ISSN: 2588-4115; Infection Epidemiology and Microbiology. 2024;10(4):297-308 10.52547/iem.10.4.297

Associations of Cardiovascular Diseases with Hepatitis B and D and Metabolic Syndrome in Mashhad, Iran: A Cross-Sectional Study

ARTICLE INFO

Article Type
Original Article

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How to cite this article
Dehghani T., Najafi-Deloui M., Aryan E., Meshkat Z., Hooshyar-Chechaklou A., Tavalaie Sh., Haghighatdoost N., Meshkat M., Khoshakhlagh M., Abolbashari S., Gholoobi A. Associations of Cardiovascular Diseases with Hepatitis B and D and Metabolic Syndrome in Mashhad, Iran: A Cross-Sectional Study. Infection Epidemiology and Microbiology. 2024;10(4): 297-308.

Article History
Received: August 07, 2023
Accepted: November 24, 2024
Published: December 20, 2024

ABSTRACT

Background: Viral infections may play a significant role in the development of heart failure, especially in people with related cardiac conditions such as myocarditis. Hepatitis B and D viruses (HBV-HDV) are potentially fatal liver infections. This study examined the influence of metabolic syndrome and its associated disorders.
Materials & Methods: This cross-sectional study investigated hepatitis D antibody and hepatitis B surface antigen (HBsAg) in239 people aged 35 to 65 years in Mashhad, Khorasan Razavi Province, Iran in 2018-2019. There were two study groups: those with cardiovascular diseases (CVD) and healthy individuals. Serum samples of all subjects in both groups were examined using enzyme-linked immunosorbent assay (ELISA).
Findings: HDV infection was detected in none of the study groups. Only one patient (0.8%) in the case group tested positive for HBsAg. The average LDL (low-density lipoprotein) (p= .8) and cholesterol (p= .3) levels in terms of lipid profiles were similar in both groups. Although the mean high-density lipoprotein (HDL) level in the patient group was lower, the mean triglyceride level in this group was higher than in the control group. Fasting blood sugar (FBS) (p= .009) and aspartate aminotransferase (AST) levels were significantly higher in CVD patients, while 59.3% of them exhibited metabolic syndrome.
Conclusion: This study results demonstrate no connection between HBV/HDV infection and cardiovascular diseases. The findings confirm that metabolic syndrome and hyperglycemia are underlying factors in cardiovascular diseases. Changes in HDL and triglyceride levels could impact cardiovascular diseases more than other lipids.

Keywords: Cardiovascular diseases, Hepatitis B, Hepatitis D, Hepatitis B surface antigens, Metabolic syndromes

CITATION LINKS

[1] Roth GA, et al. Global burden of... [2] Mensah GA, Roth GA, Fuster V. The global... [3] Kaptoge S, et al. World Health... [4] Saki N, Prevalence of cardiovascular... [5] Cowan LT, et al. Triggering... [6] Fahed G, et al. Metabolic syndrome... [7] Kahn R,The metabolic syndrome... [8] Bruno G, et al. Metabolic syndrome... [9] Resnick HE, et al. Insulin... [10] Simanek AM, Dowd JB, Aiello AE. Persistent... [11] Sorriento D, Iaccarino G. Inflammation... [12] Khademi F, Bacterial infections... [13] Musher DM, The association... [14] Monsey L, The association of... [15] Xue L, Clinical study of... [16] Yombi JC, Staphylococcal versus... [17] Hanson PJ, et al. Advanced detection... [18] Kong KA, Association between... [19] Duan J, Deleterious effects of viral... [20] Schultheiss HP, Cardiovascular consequences of... [21] Leone O, The spectrum of myocarditis... [22] Warren-Gash C, et al. Influenza infection and... [23] Kwong JC, et al. Acute myocardial... [24] Gopal R, Immune mechanisms in cardiovascular... [25] Xie Y, Long-term cardiovascular outcomes of... [26] Feinstein MJ. HIV and cardiovascular... [27] Pyarali F, et al. Cardiovascular disease and... [28] Nikitskaya E, et al. Cytomegalovirus-productive... [29] Jeong SJ, et al. Anti-cytomegalovirus... [30] Adinolfi LE, Rinaldi L, Nevola R. Chronic hepatitis C... [31] Babiker A, Risk of cardiovascular... [32] Salehi-Vaziri M, Hepatitis B virus infection... [33] Shakeri MT, et al. The prevalence of hepatitis B... [34] Huang PL. A comprehensive definition for... [35] Ambrose JA, Barua RS. The pathophysiology of... [36] Yano Y, et al. Association of blood... [37] Wu CY, High blood pressure and... [38] Tune JD, Cardiovascular consequences of... [39] Zhao X, Wang D, Qin L. Lipid profile... [40] Bertoluci MC, Rocha VZ. Cardiovascular risk... [41] Sung J, Hepatitis B virus seropositivity... [42] Wang CH, Chronic hepatitis B infection... [43] Wu VC, et al. Comparison of... [44] Chun HS, et al. Prevalence and risk.. [45] Demir M, Demir C. Effect of hepatitis B virus...

