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Original Contribution

Hepatitis C Virus Infection and the Development of Type 2 Diabetes in a Community-based Longitudinal Study

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The temporal relation of hepatitis C virus (HCV) infection to the development of type 2 diabetes remains unknown. The authors followed 4,958 persons aged ≥40 years without diabetes (3,486 seronegative, 812 anti-HCV+, 116 with hepatitis B virus/HCV coinfection, and 544 hepatitis B surface antigen (HBsAg)+) from a community-wide cohort in southern Taiwan for 7 years (1997–2003) to study the risk of diabetes associated with HCV infection. A total of 474 participants developed diabetes. The 7-year cumulative incidence was 7.5% for HBsAg+, 8.6% for seronegative, 14.3% for anti-HCV+, and 14.7% for coinfected participants. Compared with HCV− persons, HCV+ persons had a higher cumulative incidence of diabetes (log-rank test, $p < 0.0001$). A multivariate Cox proportional hazards model showed that anti-HCV+ (hazard ratio = 1.7, 95% confidence interval: 1.3, 2.1), coinfection (hazard ratio = 1.7), overweight, obesity, and increasing age were significantly associated with diabetes ($p < 0.05$). Gender, educational level, HBsAg+ status, alcohol consumption, and smoking were not significant. After stratification by age and body mass index, the risk ratio for diabetes in anti-HCV+ participants increased when age decreased and body mass index levels increased ($p < 0.001$). Results show that HCV infection is an independent predictor of diabetes, especially for anti-HCV+ persons who are younger or have a higher body mass index.

body mass index; cohort studies; diabetes mellitus; hepatitis C

Abbreviations: HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

Hepatitis C virus (HCV) infection and type 2 diabetes are two worldwide, major public health problems with increasing complication and mortality rates (1, 2). Although most studies (3–11) report that HCV infection is significantly associated with diabetes, some either find no significant association (12) or reject the hypothesis that HCV infection triggers diabetes (13). All of these studies are cross-sectional, and some had small populations or included participants with advanced liver diseases (6, 9, 11) such as cirrhosis and hepatoma, which cause glucose intolerance and insulin resistance (11, 14). It is not clear, therefore, whether HCV infection has a temporal relation with the development of diabetes. Recent studies (15–17) report that HCV infection was the main predictor for the development of diabetes after liver transplantation. However, most of the patients in these studies were old, had advanced liver diseases, and had received immunosuppressive therapy, all of which are highly associated with diabetes (18). One case-cohort study (19) did suggest that HCV infection increased the risk of diabetes but did not include enough cases to draw

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a definitive conclusion. To our knowledge, the temporal relation has not been conclusively demonstrated or confirmed in a community-based setting, however. Therefore, our primary aim was to elucidate the relation in a community cohort with a high prevalence of HCV infection (20).

Hepatitis B virus (HBV) and HBV/HCV coinfections are well-known etiologic factors related to hepatocellular carcinoma (21). Although some studies show that HBV infection is not associated with diabetes (3, 8, 10, 11), no known report confirms the temporal relation in a cohort or prospective study. The number of coinfections is substantial, especially in areas where the two viruses are endemic and for those persons with a high risk of unsafe medical injections (20, 22), but, to our knowledge, the relation between coinfection and diabetes has not been reported. Therefore, our secondary aim was to use the characteristics of a community with high prevalences of HBV, HCV, and coinfections (20) to illustrate the temporal relation between various viral hepatitis statuses and diabetes.

MATERIALS AND METHODS

A-Lein Township, in southern Taiwan's Kaohsiung County, has a population of about 31,000. The A-Lein Community Health Center is the only public clinic and health station in this township. We have conducted a free community-wide screening for HBV and HCV infection for residents aged 35 years or older since January 1996 because of the township's high hepatoma mortality rate (20). Villagers came for screening voluntarily after health promotion campaigns. On January 1, 1997, we had collected information on 5,490 adult participants who were aged 40 years or older and had complete data sets about their hepatitis and diabetes statuses. We excluded 532 who met the 1997 American Diabetes Association diagnostic criteria for type 2 diabetes: a fasting blood sugar level of $\geq$126 mg/dl, or symptoms of diabetes plus a casual blood sugar level of $\geq$200 mg/dl at baseline, or use of any hypoglycemic drugs before January 1, 1997. We then followed the remaining 4,958 participants for 7 years, until December 31, 2003. In Taiwan, more than 96 percent of the residents are covered by National Health Insurance, a government-run, single-payer national health insurance plan initiated in 1995. A periodic free adult preventive health examination for all those aged 40 years or older is provided by the National Health Insurance program.

