

# Blood Glucose and Renal Function Evaluation in Patients with Viral Hepatitis

Wen-Tung Hsu<sup>1</sup>  
Deng-Ho Yang<sup>1-4</sup>  
Chun-Cheng Liao<sup>3,5</sup>  
Jia -Wen Chen<sup>6</sup>  
Wen-Hsiu Hsu<sup>3,7</sup>  
Chia-Wen Kuo<sup>3,8</sup>  
Hung-Chang Hsu<sup>9</sup>  
Sheng-Huang Chang<sup>10</sup>  
Li-Mien Chen<sup>2,3</sup>

<sup>1</sup>Division of Laboratory, Taichung Armed Force General Hospital, Taichung, Taiwan, Republic of China; <sup>2</sup>Department of Internal Medicine, Taichung Armed Force General Hospital, Taichung, Taiwan, Republic of China; <sup>3</sup>School of Medicine, National Defense Medical Center, Taipei, Taiwan, Republic of China; <sup>4</sup>Department of Medical Laboratory Science and Biotechnology, Central Taiwan University of Science and Technology, Taichung, Taiwan, Republic of China; <sup>5</sup>Department of Family Medicine, Taichung Armed Force General Hospital, Taichung, Taiwan, Republic of China; <sup>6</sup>Medicine Laboratory, Ministry of Health and Welfare Feng Yuan Hospital, Taichung, Taiwan, Republic of China; <sup>7</sup>Division of Gastroenterology, Taichung Armed Force General Hospital, Taichung, Taiwan, Republic of China; <sup>8</sup>Division of Nephrology, Taichung Armed Force General Hospital, Taichung, Taiwan, Republic of China; <sup>9</sup>Division of Laboratory, Ching Chyuan Hospital, Taichung, Taiwan, Republic of China; <sup>10</sup>Tsaotun Psychiatric Center, Ministry of Health and Welfare, Nantou, Taiwan, Republic of China

Correspondence: Li-Mien Chen  
Department of Internal Medicine,  
Taichung Armed Force General Hospital,  
No. 348, Sec. 2, Chung-Shan Road,  
Taiping, Taichung, Taiwan, Republic of  
China  
Email c332860@ms65.hinet.net

**Purpose:** To evaluate the blood glucose and renal function, determine the prevalence of hyperglycemia/diabetes mellitus (DM) and renal disease (nephropathy), and investigate the association between hyperglycemia/DM and renal disease in patients with viral hepatitis (VH).

**Patients and Methods:** A total of 491 subjects were included in the study. Patients with VH were further divided into the hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and HBV-HCV co-infection subgroups. Fasting blood glucose, glycated hemoglobin (HbA1c), glycated albumin (GA), glutamic oxaloacetic transaminase (GOT), creatinine (Cr), and cystatin C (Cys C) levels were measured. Urine microalbumin levels were also assessed. Formulas for estimated average glucose calculated using glycated albumin (eAG(GA)), estimated average glucose calculated using HbA1c (eAG(HbA1c)), and estimated glomerular filtration rate calculated using cystatin C (eGFRcys) were used to evaluate the average glucose and renal function.

**Results:** The prevalence of hyperglycemia/DM and renal disease was significantly higher in the VH group, especially in the HCV subgroup. The prevalence of renal disease was significantly higher in patients with VH with eAG(GA)  $\geq 200$  mg/dL.

**Conclusion:** Our study used multiple parameters to evaluate blood glucose and renal function in patients with VH and found that hyperglycemia/DM and renal disease are closely associated with VH, especially in subjects with HCV infection. Patients with VH, especially those with HCV infection and hyperglycemia/DM, were particularly vulnerable to renal disease.

**Keywords:** viral hepatitis, hyperglycemia, diabetes mellitus, renal disease, nephropathy

## Introduction

Viral hepatitis (VH) is one of the most serious public health issues worldwide. Millions of people are infected each year, and 1.4 million people die from VH-related complications (such as cirrhosis and liver cancer). According to the World Health Organization (WHO), hepatitis B (HBV) and hepatitis C (HCV) viruses are the main causes of VH infection.<sup>1</sup> It is estimated that 325 million people worldwide have hepatitis B and/or hepatitis C. Among those with VH-related complications, hepatitis B and/or C accounted for 96% of the mortality.<sup>2</sup>

VH infection often has extrahepatic manifestations (XMs), such as hyperglycemia/DM and renal disease.<sup>3</sup> In a meta-analysis by Younossi et al the prevalence of diabetes was reported to be 15% in Western countries;<sup>4</sup> additionally, in a systematic review with meta-analysis they reported that the pooled prevalence of type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) was 19.0% and 9.2%, respectively, in East Asian patients with HCV.<sup>3,5</sup>

The aim of this study was to evaluate the blood glucose level and renal function, determine the prevalence of hyperglycemia/DM and renal disease (nephropathy), and investigate the association between hyperglycemia/DM and renal disease in patients with VH.

