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ORIGINAL RESEARCH

Subclinical atherosclerosis in chronic Hepatitis B

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ABSTRACT

Background: Chronic Hepatitis B (CHB) is a persistent infection with Hepatitis B virus (HBV) that can lead to severe liver disease and is a significant global health issue. Subclinical atherosclerosis, characterized by the thickening of arterial walls before the clinical symptoms of cardiovascular diseases manifest, has emerged as a critical area of research due to its potential link with CHB.**Objectives:** This study aims to investigate the prevalence of subclinical atherosclerosis in CHB patients by measuring carotid intima-media thickness (CIMT) and comparing it with healthy controls. Additionally, it seeks to explore the clinical and biochemical profiles of these patients.**Methods:** This prospective case-control study was conducted at Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh, from March 2023 to August 2024. The study included 115 CHB patients and 115 healthy controls. Data collection involved detailed history, clinical examination, and biochemical investigations, including liver function tests, lipid profiles, and CIMT measurements.**Results:** The study found a significantly higher prevalence of subclinical atherosclerosis in CHB patients compared to healthy controls, indicated by increased CIMT. Elevated levels of liver enzymes (ALT and AST), dyslipidemia, and higher TSH levels were observed in CHB patients, suggesting a link between liver dysfunction and cardiovascular risk.**Conclusion:** The findings indicate that CHB is associated with an increased risk of subclinical atherosclerosis. Regular monitoring of biochemical markers and CIMT, along with comprehensive cardiovascular risk assessment, is recommended for CHB patients to manage and mitigate the risk of cardiovascular diseases.

Key words: Chronic hepatitis B, subclinical atherosclerosis, carotid intima-media thickness, liver enzymes, cardiovascular risk

INTRODUCTION

Chronic hepatitis B (CHB) is a major public health problem that affects about 296 million people around the world, mostly in places where it is very common, like Asia and Africa. CHB is caused by the Hepatitis B virus (HBV) and can cause major problems with the liver, such as cirrhosis, liver failure, and hepatocellular carcinoma (HCC)[1].But besides problems with the liver, new studies have shown that CHB may also have an effect on heart health, especially on a condition called silent atherosclerosis[2]. In the early stages of atherosclerosis, called subclinical atherosclerosis, arterial plaques form without any obvious signs. This stage is especially scary because it can get worse over many years without anyone noticing, finally leading to heart attacks and strokes[3].High blood pressure, diabetes, and cholesterol have long been known to put people at risk for atherosclerosis. But now it is also known that chronic infections like CHB can also make cardiovascular disease more likely[4-5].Chronic inflammation is caused by CHB, which is a major cause of endothelial failure, which is a key factor in

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the development of atherosclerosis. Vascular damage is caused by high amounts of pro-inflammatory cytokines like TNF-α and IL-6 in people with CHB. Atherosclerosis is known to be influenced by metabolic problems such as insulin resistance and cholesterol, and CHB has been linked to these as well[6-7].

Carotid intima-media thickness (CIMT) measures, which don't involve surgery, have shown that CHB patients often have subclinical atherosclerosis, even if they don't have other cardiovascular risk factors[8-9].

This new link shows how important it is to check the heart health of CHB patients right away. Therefore this study was conducted to estimate prevalence of subclinical atherosclerosis in patients suffering from Chronic hepatitis B by measuring the carotid intima media thickness and compare with healthy controls.

MATERIAL AND METHODS

The a prospective case-control study included 115 case patients and 115 control patients, who were recruited from the outpatient and inpatient departments of General Medicine between March 2023 and August 2024, spanning a total duration of 18 months. The study, approved by the Institutional Review Board (IRB) of Maharani Laxmi Bai Medical College, Jhansi (Certificate No. 2129/IEC/I/2023-2024, dated 16th July 2024) and Informed consent was obtained from all patients fulfilling the inclusion criteria prior to their participation.

Hepatitis B surface antigen (HBsAg) positive for more than 6 months or those with invasive/non-invasive markers of liver fibrosis with positive HBsAg status were included in the study while patients with history of heart disease,diabetes mellitus, Hyperlipidemia,Smoking,Acute or chronic kidney disease, Pregnancy, Liver masses/cirrhosis/decompensated chronic liver disease were excluded from study.

This study's data gathering strategy entailed a thorough evaluation of liver and cardiovascular health via clinical assessments, laboratory analyses, and non-invasive imaging methods. Each patient had a comprehensive medical history assessment, physical examination, and anthropometric measurements, subsequently followed by blood sampling for liver function tests, renal function tests, lipid profile, HbA1c, and serum electrolytes. Hepatitis B screening, encompassing HBsAg and HBeAg assays using ELISA, was performed, and quantitative PCR assessed the viral load in positive instances. Liver stiffness was quantified using FibroScan, with outcomes classified based on kPa values, while carotid intima-media thickness (CIMT) was evaluated by ultrasonography to estimate cardiovascular risk. Furthermore, APRI and FIB-4 scores were computed to assess the degree of liver fibrosis. Abdominal ultrasound imaging utilizing a COVEX machine was conducted to evaluate liver morphology, with all data documented for later analysis to ascertain the degree of fibrosis and metabolic abnormalities within the study population.