Introduction

Cardiovascular diseases (CVDs), including ischemic heart disease, stroke, heart failure, peripheral arterial disease, and various cardiac and vascular disorders, are the leading cause of death worldwide. Poor quality of life is a major contributing factor [1, 2]. According to estimates, 17.8 million people have died because of CVDs in 2017, and those under 70 years of age account for one-third of these deaths (1)[3]. Cardiovascular diseases account for 46% of all deaths and 20-23% of all disease burdens in Iran [4]. Numerous chronic risk factors for cardiovascular diseases (CVD) have been identified in various studies, including elevated blood pressure, raised serum cholesterol levels, and smoking. According to some studies, acute infections are linked to CVD events such as acute coronary heart disease (CHD) and ischemic stroke [5].

Metabolic syndrome (MetS) is a group of metabolic disorders, which are caused by various genetic and acquired factors and characterized by insulin resistance, atherogenic dyslipidemia, central obesity, and hypertension [6] Numerous studies have demonstrated that patients diagnosed with metabolic syndrome are more likely to develop cardiovascular diseases. However, there are significant exceptions to the extensive evidence highlighting the negative impact of metabolic syndrome Metabolic syndrome (MetS) is a group of metabolic disorders, which are caused by various genetic and acquired factors and characterized by insulin resistance, atherogenic dyslipidemia, central obesity, and hypertension [6] Numerous studies have demonstrated that patients diagnosed with metabolic syndrome are more likely to develop cardiovascular diseases. However, there are significant exceptions to the extensive evidence highlighting the negative impact of metabolic syndrome [7–9].

Mechanisms of pro-inflammatory responses associated with pathogens may play a role in human heart diseases [10]. Research has demonstrated that inflammation serves as a significant risk factor for cardiovascular events and plays a role in the incidence of both cardiac and vascular diseases. This inflammatory process could be targeted through both specific and non-specific therapeutic approaches [11].

Several lines of evidence suggest that bacterial pathogens are associated with the pathogenesis of CVD besides various risk factors [12]. The absolute risk of cardiovascular events following instances of community-acquired pneumonia has been investigated in several studies [5]. Pneumococcal pneumonia patients are at high risk of concomitant acute cardiac events, such as heart attack, severe arrhythmia, or new/worsening congestive heart failure. This combination dramatically raises the risk of pneumonia-related death [13]. Chlamydia pneumoniae is an obligate intracellular bacterium that infects humans and mainly targets endothelial cells, it is one of the pathogens consistently linked to CVD initiation and development [14,15]. Streptococcus and Staphylococcus account for 80 to 90% of infectious endocarditis cases, in which an organism is identified [16].