## Patients and Methods

### Ethics Statement and Research Data Collection

After obtaining approval from the Human Body Trials/Research Program of the Tri-Service General Hospital (Research IRB review number: TC102-01), volunteers who signed the informed consent were randomly recruited from the Department of Metabolism, Gastroenterology, and Nephrology. A preliminary screening was conducted to identify subjects as healthy controls and patients with VH and classify the disease groups according to the participant's health status, clinical examination results (medical history and physical examination), physiological data, etc.

### Testing Method

**Specimen collection:** Blood samples were collected, after a 10-h overnight fast, in a test tube without any anticoagulant. The samples were allowed to stand at room temperature for 30 minutes and coagulate completely; they were then centrifuged at 1800 g for 10 min. The serum was immediately separated for creatinine (Cr), glucose, glycated hemoglobin (HbA1c), glycated albumin (GA), glutamic oxaloacetic transaminase (GOT),  $\beta_2$  microglobulin, and cystatin C (Cys C) assays. Fresh mid-section urine samples were collected and centrifuged at 1800 g for 5 min for the microalbumin assay.

**Test grouping:** The study participants were divided into the control and VH groups. Patients in the VH group were divided into hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis B+C (HBV-HCV) coinfecting subgroups. Based on the estimated average glucose level calculated using glycated albumin (eAG (GA)), the HBV, HCV, and HBV-HCV subgroups were further divided into eAG(GA)  $\geq 200$  mg/dL and eAG(GA)  $< 200$  mg/dL groups. Nephropathy was defined as the third stage of CKD and an estimated glomerular filtration rate (eGFR)  $< 60$  mL/min in our study.<sup>6,7</sup> Descriptive statistical analysis was performed to compare the differences between the groups.

**Testing equipment:** For the urine/biochemical tests, the "Beckman Coulter" Automated Chemistry Analyzer

AU680 (Beckman Coulter Mishima K.K. Shizuoka, Japan) was used; for HbA1c tests, the "TOSOH" Automated G7 HPLC Glycohemoglobin Analyzer (International Diagnostic Equipment [IDE], Temecula, CA, USA) was used.

**Test reagents:** The following were the test reagents used: Cr, glucose, GOT,  $\beta_2$  microglobulin, urine microalbumin ([MA], Olympus Diagnostic GmbH, Lismeehan, O'Callaghan's Mills, Co. Clare, Ireland), HbA1c (Tosoh Bioscience GmbH, Griesheim, Germany), glycated albumin (Lucica GA-L) (Asahi Kasei Pharma Corporation, Tokyo, Japan), cysteine acid protein C, and "Siemens" N Latex Cystatin C (Siemens Healthcare Diagnostics Product GmbH, Marburg, Germany).

### Formulas

1. Estimated average glucose calculated using glycated albumin:  $eAG(GA) \text{ (mg/dL)} = 4.71GA\% + 73.35^8$
2. Estimated average glucose calculated using HbA1c:  $eAG(HbA1c) \text{ (mg/dL)} = 28.7 \times HbA1c(\%) - 46.7^{9,10}$
3. Estimated glomerular filtration rate calculated using cystatin C (eGFRcys):  $eGFRcys \text{ (mL/min/1.73m}^2\text{)} = 76.7 \times sCystatin C^{-1.19}^{11}$

### Statistical Methods

The narrative statistical results were compared between the groups. The variables were expressed as the mean and standard deviation of concentration and dispersion to describe the characteristics of the participants. Differences between the demographic variables with respect to the dependent variable were assessed for significance using the chi-square test as appropriate. Statistical software SPSS (version 18; SPSS, Chicago, IL, USA) was used analyses. For continuous variables and normally distributed variables, Student's *t*-test or analysis of variance was used to confirm the degree of difference between the groups. Univariate and multivariate logistic regression models (Enter method) were performed to investigate the association between hyperglycemia and nephropathy in both viral hepatitis and non-viral hepatitis subgroups where demographic variables were included as confounders. The logistic regression models were analyzed to determine the possible risk factors for nephropathy, and the significance was set at  $p < 0.05$ .