In this community, we have offered diabetes screening for the villagers aged 40 years or older annually since 1991. All 4,958 participants had their blood sugar checked at least every other year at the A-Lein Community Health Center or at other clinics or hospitals, where their diabetes status was confirmed in a telephone interview by a physician or a trained nurse. Diabetes status was tested annually for the last 3 years of the study.

Any participants with impaired glucose tolerance—a fasting blood sugar level of $\geq$110 mg/dl and $<$126 mg/dl, and a casual blood sugar level of $\geq$140 mg/dl and $<$200 mg/dl, were asked for a recheck in half a year. The date of diabetes listed in the statistical analysis was defined as the year that the diabetes status was first found. All participants studied were anti–human-immunodeficiency-virus negative because there were and still are no anti–human-immunodeficiency-virus-positive participants reported in this township. The study was approved by the Research Committee of the Kaohsiung County Bureau of Health.

Blood samples were collected and questionnaires administered during the hepatitis screening. The questionnaire asked for demographic data, anthropometric measures, and specifics regarding alcohol consumption and smoking habits. Body mass index was computed as weight in kilograms (with the participant wearing a scrub suit and no shoes) divided by height in meters squared (kg/m^2). Because the appropriate body mass index for an Asian population might be different from the standard for a Western population (23), we subclassified normal weight as a body mass index of $<$24, overweight as a body mass index of $\geq$24 and $<$27, and obesity as a body mass index of $\geq$27 in the current study according to the criteria of the Taiwan Department of Health.

Alcohol consumption was subclassified as frequent, occasional, or rare. For the present study, frequent alcohol consumption meant consuming an average of more than one drink (each containing the equivalent of 10 g of pure alcohol) per day in the 6 months before the interview. Smoking was subclassified as one pack of 20 cigarettes or more per day (heavy smoking), less than one pack per day, abstained (i.e., quit smoking at least 6 months before this study), or never smoked.

Hepatitis B surface antigen (HBsAg) and anti-HCV markers were tested at the Tainan Blood Center of the Chinese Blood Service Foundation. HBsAg was determined by using the Murex (London, United Kingdom) HBsAg (version I) enzyme immunoassay method. Anti-HCV was tested by using the third-generation Murex anti-HCV enzyme immunoassay, which contains the antigen from the HCV core, nonstructural 3, nonstructural 4, and nonstructural 5 regions. HBV+ or HCV+ cases were confirmed by using a duplication test according to the standard procedures to exclude false-positive cases. In the present study, HBsAg+ alone means HBsAg+/anti-HCV−, anti-HCV+ alone means anti-HCV+/HBsAg−, and coinfection means HBsAg+/anti-HCV+. Anti-HCV+ includes anti-HCV+ alone and coinfection, and anti-HCV− includes seronegative and HBsAg+ alone.

The Nelson-Aalen estimator of cumulative hazard function (24) and the log-rank test were used to compare the annual and cumulative incidence of diabetes between anti-HCV+ and anti-HCV− participants. Cox proportional hazards analysis was used to estimate the relative risk between the risk factors and development of type 2 diabetes for all participants. Graphic assessment of the Cox proportional hazards assumption model was used to see whether the model is appropriate to estimate the variables of the baseline survivor function. Hazard ratios and risk ratios describe the strength of the association. The data were analyzed by using Stata software (24). Statistical significance was set at $p < 0.05$.

