index and low-density lipoprotein cholesterol; * $p < 0.05$

DISCUSSION

The original purpose of defining MetS was to identify subjects at high risk for CVD and diabetes. It is well-known that NAFLD is related to increased incidence of MetS (12–15). Since the older subjects are at higher risk for NAFLD, higher risk for CVD is noted. This is because ageing is a risk itself for having NAFLD (16, 17). Hu *et al* had shown that NAFLD prevalence correlates well with age (17). Other than this, hepatitis C virus is an exacerbating factor and, thus, Rafiq and Younossi demonstrated that more than 50% of these patients would have NAFLD (10). Interestingly, in this study, the percentage of NAFLD in subjects with hepatitis C was non-significantly lower than that of those without hepatitis C (57.7% *versus* 58.7%, respectively). Therefore, it is important to further investigate whether these subjects were under higher risk for MetS.

Whether subjects with hepatitis C have higher prevalence of MetS has been controversial. Studies done by Jan *et al* and Shaheen *et al* showed that there was no increase in the prevalence (7, 8). However, Huang *et al* (9) demonstrated the opposite results. Our results supported the finding that the prevalence does not increase in subjects with hepatitis C. This is not surprising, since the incidence of NAFLD is lower as aforementioned. Moreover, it could be noted that the incidence of MetS was even significantly lower than that in group CE (Figure). Similar changes could also be noted between groups E and CE. The conclusion to be drawn from these findings is that having hepatitis C seems to be 'protective' against having MetS. This interesting phenomenon has been firstly observed by Huang *et al* (9) and further elaborated in details by Tsochatzis *et al* and Lonardo *et al* (18, 19). However, these studies investigated NAFLD and chronic hepatitis C separately or in a relatively small population. Therefore, their results are less convincing. To our knowledge, the present study is the first one to examine this 'protective effect' in subjects who had either hepatitis C, NAFLD or both of them.

To further examine the MetS components among the four groups, it is interesting to note that both TC and LDL-C were lower in group C compared to group N (Table 2). Lower TG could also be noted in group C than in group E. The decrease in the LDL-C and TG might contribute to the lesser prevalence of MetS in subjects with hepatitis C. The mechanisms of the lower lipoprotein in subjects with hepatitis C might be explained by the finding of Lerat *et al* (20). In the transgenic mice model, they found that the full-length polyproteins of hepatitis C virus could decrease plasma TG levels and SREBP1c activation. At the same time, *de novo* TG synthesis *via* the lipogenic pathway is also reduced.

Either in subjects with NAFLD or hepatitis C, TG is the most important factor which contributes to the occurrence of MetS. This could be concluded from the data presented in Tables 3a and 3b. It is noted that TG has the highest OR of the other four MetS components. Next to TG, the components with the second highest OR are not consistent between the

NAFLD group and HCV group and between genders. This result could further confirm that TG plays the most important role in the relationship between hepatitis C virus and MetS. In subjects with NAFLD, but not with chronic hepatitis C, WC is the second significant determinant. From here, we can postulate that the role of WC is different between these two conditions, which is not totally surprising since the relationship between WC and NAFLD has been well-established (4–21). Increased WC could trigger MetS possibly due to its relationship with insulin resistance which, in turn, is the core of MetS (21). For the same reason, NAFLD has been proposed to be the liver manifestation of MetS by many authors (13).

However, in subjects with chronic hepatitis C, FPG became the second substantial factor to determine having MetS. Reports have shown that high prevalence of glucose abnormalities can be associated with hepatitis C in both insulin-resistant and abnormal glucose tolerance subjects (22, 23). Here, the data further supported that the underlying pathophysiology of developing MetS was different in NAFLD and chronic hepatitis C.

The OR to have MetS, before adjustment, is significantly higher in group E than group N. This finding is compatible with our previous conclusion that the appearance of the NAFLD is related to higher OR for MetS. However, after the adjustment, the only significantly higher OR is in group E. Other than this, another important information that could be noted from Table 4 is that the OR of group C is 0.78 in men and 0.52 in women. Although not significant, it is strongly suggesting that hepatitis C has a protective effect for development of MetS in older subjects.

Although there were many similar studies done in this area, all of them were only focussing on the effect of NAFLD or chronic hepatitis C separately. The present study is the first one to investigate not only the aforementioned two conditions but also subjects with both NAFLD and chronic hepatitis C at the same time. We believe that our results would further clarify this complex relationship and contribute significantly to the already known facts.

There are limitations in this study. Compared to MetS, the CVD or diabetes outcome should be the more significant endpoints. Unfortunately, this information was not available at present. Secondly, the design of our study is only cross-sectional. In the future, if similar results could also be found in a longitudinal study, it would be more convincing. However, since the study cohort is large, we still consider that our results are reliable.

In conclusion, chronic hepatitis C is a protective factor against having MetS and this effect might be due to the lower TG level in these patients. Therefore, NAFLD is the single most important factor to cause MetS in subjects with or without hepatitis C. Further studies are warranted for the underlying mechanisms.

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AUTHORS' CONTRIBUTIONS

K Wang and Y-L Chen wrote the manuscript; Y-J Liang, Y-L Chen and D Pei did the study design; statistical analysis was performed by C-H Hsu, T-T Chao and C-Z Wu; Y-L Chen and J-D Lin interpreted the data; Y-L Chen and Y-J Liang critically revised the manuscript.

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