## Results

### Basic Data

This study included 491 participants (221 males and 270 females). Of these, 244 healthy participants were assigned to the control group and 247 patients with VH were assigned to the VH group. (Tables 1 and 2)

#### Glucose, eAG(GA), and eAG(HbA1c)

The average levels of glucose, eAG(GA), and eAG (HbA1c) were significantly higher in the VH group than in the control group, with a significant difference between the HCV subgroup and control group. (Tables 1 and 2; Figure 1A)

#### HbA1c

The prevalence of HbA1c level > 6.5% in the VH group was 21.5% and 0 in the control group. The prevalence rates of HbA1c > 6.5% in the HBV, HCV, and HBV-HCV subgroups were 20.0%, 29.3%, and 15.9%, respectively.

#### Cr, Cys C, $\beta_2$ -Microglobulin, and Urine Microalbumin

The average levels of Cr, Cys C, and  $\beta_2$ -microglobulin were higher in the VH group than in the control group, with a significant difference between the HCV subgroup and control group. The average level of urine microalbumin was higher in the VH group than in the control group. (Tables 1 and 2; Figure 1B)

**Table 1** Basic Data of the Control and VH Groups (t Test)

Group	All (N = 491)	Control (T) (n = 244)	Viral Hepatitis (V) (n = 247)	P
Male	221	85	136	
Female	270	159	111	
Age, year	50.7 $\pm$ 11.5	50.4 $\pm$ 7.6	50.9 $\pm$ 14.4	
GOT, U/L	27.4 $\pm$ 27.9	18.3 $\pm$ 4.4	34.6 $\pm$ 35.6***	<0.001***
Glucose, mg/dL	101.2 $\pm$ 29.0	94.1 $\pm$ 8.4	108.2 $\pm$ 38.8***	<0.001***
eAG(GA), mg/dL	202.8 $\pm$ 52.3	169.3 $\pm$ 16.1	208.2 $\pm$ 54.1***	<0.001***
eAG(HbA1c), mg/dL	128.5 $\pm$ 35.4	111.9 $\pm$ 7.0	131.6 $\pm$ 37.6***	<0.001***
Cr, mg/dL	0.82 $\pm$ 0.29	0.75 $\pm$ 0.17	0.89 $\pm$ 0.37***	<0.001***
Cys C, mg/L	0.90 $\pm$ 0.30	0.79 $\pm$ 0.14	0.92 $\pm$ 0.32*	=0.019*
$\beta_2$ -MG, ug/dL	2.12 $\pm$ 1.07	1.70 $\pm$ 0.50	2.19 $\pm$ 1.12**	=0.006**
MA, mg/dL (mini, max)	22.3 $\pm$ 105.2 (0, 864)	9.9 $\pm$ 29.9 (0, 127)	24.7 $\pm$ 114.2 (0, 864)	