RESULTS

The basic data for all participants—seronegative ($n = 3,486$), anti-HCV+ alone ($n = 812$), HBsAg+ alone ($n = 544$),

TABLE 1. Baseline characteristics of participants, stratified by hepatitis status, in a 7-year cohort study (1997–2003) of development of type 2 diabetes in A-Lein, Taiwan

Basic data	Seronegative ($n = 3,486$)		Anti-HCV†+ alone ($n = 812$)		HBsAg†+ alone ($n = 544$)		Coinfection ($n = 116$)	
	No.	%	No.	%	No.	%	No.	%
Mean age (years)	55.8 (11.5)‡		58.9 (10.7)*		52.0 (9.9)*		57.4 (10.3)	
p value			<0.0001		<0.0001		0.14	
Mean body mass index (kg/m^2)	24.5 (3.8)		24.5 (4.0)		24.8 (3.9)		24.9 (4.4)	
p value			1.00		0.09		0.27	
Gender								
Male	1,536	44.1	382	47.0	293*	53.9	56	48.3
Female	1,950	55.9	430	53.0	251	46.1	60	51.7
p value			0.12		<0.0001		0.37	
Educational level*								
<9 years	2,839	81.4	743*	91.5	411*	75.5	104*	89.7
≥9 years	647	18.6	69	8.5	133	24.5	12	10.3
p value			<0.0001		0.001		0.03	
Smoking habit								
≥1 packs/day§	236	6.8	68	8.4	58*	10.7	12	10.3
<1 pack/day	3,250	93.2	744	91.6	486	89.3	104	89.7
p value			0.11		0.001		0.14	
Alcohol consumption								
Frequent	171	4.9	50	6.2	31	5.7	10	8.6
Not frequent	3,315	94.1	762	93.8	513	94.3	106	91.4
p value			0.15		0.43		0.07	

* Statistically significant difference in prevalence compared with seronegative participants ($p < 0.05$).

† HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen.

‡ Values in parentheses, standard deviation.

§ Number of packs of cigarettes (20 per pack) smoked per day.

and coinfected ($n = 116$)—and comparison of the basic data for seronegative participants and other viral hepatitis positive persons are shown in table 1. Anti-HCV+ alone and coinfected participants were older and had less education (<9 years) than HBsAg+ alone and seronegative participants ($p < 0.05$), but there were no significant differences in body mass index, heavy smoking, or frequent alcohol consumption between the two groups (table 1).

After 7 years of follow-up, 474 participants developed diabetes. The 7-year cumulative incidence was 9.6 percent, from 7.5 percent in the HBsAg+ alone and 8.6 percent in the seronegative groups to 14.3 percent in the anti-HCV+ alone and 14.7 percent in the coinfection groups. A comparison of the baseline characteristics of the participants with diabetes and those without diabetes showed that those with diabetes were significantly older, had a higher average body mass index, consumed alcohol more frequently, and had lower educational levels. A univariate Cox regression analysis, however, showed no significant differences for gender or for smoking habits. Moreover, anti-HCV+ alone and coinfected participants were more likely to develop diabetes than were seronegative participants (hazard ratio = 1.7, 95 percent confidence interval: 1.4, 2.1 and hazard ratio = 1.8, 95 percent confidence interval: 1.1, 2.7, respectively). No significant difference was found between HBsAg+ alone and seronegative participants (table 2).

A multivariate Cox proportional hazards model analysis, after adjustment for risk factors for diabetes, such as gender, educational level, overweight, obesity, age, smoking, and alcohol consumption, showed that anti-HCV+ alone (hazard ratio = 1.7, 95 percent confidence interval: 1.3, 2.1), coinfection (hazard ratio = 1.7, 95 percent confidence interval: 1.1, 2.8), overweight (body mass index ≥24 and <27 kg/m^2), obesity (body mass index ≥27 kg/m^2), and increasing age were significantly associated with the development of diabetes. Gender, educational level, HBsAg+ alone, frequent alcohol consumption, and smoking habits were not significant factors (table 3).

Because the risk ratios and hazard ratios for anti-HCV+ alone and coinfection were nearly identical, and those for HBsAg+ alone are almost equal to 1, we combined anti-HCV+ alone and coinfection as anti-HCV+, and HBsAg+ alone and seronegative as anti-HCV−. The Nelson-Aalen estimator of cumulative hazard function (24) showed that,

TABLE 2. Comparison of the baseline characteristics of the community cohort for the development of diabetes from 1997 to 2003 in A-Lein, Taiwan ($N = 4,958$)