Many of the clinical indications of heart failure may be traced back to a viral infection as a primary cause, especially in people with other cardiovascular disorders such as myocarditis and dilated cardiomyopathy (DCM) [17]. Among viral infections, acute viral pneumonia could cause heart failure, acute myocardial infarction (AMI), arrhythmia, and myocarditis,[14,15]. So far, several cardiotropic viruses have been linked to myocarditis and inflammatory cardiomyopathy. Coxsackievirus B3, parvovirus B19, influenza (A, B), human herpesvirus 6 (HHV6), human immunodeficiency virus (HIV), hepatitis C virus (HCV), human cytomegalovirus (CMV), and

Epstein–Barr virus (EBV) are the most commonly detected viruses [20, 21]. The incidence rate of AMI is consistently higher in patients with influenza infections and influenza-like illnesses [22–24]. Data indicate that individuals who contract COVID-19 are more likely to develop cardiovascular diseases (CVD) after the initial 30-day period. Even among individuals who are not hospitalized during the acute phase of the illness, the same risks and associated costs persist and gradually increase [25]. The risk of CVD, from myocardial infarction to heart failure, is elevated among individuals who are HIV-positive [26, 27]. According to several studies, CMV may play a role in the evolution of atherosclerosis [28, 29]. HCV infection, especially chronic HCV infection, increases the risk of CVD in the subclinical stage. Most studies examining the impact of HCV treatment on CVD morbidity and mortality have found that patients are successfully treated and achieve persistent viral suppression with improvements in subclinical and clinical CVD endpoints [30, 31]. The connection between cardiovascular diseases and various forms of hepatitis remains a subject of debate. The prevalence of HBV infection in Iran before and after 2010 was 2.9 and 1.3%, respectively [32]. In the population of Mashhad, the prevalence of HBV infection has been recorded at 0.53 [33], and due to the lack of sufficient research in this field, this study examined the association between hepatitis B and D and cardiovascular diseases in this region. As part of the primary prevention measures for cardiovascular diseases, it is crucial to identify certain and possible risk factors that contribute to the development of CVD.

Objectives: Several risk factors are associated with cardiovascular diseases, including Helicobacter pylori, Chlamydia pneumoniae, Herpes simplex, and hepatitis C viruses. It is crucial to investigate the potential role of hepatitis B and D viruses in the development of these diseases. This study aims to evaluate the sero-epidemiology of hepatitis B and D viruses in patients diagnosed with cardiovascular diseases.

Materials and Methods

Study population: This cross-sectional study was conducted to investigate the presence of hepatitis B surface antigen (HBsAg) and anti-HDV antibody in serum samples of 239 individuals aged 35 to 65 years in Ghaem Hospital, Mashhad, Khorasan Razavi Province, Iran in 2018-2019. A total of 118 cardiovascular patients with heart diseases (including heart attacks, strokes, or stable angina) and 121 healthy participants without any signs of heart disease took part in the study. Cardiovascular disease of the patients was assessed primarily by filling out a questionnaire, and if the condition was present in the patient's history, it was confirmed by a cardiologist. According to the cardiologist's opinion, paraclinical procedures such as echocardiography or electrocardiography were performed if necessary to ensure the patient's condition. Inclusion criteria were as follows: individuals aged between 35 and 71 years of both genders, who lived in Mashhad city and were willing to provide their consent for participation in this research study. Exclusion criteria included: individuals with a documented history of cardiovascular diseases prior to enrollment in the study. Participants were chosen randomly, and all participants entered the study with full consent. A questionnaire was used to gather demographic and biometric data, which were then compared between the two groups.

ELISA: Serum samples of all subjects in the patient and control groups were examined for the presence of hepatitis D antibody and hepatitis B surface antigen (HBsAg) by enzyme-linked immunosorbent assay (ELISA). For this purpose, the ELISA

commercial kit (Diapro, Italy) was used, and the tests were performed according to the kit instructions. Following the manufacturer's recommendations, the cut-off value was calculated after reading the plates.