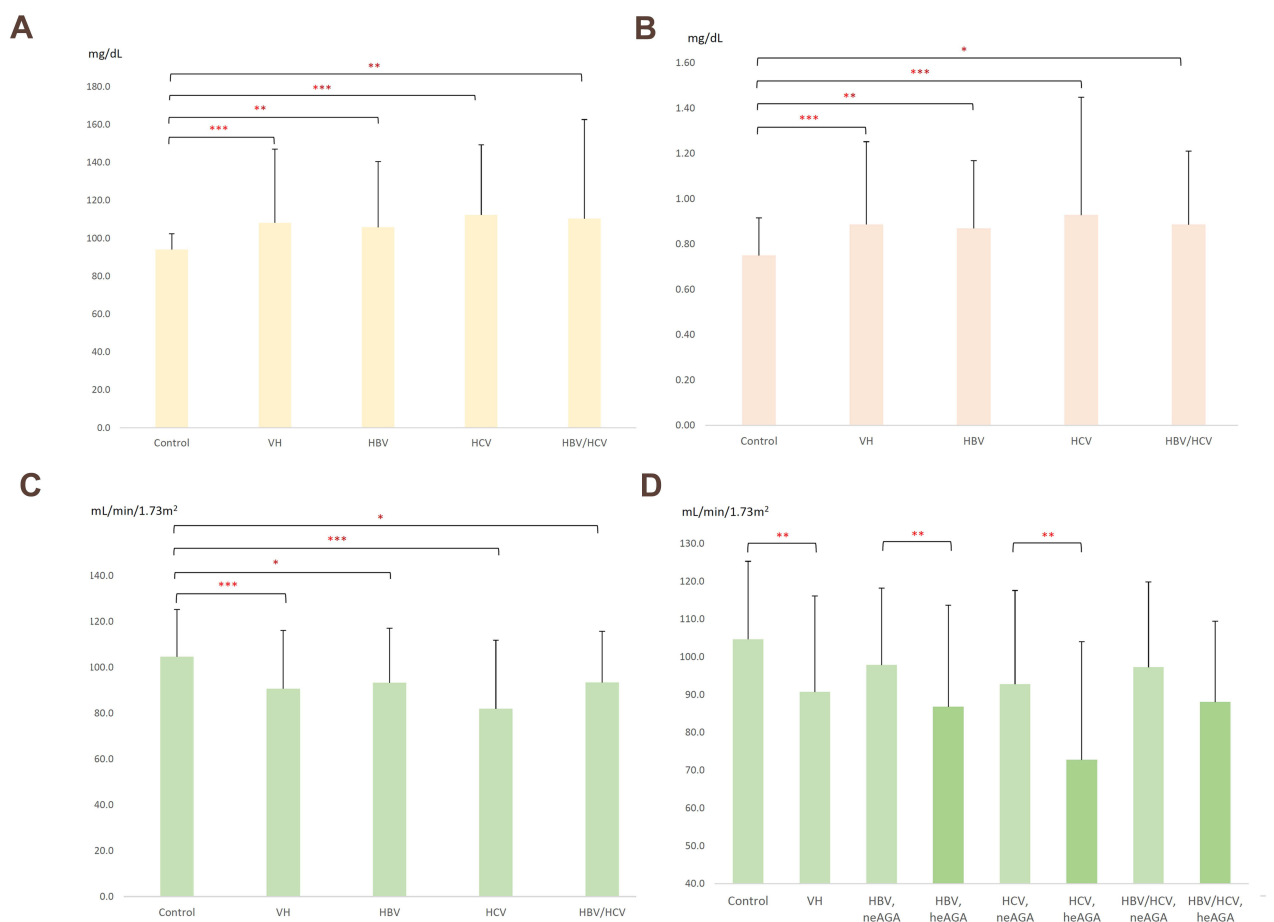
**Notes:** \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001; compare each with the control group.

**Abbreviations:** GOT, glutamic oxaloacetic transaminase; eAG(GA), estimated average glucose of glycated albumin; eAG(HbA1c); HbA1c-derived average glucose; Cr, serum creatinine; Cys C, cystatin C;  $\beta_2$ -MG,  $\beta_2$ -microglobulin; MA, microalbumin; eGFRcys, estimated glomerular filtration rate level with calculated by Cys C.

**Table 2** Basic Data of the Three Subgroups of HBV, HCV, and HBV-HCV (ANOVA)

Group	Control (T) (n = 244)	HBV (B) (n = 145)	HCV (C) (n = 58)	HBV-HCV (O) (n = 44)	p	Scheffe Post Hot
Male	85	84	22	30		
Female	159	61	36	14		
Age, year	50.4 $\pm$ 7.6	49.7 $\pm$ 15.2	53.9 $\pm$ 11.7	50.7 $\pm$ 14.7	0.120	
GOT, U/L	18.3 $\pm$ 4.4	31.1 $\pm$ 35.0	34.7 $\pm$ 31.6	46.0 $\pm$ 27.9	<0.001	T<B, C, O; B<O; C<O
Glucose, mg/dL	94.1 $\pm$ 8.4	105.9 $\pm$ 34.7	112.4 $\pm$ 37.0	110.4 $\pm$ 52.3	<0.001	T<B, C, O
eAG(GA), mg/dL	169.3 $\pm$ 16.1	204.7 $\pm$ 52.0	223.6 $\pm$ 65.2	201.0 $\pm$ 42.3	<0.001	T<B, C
eAG(HbA1c), mg/dL	111.9 $\pm$ 7.0	129.9 $\pm$ 36.3	137.7 $\pm$ 42.9	129.0 $\pm$ 34.1	<0.001	T<B, C
Cr, mg/dL	0.75 $\pm$ 0.17	0.87 $\pm$ 0.30	0.93 $\pm$ 0.52	0.89 $\pm$ 0.32	<0.001	T<B, C, O
Cys C, mg/L	0.79 $\pm$ 0.14	0.89 $\pm$ 0.25	1.05 $\pm$ 0.50	0.89 $\pm$ 0.20	<0.001	T< C; B< C
$\beta_2$ -MG, ug/dL	1.70 $\pm$ 0.50	2.05 $\pm$ 0.94	2.65 $\pm$ 1.55	2.07 $\pm$ 0.83	<0.001	T< C; B< C
MA, mg/dL (mini, max)	9.9 $\pm$ 29.9 (0, 127)	25.8 $\pm$ 120.1 (0, 864)	16.3 $\pm$ 59.6 (0, 430)	32.4 $\pm$ 63.5 (0, 795)	0.659	