Basic data	Diabetes+ ($n = 474$)		Diabetes− ($n = 4,484$)		HR†	95% CI†
	No.	%	No.	%		
Age (years)	57.5 (10.1)‡		55.8 (11.4)		$p < 0.01$ (t test)	
Body mass index (kg/m^2)	26.4 (3.9)		24.6 (3.8)		$p < 0.0001$ (t test)	
Gender					0.9	0.8, 1.1
Male	210	44.3	2,057	45.9		
Female	264	55.7	2,427	54.1		
Smoking habit					1.3	1.0, 1.8
Yes	46	9.7	328	7.3		
No	428	90.3	4,156	92.7		
Alcohol consumption					1.5*	1.1, 2.1
Frequent	36	7.6	226	5.0		
Not frequent or no	438	92.4	4,258	95.0		
Educational level					0.6*	0.5, 0.8
≥9 years	57	12.0	804	17.9		
<9 years	417	88.0	3,680	82.1		
Hepatitis status§						
Seronegative	300	63.3	3,186	71.1	1.0	
HBsAg+ alone¶	41	8.7	503	82.3	0.9	0.8, 1.1
Anti-HCV+ alone#	116	24.5	696	15.5	1.7**	1.4, 2.1
Coinfection	17	3.6	99	2.2	1.8*	1.1, 2.7
Body mass index (kg/m^2)						
<24	130	24.4	1,775	39.6	1	
≥24 and <27	153	32.3	1,116	24.9	1.8**	1.4, 2.3
≥27	191	40.3	1,593	35.5	1.6**	1.3, 2.0

* $p < 0.05$; ** $p < 0.001$.

† HR, hazard ratio obtained by univariate Cox regression analysis; CI, confidence interval.

‡ Values in parentheses, standard deviation.

§ Hepatitis B surface antigen (HBsAg) alone, anti–hepatitis C virus (HCV) alone, and coinfection all compared with the HBsAg−/HCV− reference group.

¶ HBsAg+ alone: HBsAg+/anti-HCV−.

Anti-HCV+ alone: anti-HCV+/HBsAg−.

compared with anti-HCV− participants, anti-HCV+ participants had a significantly higher cumulative incidence of diabetes ($p < 0.0001$, log-rank test) (figure 1).

Anti-HCV+ persons ($n = 928$) had a higher cumulative incidence (risk) of diabetes (14.3 percent) than did anti-HCV− persons ($n = 4,030$) (8.5 percent; risk ratio = 1.7, 95 percent confidence interval: 1.4, 2.0). In stratified age groups, the risk ratio for the development of diabetes between ages 40 and 64 years varied inversely with age, ranging from risk ratio = 2.2, 95 percent confidence interval: 1.5, 3.2 in the age group 40–49 years to risk ratio = 1.7, 95 percent confidence interval: 1.3, 2.2 in the age group 50–64 years ($p < 0.001$). For those aged ≥65 years, there was no significant difference (table 4). In stratified body mass index groups, anti-HCV+ participants were more likely than anti-HCV− participants to develop diabetes (risk ratio = 1.6 for normal weight, risk ratio = 1.8 for overweight, and risk ratio = 1.9 for obesity ($p < 0.05$)). The cumulative incidence of diabetes for anti-HCV+ persons who were overweight (19.1 percent) or obese (17.5 percent) was about three times greater than for anti-HCV− persons who were normal weight (6.1 percent). The risk of diabetes doubled when the body weight of anti-HCV+ participants increased from normal to overweight (9.5 percent vs. 19.1 percent), but it increased only 1.7 times for anti-HCV− persons from normal to overweight (6.1 percent vs. 10.5 percent) (table 4).

A multivariate Cox regression analysis, including the risk factors in table 3 and the interaction term between age and anti-HCV+, showed that the age × HCV interaction variable was significant (hazard ratio = 0.98, 95 percent confidence interval: 0.96, 0.998). In addition, the hazard ratio of anti-HCV+ alone increased (hazard ratio = 6.0, 95 percent confidence interval: 1.9, 18.9), but other statistical results were similar to those in table 3 (table 5). These findings

TABLE 3. Results of a multivariate Cox proportional hazards model† for the development of type 2 diabetes in a cohort study population from 1997 to 2003 in A-Lein, Taiwan ($N = 4,958$)