Diagnosis of Metabolic syndrome: To be classified as having metabolic syndrome [34], at least three of the following five criteria should be met:

1.Elevated fasting blood sugar (FBS): 100 mg/dl or above

2.Elevated blood pressure: 130/85 mmHg or above

3.Decreased high-density lipoprotein (HDL) levels: less than 40 mg/dl for men and less than 50 mg/dl for women

4.Elevated triglyceride levels: 150 mg/dl or above

5.Excessive waist circumference: over 102 cm for men and 89 cm for women

Statistical analysis: Data were entered into SPSS software Version 18, and the significance level of the tests was considered to be less than 0.05. The normal distribution of the data was measured using Kolmogorov-Smirnov test. Chi-square test was performed to investigate the connection between the prevalence of anti-HDV antibody and HBsAg with qualitative characteristics (education, occupation, gender, and smoking). Fisher's exact test was used in cases where more than 20% of the expected frequencies were less than 5 (Cochran). Quantitative data mean and standard deviation (SD) were calculated, and t-test was used to compare mean values between groups.

Findings

A total of 239 individuals in the age range of 35 to 65 were examined in this study. The presence or absence of HBsAg served as a gauge for the participants' level of contamination. Only one (0.8%) patient in the case group tested positive for HBsAg,

Table 1) Demographic data

Variable		Study Group		Control		*P*-Value
		Numbers	Percentage %	Numbers	Percentage %	
Sex	Male	56	47.5	46	38	.14*
	Female	62	52.6	75	62	
Occupation	Employed	37	31.4	34	28.1	.62*
	Unemployed	63	53.4	63	52.1	
	Retired	18	15.3	24	19.8	
Education	Uneducated	21	17.8	13	10.7	.018**
	Primary school	61	51.7	44	36.4	
	High School	27	22.9	45	37.2	
	Associate degree	5	4.2	7	5.8	
	Bachelor's degree	3	2.5	9	7.4	
	Master and above	1	0.8	3	2.5	
Marital status	Married	113	95.8	106	87.6	.092**
	Unmarried	4	3.4	11	9.1	
	Divorced	1	0.8	4	3.3	
Smoking	Smoker	31	26.3	18	14.9	.011*
	Nonsmoker	65	55.1	89	73.6	
	Ex-smokers	22	18.6	14	11.6	

*: Chi-square test, **: Fisher's exact test

and the rest tested negative. The statistical analysis results revealed that this variable was not significantly different between the two groups. (p= .494). The ELISA test results showed no hepatitis D virus infection in the case and control groups.

The demographic data analysis results showed no statistically significant difference in terms of gender, occupation, or marital status between the two groups. However, there was a notable difference in terms of education level and smoking status between the two groups. In the case group, 55.1% of the participants were nonsmokers, as opposed to 73.6% in the control group (p= .011) (Table 1).

The average age of the participants in the case and control groups was 52 ± 5.3 and 50.67 ± 6.89 years, respectively. This alteration was not statistically significant (independent t-test, p= .095). The average height, weight, body mass index (BMI), waist circumference, and hip circumference of the participants in each group were examined. Little difference was observed between the two groups. A BMI value equal to or greater than 25 is classified as "overweight," while a BMI value equal to or greater than 30 is categorized as "obesity." Overweight was observed in 22.3 and 20.3% of the participants in the control and CVD groups, respectively. However, the average waist circumference was significantly

Table 2) Age and biometric information average

Variable	Study Group	Control	P-Value
Age	52 ± 5.3	50.67 ± 6.89	.095*
Height (m)	1.59 ± 0.9	1.59 ± 0.8	.89*
Weight (kg)	73.98 ± 12.24	71.83 ± 11.37	.61*
BMI	29.19 ± 4.67	28.41 ± 4.74	.20*
Hip (cm)	104.55 ± 10.38	102.63 ± 10.48	.157*
Waist (cm)	99.51 ± 10.93	95.38 ± 12.27	.007*