**Abbreviations:** GOT, glutamic oxaloacetic transaminase; eAG(GA), estimated average glucose of glycated albumin; eAG(HbA1c); HbA1c-derived average glucose; Cr, serum creatinine; Cys C, cystatin C;  $\beta_2$ -MG,  $\beta_2$ -microglobulin; MA, microalbumin; eGFRcys, estimated glomerular filtration rate level with calculated by Cys C.



**Figure 1** The glucose values (A) creatinine values (B) and eGFRcys (C) of the HBV, HCV, HBV-HCV subgroups and the control group showed significant differences; (D) average level of eGFRcys was different between the high eAG(GA) and low eAG(GA) groups of patients with viral hepatitis. (\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ ).

### eGFRcys

The average level of eGFRcys in the VH group was lower than that in the control group, with significant differences between the HCV subgroup and the control group. The prevalence rates of eGFRcys  $<60$  were 10.1% and 22.4% in the VH group and HCV subgroup, respectively, and 0.4% in the control group. (Table 3; Figure 1C)

The chi-square test showed that among 247 (50.3%) patients with VH, 26 had nephropathy (eGFRcys  $<60$ ). The proportion of patients with nephropathy in the VH group was 10.1% (25 patients), which was higher than the proportion of patients with nephropathy in the non-VH group at 0.4% (1 patient); the difference was statistically significant (\*\*\* $P < 0.001$ ). Among the 26 patients with nephropathy (eGFRcys  $<60$ ), the proportion of patients with VH with combined nephropathy and hyperglycemia was 15.7% (18 patients), while the proportion in the non-VH group was 2.1%

(8 patients); the difference was statistically significant (\*\*\* $P < 0.001$ ). The prevalence rates of eGFRcys  $<60$  mL/min/1.73m<sup>2</sup> in the HBV, HCV, and HBV-HCV subgroups were 7.6% (11 patients), 22.4% (13 patients), and 2.3% (1 patient), respectively. (Table 3).

### Glucose, eAG(HbA1c), Cr, Cys C, and $\beta_2$ -Microglobulin in the VH Groups with eAG(GA) $\geq 200$ mg/dL and eAG(GA) $< 200$ mg/dL

The average glucose, eAG(HbA1c), Cr, Cys C, and  $\beta_2$ -microglobulin levels were higher in the VH with eAG(GA)  $\geq 200$  mg/dL subgroup than in the VH with eAG(GA)  $< 200$  mg/dL subgroup. More patients with HBV, HCV, and HBV-HCV with eAG(GA)  $\geq 200$  mg/dL were seen compared with those with eAG(GA)  $< 200$  mg/dL, and there were significant differences between the HBV and HCV subgroups and the control group. Marked differences also existed in this regard between the HCV subgroup and control group. (Table 4)

**Table 3** The Compare of Prevalence Rates of eGFRcys <60 mL/Min/1.73m<sup>2</sup> in the Control Group, VH Group, and Subgroups (Chi-Square Test)