Risk factor	HR‡	95% CI‡
Gender (male vs. female)	0.9	0.7, 1.1
Age (continuous)	1.0*	1.0, 1.0
Educational level (≥9 years vs. <9 years)	0.8	0.6, 1.0
HBsAg alone§ (+ vs. −)	0.9	0.6, 1.3
Anti-HCV alone¶ (+ vs. −)	1.7**	1.3, 2.1
Coinfection (+ vs. −)	1.7**	1.1, 2.8
Overweight (body mass index ≥24 and <27 kg/m^2)	1.9**	1.5, 2.4
Obesity (body mass index ≥27 kg/m^2)	1.7**	1.4, 2.2
Smoking (≥1 packs/day# vs. <1 pack/day)	1.4	1.0, 1.9
Alcohol consumption (frequent vs. not frequent)	1.4	1.0, 2.0

* $p < 0.05$; ** $p < 0.001$.

† Hepatitis B surface antigen (HBsAg) alone, anti–hepatitis C virus (HCV) alone, and coinfection all compared with the HBsAg−/HCV− reference group.

‡ HR, hazard ratio; CI, confidence interval.

§ HBsAg+ alone: HBsAg+/anti-HCV−.

¶ Anti-HCV+ alone: anti-HCV+/HBsAg−.

Number of packs of cigarettes (20 per pack) smoked per day.

imply that age negatively affects the relation between HCV and diabetes.

DISCUSSION

Our major finding in this community-wide and population-based cohort study, after adjusting for established risk factors for diabetes—age, gender, educational level, body mass index, smoking, and alcohol consumption—in a multivariate Cox proportional hazards analysis, was that persons with HCV infection had a significantly (70 percent) higher incidence of diabetes than those without HCV infection. HBV plus HCV coinfected and anti-HCV+–alone persons had nearly the same risk, which indicates that HCV infection increases the risk of diabetes but HBV infection does not. This finding is consistent with past studies (3–11, 15–17, 19) showing that HCV infection, but not HBV infection (3, 8, 10, 11), is highly associated with diabetes. It indicates that type 2 diabetes might be caused by long-term interaction of HCV and its host.

We also found that the risk of developing diabetes for persons with HCV infection increases with decreased age when compared with age-group counterparts without HCV infection, a finding confirmed by using both univariate and multivariate Cox regression analysis (tables 4 and 5). These findings have some important clinical and public health implications. First, they imply that the younger the persons with HCV infection, the greater the risk that they will develop diabetes than will their age-group counterparts without HCV infection. Therefore, screening for and prevention of diabetes in persons with HCV infection could be started earlier than the suggested age of ≥45 years for the general population (25), especially for those with higher body mass index levels or with other risk factors for diabetes. In addition, young adults with diabetes in communities with a high prevalence of HCV infection could be tested for an underlying HCV infection. Second, the comorbidity of diabetes and HCV infection at a younger age might exacerbate liver problems because these two conditions greatly increase the progression of hepatic fibrosis (26) and the risk of hepatocellular carcinoma (27). Whether this comorbidity exacerbates diabetic micro- or macrovascular complications, such as atherosclerosis, needs further study (28, 29).

Overweight and obesity are major causes of nonalcoholic fatty liver disease, insulin resistance, and type 2 diabetes (28, 30). In the current study, overweight, obesity, and anti-HCV+ were three independent factors for diabetes, with approximately equal hazard ratios. This finding shows, therefore, that the diabetogenic effect of HCV infection is approximately equal to the effect of overweight and obesity, well-known risk factors for type 2 diabetes (1). In the current study, coexistence of HCV infection and overweight or obesity showed a synergetic effect on the development of diabetes; the risk of diabetes for anti-HCV+ persons who are either overweight or obese is about three times that for anti-HCV− persons of normal weight. Thus, coexistence of HCV infection and overweight increases the risk of developing diabetes. This finding is important for public health and clinical practice because the prevalence of HCV infection is endemic in some developing countries or, in particular, high-risk groups in developed countries because of unsafe injections and intravenous drug use (2, 20, 31). Developing countries also face the problem of an increase in the prevalence of overweight and obesity (1). Therefore, it is particularly important for HCV-infected persons to change their lifestyle to control their body weight to prevent the development of diabetes.