*: Independent sample T-test

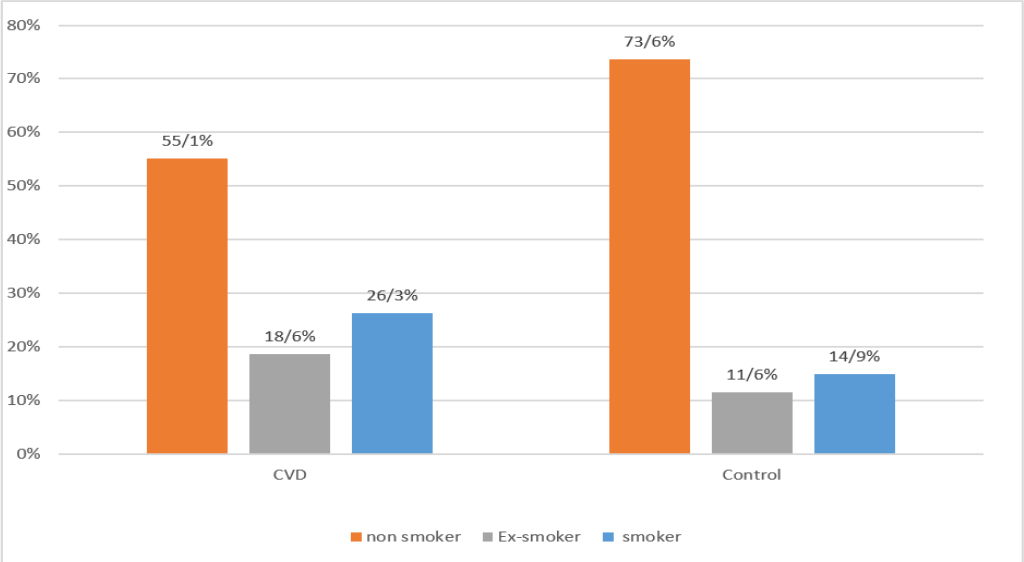

Figure 1) Comparison of smoking status between the two study groups. The proportion of non-smokers was higher in the control group than in the CVD group (p= .011).

higher in the CVD group than in the control group (Table 2). There was no significant difference in average systolic and diastolic blood pressure and number of pulses per minute between the case and control groups. The average low-density lipoprotein (LDL) and cholesterol levels in the case group were not entirely different from those in the control group. The average high-density lipoprotein (HDL) level in the case group was much lower than in the control group. In contrast, the average triglyceride level in

Table 3) Biochemical indices and blood pressure

Variable		Study Group	Control	*P*-Value
Systolic pressure		132.17 ± 21.53	128.33 ± 23.28	.187*
Diastolic pressure		82.94 ± 11.61	83.05 ± 11.82	.943*
Heart rate		71.80 ± 9.63	70.17 ± 10.43	.213*
Cholesterol		201.39 ± 45.92	195.55 ± 41.76	.305*
LDL		121.98 ± 36.56	123.04 ± 37.86	.826*
HDL		39.54 ± 8.54	42.13 ± 8.73	.022*
Triglycerides		179.14 ±123.43	144.28 ± 101.65	.018*
FBS		123.01 ± 66.46	101.69 ± 57.73	.009*
ALT		15.74 ± 7.73	15.68 ± 6.18	.963*
AST		22.86 ± 10.53	19.08 ± 5.85	.012*
Metabolic syndrome	Yes	70 (59.3 %)	49 (40.5 %)	.004**
	No	48 (40.7 %)	72 (59.5 %)	

*: Independent sample T-test, **:Chi-square test. Heart rate is considered as the number of pulses per minute. LDL: low-density lipoprotein, FBS: fasting blood sugar, AST: aspartate aminotransferase, ALT: alanine amino-transferase