Group	eGFRcys			X <sup>2</sup>
	Mean ± SD	≥ 60; N (%)	< 60; N (%)	
Control	104.7 ± 20.6	243 (99.6)	1 (0.4)	<0.001***
Viral Hepatitis	90.7 ± 25.4	222 (89.9)	25 (10.1)	<0.001***
HBV	93.3 ± 23.8	134 (92.4)	11 (7.6)	
HCV	82.0 ± 29.9	45 (77.6)	13 (22.4)	
HBV-HCV	93.5 ± 22.3	43 (97.7)	1 (2.3)	
HbA1c				<0.001***
≤ 6.5%	97.9 ± 22.4	368 (97.9)	8 (2.1)	
> 6.5%	83.4 ± 24.1	97 (84.3)	18 (15.7)	

**Notes:** \*\*\*P <0.001; compare each with the control group.

**Abbreviations:** HBV, hepatitis B virus; HCV, hepatitis C virus; HBV-HCV, hepatitis B+C co-infected; HbA1c, glycated hemoglobin.

### eGFRcys in the VH with eAG(GA) ≥200 mg/dL and VH with eAG(GA) <200 mg/dL Subgroups

The average eGFRcys level in the VH with eAG(GA) ≥200 mg/dL subgroup was significantly lower than that in the VH with eAG(GA) <200 mg/dL subgroup. The average level of eGFRcys in patients with HBV, HCV, and HBV-HCV with eAG(GA) ≥200 mg/dL was lower than that in patients with eAG(GA) <200 mg/dL, with significant differences between the HBV and HCV subgroups and the control group. (Table 4; Figure 1D)

## Discussion

VH reduces insulin sensitivity and increases insulin resistance, which is an important factor in the development of

hyperglycemia/DM secondary to chronic liver disease.<sup>14,15,16</sup> Approximately 80% of the patients with chronic liver diseases develop glucose intolerance, and 20–30% eventually develop frank DM.<sup>15,17,18</sup> In one study, patients with hepatitis B with liver cirrhosis but no symptoms of DM showed impaired glucose tolerance (incidence rate, 20.53%), and patients with severe liver cirrhosis showed DM (incidence rate, 24.11%).<sup>19</sup> Chronic hepatitis C infection is also associated with DM.<sup>20</sup> The prevalence of CKD was reported to be higher in patients infected with HBV than in non-infected individuals.<sup>21</sup>

HbA1c, expressed as a percentage, is an important indicator of blood glucose control in patients with DM. It is widely used as a reference for evaluating the efficacy of medication and drug titration in the treatment of DM. Linear regression analysis of HbA1c and eAG(HbA1c) values showed a significant correlation; therefore, HbA1c levels can be expressed as eAG(HbA1c) for most patients with DM using the formula: eAG(HbA1c) (mg/dL) = 28.7 × HbA1c - 46.7.<sup>9,10</sup> GA can more accurately reflect the recent blood sugar control in patients with diabetes-associated end-stage renal disease (ESRD) than HbA1c. The correlation equation used to convert GA into eAG(GA) concentration, ie, eAG(GA) (mg/dL) = 4.71×GA%+73.35, provides an easy-to-understand blood glucose level for the patients' reference.<sup>8</sup> Therefore, we used the average glucose, HbA1c, eAG(GA), and eAG(HbA1c) levels to evaluate the glucose status of patients in our study.

Testing for proteinuria is useful in the diagnosis of CKD. The National Kidney Foundation's "K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease:

**Table 4** The Average Levels of eGFRcys, eAG(GA), Glucose, eAG(HbA1c), Cr, Cys C, and β<sub>2</sub>-Microglobulin in the High eAGe(GA) and Low eAG(GA) Groups of Patients with Viral Hepatitis (ANOVA)

Group	eGFRcys (mL/min/ 1.73 m <sup>2</sup> )	Glucose (mg/dL)	eAG(GA) (mg/dL)	eAG(HbA1c) (mg/dL)	Cr (mg/dL)	Cys (mg/L)	β <sub>2</sub> MG (ug/dL)
Control	104.7±20.6	94.1±8.4	169.3±16.1	111.9±7.0	0.75±0.17	0.79±0.14	1.70±0.50
VH, neAG(GA)	96.8±21.5	97.0±18.8	176.5±14.3	117.7±18.0	0.83±0.20	0.86±0.21	1.88±0.75
VH, heAG(GA)	83.1±27.8***	121.7±51.1***	249.0±59.0***	148.4±47.1***	0.95±0.49*	1.01±0.41**	2.58±1.36***
HBV, neAG(GA)	97.9±20.3	97.3±19.0	177.0±14.3	119.4±17.1	0.83±0.20	0.85±0.18	1.82±0.66
HBV, heAG(GA)	86.8±26.8**	117.0±45.8***	243.9±60.4***	143.6±48.4***	0.92±0.39	0.95±0.32	2.35±1.16**
HCV, neAG(GA)	92.8±24.8	95.0±12.0	178.5±16.0	112.8±19.5	0.79±0.21	0.92±0.32	2.12±1.11
HCV, heAG(GA)	72.8±31.2**	127.5±44.4***	265.2±66.0***	159.4±46.0***	1.05±0.67***	1.18±0.62**	3.11±1.74***
HBV-HCV, neAG(GA)	97.3±22.6	98.2±20.2	172.9±12.5	117.2±18.9	0.89±0.16	0.85±0.17	1.82±0.55
HBV-HCV, heAG(GA)	88.1±21.4	128.1±75.9***	240.8±37.2***	146.0±43.6**	0.89±0.48	0.94±0.24	2.43±1.02