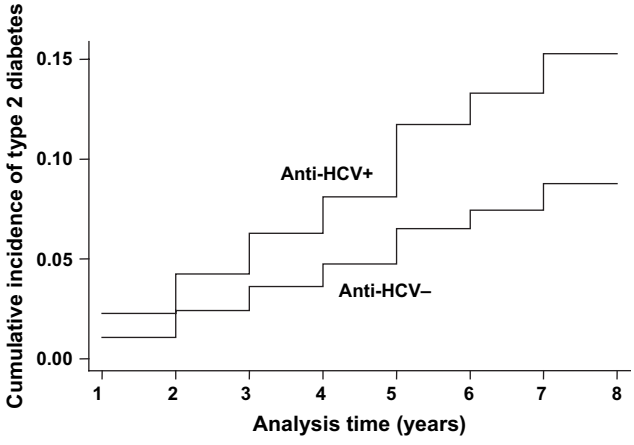

FIGURE 1. Cumulative incidence of type 2 diabetes between anti–hepatitis C virus (HCV)+ and anti-HCV− persons in A-Lein, Taiwan, during a 7-year period (1997–2003) ($p < 0.0001$, log-rank test).

TABLE 4. Risk ratios for the development of type 2 diabetes between anti-HCV+* and anti-HCV−† persons during a 7-year follow-up (1997–2003), stratified by age group and body mass index, in A-Lein, Taiwan ($N = 4,958$)

	Anti-HCV+ diabetes+/total	Risk (%)	Anti-HCV− diabetes+/total	Risk (%)	RR‡	95% CI‡	*p* value
Total	133/928	14.3	341/4,030	8.5	1.7	1.4, 2.0	<0.0001
Age group (years)							
40–49	30/218	13.8	99/1,593	6.2	2.2	1.5, 3.2	<0.0001
50–64	73/435	16.8	146/1,485	9.8	1.7	1.3, 2.2	0.0001
≥65	30/275	10.9	96/952	10.1	1.1	0.7, 1.6	0.691
Body mass index level (kg/m^2)							
<24	39/411	9.5	91/1,494	6.1	1.6	1.1, 2.2	0.015
≥24 and <27	44/231	19.1	109/1,038	10.5	1.8	1.3, 2.5	0.0003
≥27	50/286	17.5	141/1,498	9.4	1.9	1.4, 2.5	0.0001

* Anti–hepatitis C (HCV)+: anti-HCV+/hepatitis B surface antigen (HBsAg)− and coinfection.
† Anti-HCV−: HBsAg+/anti-HCV− and seronegative participants.
‡ RR, risk ratio; CI, confidence interval.

The mechanisms through which HCV infection increases the risk of diabetes are not very clear, but considerable evidence suggests that the effects of viral proteins on cellular processes involved in hepatic lipid metabolisms, early defects in insulin signaling pathways, hepatic steatosis, insulin resistance, and impaired insulin secretion might be associated with the development of diabetes (26, 28, 32–35). Insulin resistance was recently confirmed in an experiment using a transgenic mouse model with an HCV core gene (34). The experiment showed elevated circulating insulin levels, a loss of glucose tolerance, and the development of overt diabetes after a high-fat challenge. In the current study, participants with HCV infection who were also overweight or obese had a significantly increased risk of developing diabetes compared with those who were not. It implies that anti-HCV+ persons who are overweight or obese will exacerbate their insulin resistance and enhance the progression into diabetic status. Moreover, defective insulin inhibition of hepatic glucose production; a high level of elevated tumor necrosis factor-α, which is known to inhibit insulin-receptor substrates-1 phosphorylation; and insulin sensitivity restored by administration of an anti-tumor-necrosis-factor-α antibody were also confirmed (34). In the histologic examination, an approximately threefold increase in islet mass was found in transgenic mice compared with healthy controls (34). One other study (36) showed that HCV is present in human pancreatic β cells and has a direct cytopathic effect at the islet-cell level, accompanied by morphologic changes and functional defects in insulin secretion. Whether the hepatic inflammatory status, hepatic histologic stage, genotype of HCV, response to antiviral treatment, or other factors influence anti-HCV+ persons to develop diabetes is worth further study.