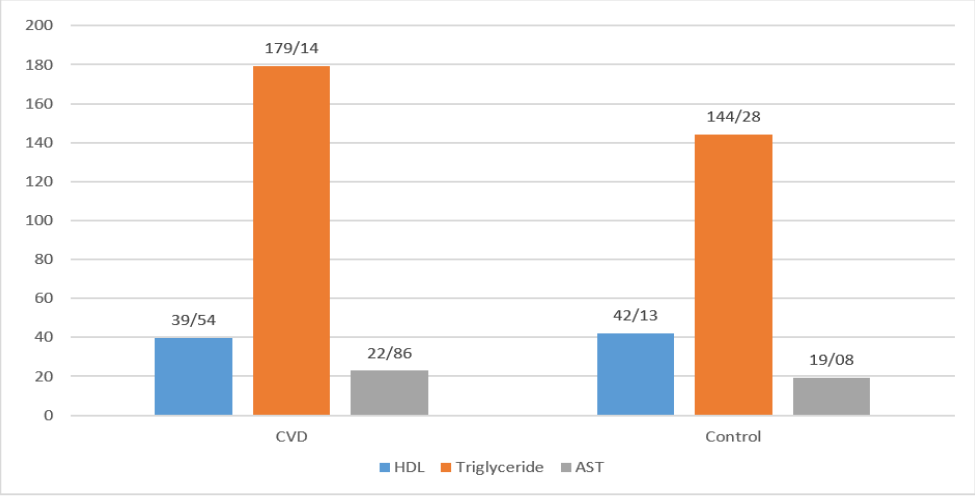

Figure 2) Average levels of triglyceride, HDL, and AST. Triglyceride (p= .018), HDL (p= .022), and AST (p= .012) in the CVD group were significantly higher.

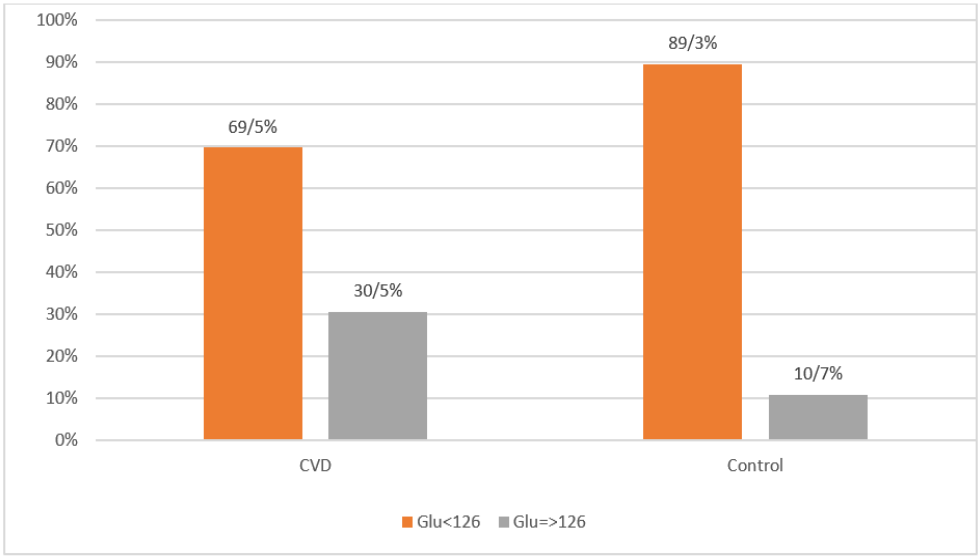

Figure 3) Blood glucose level in the two study groups with a cut-off point of 126 mg/dl, which was significantly higher in the CVD group (p= .009)

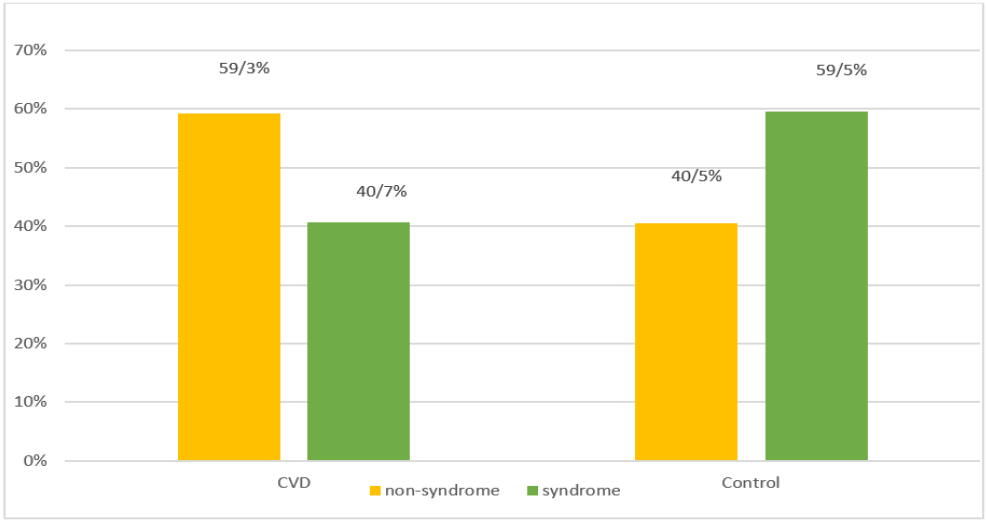

Figure 4) Metabolic syndrome in the two study groups, which was significantly higher in the CVD group (p= .004)