**Notes:** \*P <0.05, \*\*P <0.01, \*\*\*P <0.001; Compare each with the control group.

**Abbreviations:** eAG(GA), estimated average glucose of glycated albumin; neAG(GA), eAG(GA) <200 mg/dL group; heAG(GA), eAG(GA) ≥200 mg/dL group.



Evaluation, Classification, and Stratification” recommend using eGFR for the assessment of kidney function.<sup>22</sup> eGFR and urine microalbumin (MA) are also validated as useful tools for the evaluation of renal insufficiency in patients with peripheral arterial disease.<sup>23</sup> Five-stage eGFR is considered the best indicator of renal function and is widely used in screening patients with CKD.<sup>24</sup> Usually, the eGFR is based on the patient’s serum creatinine (Cr) level.<sup>25,26</sup> However, eGFRcr obtained using Cr levels might underestimate the true value of eGFR in patients with an eGFR of 60–80 mL/min/1.73m<sup>2</sup><sup>27</sup> and 45–60 mL/min/1.73m<sup>2</sup>.<sup>28</sup> Studies have found that the production of Cys C is more stable than that of Cr.<sup>6,29</sup> Cys C can be used to estimate eGFRcys as an alternative to eGFRcr as it shows lower variability<sup>11</sup> and better correlation with the morbidity and mortality rates for different population subsets (including those with CKD).<sup>28</sup> Hence, the Kidney Disease: Improving Global Outcomes (KDIGO) recommends that regardless of renal damage and/or renal insufficiency, eGFRcys should be measured when the eGFRcr is between 45 and 60 mL/min/1.73m<sup>2</sup> to reduce the risk of underestimation.<sup>6</sup> Therefore, we used urine microalbumin, serum Cr, and eGFRcys levels to evaluate the renal function in our study.

In our study, 21.46% of the patients with VH were at a risk of developing hyperglycemia and 10.12% were at a risk of developing of CKD with hyperglycemia. Our study revealed a significant association between XMs (such as DM and nephropathy) and chronic viral liver disease. Type 2 DM and CKD have a considerable impact on follow-up medical care, labor, and economy and are associated with poor prognosis and management challenges; hence, disease prevention, screening, and clinical management strategies are urgently required.<sup>12,13</sup>

Our results showed that the average levels of glucose, eAG(GA), and eAG(HbA1c) were significantly higher in the VH group than in the control group, indicating that VH is closely associated with the occurrence of type 2 DM.

We also found that the average levels of Cr, Cys C,  $\beta_2$ -microglobulin, and microalbumin were significantly higher in the VH group, especially in the HCV subgroup than in the control group. The average levels of eGFRcys were significantly higher in the control group than in the three subgroups, indicating that VH is closely related to the occurrence of CKD.

The Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2020 states that in a patient with classic symptoms, the plasma glucose level is adequate to diagnose DM (symptoms of hyperglycemia or hyperglycemic crisis plus a random plasma glucose level of  $\geq 200$  mg/dL).