This study has some limitations. First, HCV-RNA was not tested to elucidate the relation between actual viral status and past infection, and 15–26 percent of the anti-HCV+ participants were HCV-RNA− and indicated past infection (2, 37). The strength of association between HCV infection and type 2 diabetes might be increased after removing these HCV-RNA− persons from analysis. Second, other risk factors for diabetes, such as family history and physical

TABLE 5. Results of a multivariate Cox proportional hazards model,† including the interaction term between age and anti-HCV+, for the development of type 2 diabetes in a cohort study population from 1997 to 2003 in A-Lein, Taiwan ($N = 4,958$)

Risk factor	HR‡	95% CI‡	*p* value
Gender (male vs. female)	0.9	0.7, 1.1	0.28
Age (continuous)	1.01*	1.00, 1.02	0.001
Educational level (≥9 years vs. <9 years)	0.8	0.6, 1.02	0.065
HBsAg alone§ (+ vs. −)	0.9	0.7, 1.3	0.665
Anti-HCV alone¶ (+ vs. −)	6.0*	1.9, 18.9	0.002
Coinfection (+ vs. −)	1.7*	1.1, 2.8	0.03
Overweight (body mass index ≥24 and <27 kg/m^2)	1.9**	1.5, 2.4	<0.001
Obesity (body mass index ≥27 kg/m^2)	1.7**	1.4, 2.2	<0.001
Smoking (≥1 packs/day# vs. <1 pack/day)	1.3	1.0, 1.9	0.08
Alcohol consumption (frequent vs. not frequent)	1.4	1.0, 2.1	0.058
Age × anti-HCV+ interaction	0.98*	0.96, 0.998	0.028

* $p < 0.05$; **$p < 0.001$.
† Hepatitis B surface antigen (HBsAg) alone, anti–hepatitis C virus (HCV) alone, and coinfection all compared with the HBsAg−/HCV− reference group.
‡ HR, hazard ratio; CI, confidence interval.
§ HBsAg+ alone: HBsAg+/anti-HCV−.
¶ Anti-HCV+ alone: anti-HCV+/HBsAg−.
# Number of packs of cigarettes (20 per pack) smoked per day.

activity, were not studied. However, this cohort was followed from a community-wide population study for hepatitis screening (20); therefore, the selection bias for these factors might be negligible between anti-HCV+ and anti-HCV− participants. Otherwise, there might be a selection bias for later diabetes screening even though every participant was called for diabetes screening. Persons with an HBV or HCV infection might have been more likely than seronegative persons to come for screening, but because the screening was free, forgoing a screening probably was rare. Third, the period for the blood sugar check, which was every other year or annually, could not be strictly controlled, but the delay for a diabetes diagnosis might be negligible for a long-term follow-up because of a low incidence rate, about 1–2 percent per year. Participants with glucose intolerance were called in for a recheck in half a year.

Fourth, the severity of hepatic fibrosis would affect the incidence of diabetes, but it was not shown in the current study. However, this cohort was collected from a community-wide hepatitis screening, and, using abdominal sonography, we had conducted a cross-sectional study in which liver disease severity in most of the HBV+ and HCV+ participants was distributed normally (3). From the ultrasonographic data we used for the present study, we found that the ultrasonographic results for 70 percent of new incident diabetes cases showed normal or fatty liver, and about 11 percent were from participants with ultrasonographic results showing cirrhosis or hepatocellular carcinoma. Because the ultrasonographic data were not complete when compared with those for the whole cohort, we therefore decided not to add the ultrasonographic variable to the current study. Most participants with HCV had become infected because of unsanitary medical injections, blood transfusions, and an unknown origin, in that order (20). The duration of HCV infection might have affected the stage of hepatic fibrosis, but it is unknown in the current study. Therefore, whether the true duration of HCV exposure will affect the results requires further study. Fifth, excepting the discussed mechanism for the development of diabetes, whether those persons with HCV infection might have been exposed through some means that increased their risk of diabetes, such as steroid use or other drugs used in medical injections, also needs further study.

In conclusion, this study demonstrated that HCV infection, including HBV/HCV coinfection but not HBV infection, increased the risk of diabetes. The risk of diabetes for HCV-infected persons increased with decreased age. A synergetic effect on the risk of diabetes was found in overweight and obese persons infected with HCV. To prevent the development of diabetes and subsequent complications from comorbidity in HCV-infected persons, lifestyle change and body weight control are strongly recommended. Regular diabetes screening for anti-HCV+ persons is indicated and can be started at a younger age, especially for those at high risk.

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