the case group was significantly higher than in the control group. The blood glucose level in the case group was considerably higher than in the control group. The statistical analysis results showed that the average aspartate aminotransferase (AST) level in the case group was significantly higher than in the control group. However, the average alanine aminotransferase (ALT) level was not entirely different between the two study groups. The percentage of people with metabolic syndrome was significantly higher in the case group than in the control group (Table 3).

Discussion

In Mashhad, the overall prevalence of HBsAg among cardiovascular patients aged 35 to 65 years was 0.8%, and only one out of 118 participants in the CVD

group carried this antigen. Neither the case group nor the control group had hepatitis D virus infection. There was no statistically significant difference in age, gender, occupation, or marital status between the case and control groups. The education level of the case group was much lower than that of the control group. Smoking causes inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol. However, the particular toxic components of cigarette smoke and the mechanisms behind cardiovascular dysfunction caused by cigarette smoking remain largely unclear. Recent experimental and clinical findings support the idea that exposure to cigarette smoke increases oxidative stress, which may act as a possible trigger for cardiovascular failure [35]. In this study, the two groups had considerably different smoking habits. In the scientific literature directly related to the prevalence of cardiovascular diseases, other established criteria for evaluating overweight and obesity include body mass index, waist circumference, and hip size. It was noted that there was no discernible variation between the two study groups in terms of height, weight, body mass index, or hip circumference. However, the average waist size in the case group was 99.51 ± 10.93 cm, which was substantially different from that (95.38 ± 12.27 cm) in the control group.

Studies have shown that those with hypertension are more likely to experience a subsequent cardiovascular event than those with normal blood pressure [36, 37]. But in this investigation, there was no discernible difference in the average systolic and diastolic blood pressure or heart rate between the case and control groups. Metabolic syndrome is characterized by the coexistence of obesity-associated cardiovascular risk factors, including abdominal obesity, impaired glucose tolerance, hypertriglyceridemia, reduced HDL cholesterol, and hypertension [38]. The statistical analysis results revealed that there were more individuals with metabolic syndrome in the case group than in the control group.

Numerous studies have shown how the lipid profile affects CVD development. Constriction and abstraction of cardiac arteries, which are strongly connected with the risk of CVD, may be impacted by elevated triglyceride and total cholesterol levels. Elevated LDL may also cause arteriosclerosis because LDL accumulates in the artery's intima-media, which may subsequently encourage thrombocytopoiesis. However, those with higher HDL levels may be at lower CVD risk [39]. In this study, the average LDL and cholesterol levels in the case group were not significantly different from those in the control group. However, the average HDL level in the case group was considerably lower than in the control group, and the average triglyceride level in the case group was significantly higher than in the control group.

Diabetes has long been regarded as a "cardiovascular risk equivalent". This claim was previously based on a study from Finland, which found that type 2 diabetic patients without coronary heart disease (CHD) episodes had similar coronary mortality to non-diabetic patients with a history of coronary events. Diabetes worsens the patient's prognosis even after the first CHD episode because it increases the cardiac mortality rate [40]. In this research, the blood glucose level in the patient group was significantly higher than in the control group. The statistical analysis results showed that the average AST level in the case group was substantially higher than in the control group. But the mean ALT level was not significantly different between the two study groups.