**Table 5** The Risk of Renal Impairment in the Control Group, VH Group, and Combine Hyperglycemia with VH Subgroups (Logistic Regression Models)

Group	OR	P	95% C.I. for OR	
			Lower	Upper
Viral Hepatitis				
Control	ref			
VH	1.604	0.001***	1.20	2.14
Hyperglycemia	1.832	0.010**	1.16	2.90
Hyperglycemia with VH	36.98	0.001**	4.44	307.72

**Notes:** \*\*P <0.01, \*\*\*P <0.001; compare each with the control group.

**Abbreviation:** VH, viral hepatitis.

Considering that the GA can accurately reflect the recent blood sugar levels and high blood glucose values after meals (post cibum), it meets the requirements of the American Diabetes Association (ADA) for the diagnosis of DM, and the reference level of eAG(GA) is 200 mg/dL, which we used in our study.<sup>30</sup>

We found that the average levels of glucose, eAG (HbA1c), Cr, Cys C, and  $\beta_2$ -microglobulin were statistically and significantly higher in the VH patients with eAG(GA)  $\geq 200$  mg/dL than in the VH patients with eAG(GA) <200mg/dL. eGFRcys is commonly used in the clinical evaluation of CKD. The average level of eGFRcys was significantly lower in the patients with VH with eAG(GA)  $\geq 200$  mg/dL than in those with eAG(GA) <200 mg/dL.

An analysis using the logistic regression model found that the risk of renal impairment in the viral hepatitis group was 1.604-fold that of the non-viral hepatitis group. The risk of renal impairment in the hyperglycemia group was 1.832-fold that of the non-hyperglycemia group. The risk of renal impairment in patients with VH and hyperglycemia was 36.978-fold that of patients with no VH and hyperglycemia. The results indicate that VH is closely related to the occurrence of CKD, and hyperglycemia/DM increases the risk of nephropathy in patients with VH. (Table 5).

The possible mechanism could be reduced insulin sensitivity caused by VH, and increased insulin resistance, leading to the development of hyperglycemia/DM,<sup>15,16</sup> which can lead to renal atherosclerosis and chronic inflammation.<sup>31–33</sup> However, further research is necessary to confirm the mechanism.

The KDIGO guidelines clearly state that patients with kidney disease who are infected with HCV can be administered anti-viral drugs, and this will have a significant impact on follow-up care and long-term survival.<sup>6</sup> Studies have also reported that anti-HCV drugs, such as telaprevir (TVR),

peginterferon (PEG IFN), and ribavirin (RBV), can cause a significant increase in serum Cr and cys C and decrease in eGFRcr to  $< 60$  mL/min/1.73m<sup>2</sup>, especially at high doses in case of TVR.<sup>34,35</sup> All our patients with VH had been routinely followed up for at least 10 years; initially, none of them had hyperglycemia/DM and nephropathy, while some developed these conditions later, especially those VH and hyperglycemia/DM. Moreover, none of our patients used anti-viral drugs or other drugs that could affect renal function.

## Conclusion

In conclusion, our study used many parameters to evaluate the glucose level and renal function in patients with VH and found that hyperglycemia/DM and renal disease (nephropathy) are closely associated with VH, especially in those with HCV infection. Patients with concurrent VH and hyperglycemia/DM, especially those with HCV infection, are particularly at risk of developing nephropathy. Patients with VH, especially those with HCV infection, should be closely followed up to evaluate the blood glucose and renal function for the early diagnosis and management of DM and nephropathy.

## Abbreviations

DM, diabetes mellitus; VH, viral hepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; HBV-HCV, hepatitis B+C co-infected; GOT, glutamic oxaloacetic transaminase; HbA1c, glycated hemoglobin; GA, glycated albumin; eAG(GA), estimated average glucose calculated by glycated albumin; eAG(HbA1c), estimated average glucose calculated by HbA1c; CKD, chronic kidney disease; ESRD, end-stage renal disease; Cr, creatinine; Cys C, cystatin C; eGFRcys, estimated glomerular filtration rate calculated by cystatin C; MA, microalbumin; XM, extrahepatic manifestations; HD, hepatogenous diabetes; DN, diabetic nephropathy; WHO, World Health Organization.

## Ethics and Informed Consent

The study was approved by the Tri-Service General Hospital Institutional Review Board (TSGHIRB No.:TC102-01) and conducted in accordance with the principles stated in the Declaration of Helsinki. All participants in the research were given the written informed consent before the health examination to authorize the data analysis. Personal identification data was removed in the Taichung Armed Force General Hospital, so the participants remained anonymous during the whole research process. All or part of the data used in this research were authorized by and received from the

Taichung Armed Force General Hospital. All data accessed complied with relevant data protection and privacy regulations. The detail of the study population and data collection were described and reported in materials and methods.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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