Sung et al. (2007) studied a cohort

of Koreans with a high prevalence of hepatitis B virus infection to determine the relationship between HBsAg seropositivity and cardiovascular illnesses. In their study, men with hemorrhagic stroke and MI were more common among people with seropositive HBsAg and liver dysfunction than men without either of these conditions. However, the risk of stroke and MI was similar in HBsAg-seropositive and HBsAg-seronegative men with both conditions [41]. Wang et al. (2010) carried out a study to comprehend the association between HBsAg seropositivity and atherosclerosis/ cardiovascular death prospectively in Taiwan. Over 17 years, they kept track of the mortality of 22,472 patients between 30 and 65 years of age, including 18,541 HBsAg seronegative and 3931 seropositive patients. They discovered that HBsAg seropositivity was not associated with an increased risk of mortality from cardiovascular disease or atherosclerosis in the future [42]. Based on electronic medical records retrieved from the Taiwan National Health Insurance Research Database from 2000 to 2012, Wu et al. (2018) investigated the effects of chronic HBV and HCV infections in individuals who were at high risk of developing atherosclerotic disease. After five years of follow-up, the incidence of composite vascular events and all-cause death was considerably higher among patients with HCV infection than among those with HBV infection [43].

Chun et al. (2021) analyzed data retrieved from the Korean National Health and Nutrition Examination Surveys from 2008 to 2011. Patients with a past history of CVD were significantly older and had a considerably higher prevalence of hypertension, metabolic syndrome, and liver fibrosis, as well as substantially higher platelet counts, lower aspartate and alanine aminotransferase levels, higher triglyceride levels, and lower high-density lipoprotein levels. In their analysis, liver fibrosis was independently linked to a higher probability of having a history of CVD in chronich hepatitis B (CHB) patients [44].

In another study conducted by Demir and Demir (2012) in Turkey, the systolic function of the right and left ventricles of the heart was investigated in hepatitis B patients. In their study, 50 HBsAg positive patients with an average age of 33 years and 50 individuals with an average age of 28 years were included in the case and control groups, respectively. Transthoracic echocardiography was accomplished for all participants, and right and left ventricular systolic parameters were compared between these two groups. According to the results, the researchers of this study stated that HBV infection might be associated with right ventricular systolic dysfunction and pulmonary hypertension [45]. The lack of uniformity in the final results of Demir's study as well as the small sample size in the present study may be limiting factors contributing to the inconsistency between the results of the two studies.

Conclusion

Although this study could not establish a direct link between cardiovascular diseases and HDV/HBV infection, it revealed differences in the lipid profile between the two groups, which could be considered as factors contributing to the onset of cardiovascular diseases. This information could assist healthcare professionals to address these specific changes to prevent the occurrence of cardiovascular diseases. Additionally, the results highlight the significance of managing high blood glucose levels and metabolic syndromes to mitigate the risk of cardiovascular diseases. These findings could be beneficial to healthcare providers and patients alike in making informed decisions about cardiovascular disease prevention and management.

However, it is recommended to conduct similar cohort studies with larger sample sizes to reduce the risk of error in the results

Acknowledgments

We would like to extend our gratitude to the Qaem hospital laboratory located in Mashhad, Iran for their invaluable assistance in supplying the required samples. Our appreciation also goes to the professionals at the Antimicrobial Resistance Research Center at Bu Ali Research Institute, who played a pivotal role in assessing our collected samples.

Ethical permissions: The patients successfully filled out the informed consent documents. Additionally, the research received complete approval from the Ethics Committee of Mashhad University of Medical Sciences following the guidelines outlined in the Helsinki Declaration (IR.MUMS.fm.REC.1396.426). This study was extracted from a Medical Doctor's thesis with the grant number 960186.

Authors' contributions: ZM, AGh, and EA contributed to the design and clarification of the study. SA, AH, and MN contributed to laboratory analysis and data collection. MM, MGM, and MjM were involved in the analysis and interpretation of data. TD, NH, ST, and M.Kh. contributed to writing the original article. All authors approved the final version of the article.

Conflicts of interests: None declared by authors

Fundings: This study did not receive any specific funding from any public, commercial, or nonprofit organizations.

Consent to participate: All participants were informed about the investigation and completed a consent form. Serum samples were collected and preserved for further experiments. This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Code: IR.MUMS.fm.REC.1396.426 and IR.MUMS.fm.REC.1390.435).

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