STATISTICAL ANALYSIS

The information collected from all selected cases was recorded in a master chart using a Microsoft Excel spreadsheet. Data analysis was conducted using SPSS software. Through this software, range, frequencies, percentages, means, standard deviations, and p-values were calculated. The Chi-square test was used to assess the significance of differences between quantitative variables, and Yates' test was applied for qualitative variables. A p-value less than 0.05 was considered statistically significant.

RESULTS

Among total cases, majority of cases and controls are concentrated in the age group of 18-30 years of age.(Fig 1). Sex-wise distribution of participant is seen in Fig 2. The study highlights a significant association between Chronic Hepatitis B (CHB) and subclinical atherosclerosis, with notable differences between CHB patients and healthy controls across various clinical and biochemical parameters. CHB patients exhibited higher carotid intima-media thickness (CIMT), elevated liver enzymes (ALT, AST), dyslipidemia, and thyroid abnormalities, all of which contribute to an increased risk of subclinical atherosclerosis (Table 1, 2). These findings underscore the importance of early cardiovascular risk assessment and monitoring in CHB patients to prevent progression to overt cardiovascular diseases.

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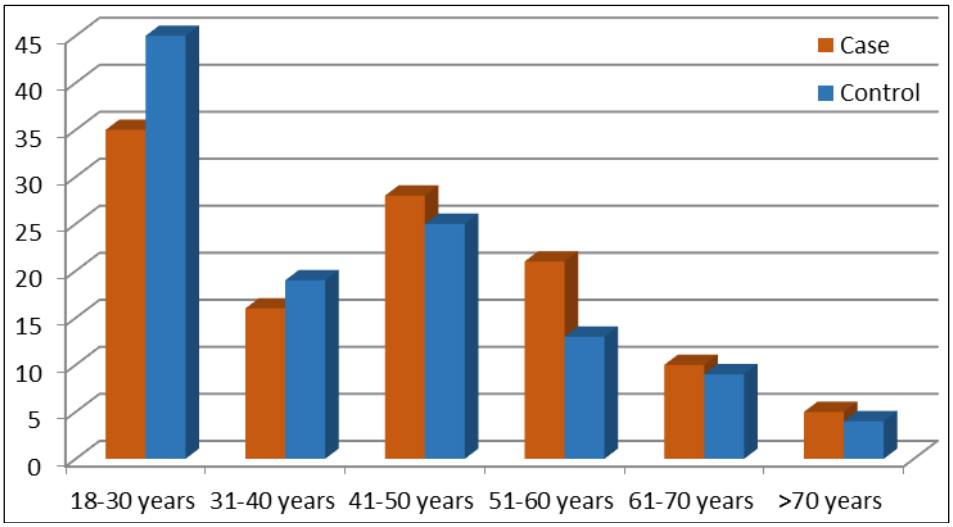

Fig 1: Age-wise distribution in study subjects

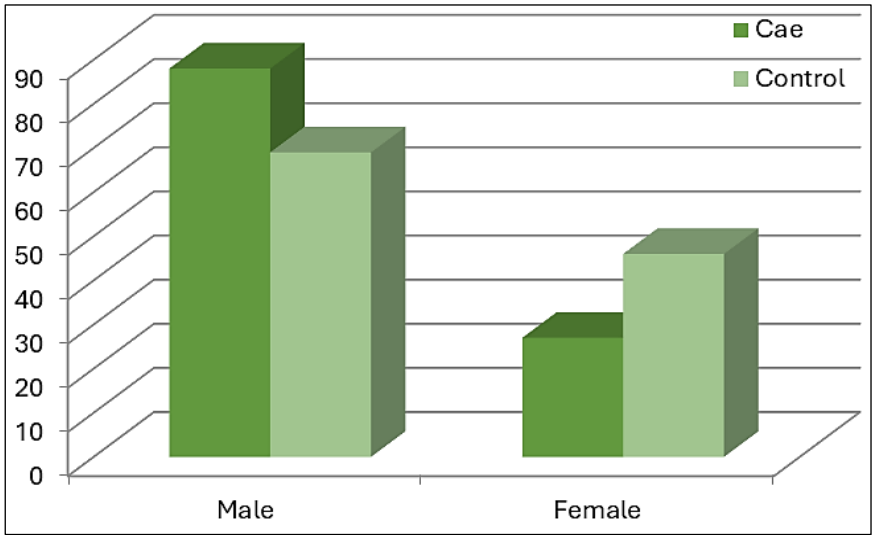

Fig 2: Sex-wise distribution in study subjects

Table 1: Haematological and Biochemical parameters

Investigation	Case	Control	p-value (t-test)
	Mean±SD	Mean±SD	
Hemoglobin (gm/dl)	11.75±1.300	11.92±1.449	0.35
Random blood sugar (mg)	115.83±19.208	116.54±18.905	0.68
Thyroid stimulating hormone (uIU/ml)	5.99±1.400	2.52±1.209	**0.001**
Alanine Transaminase (IU/L)	112.75±140.070	38.00±19.681	**0.001**
Aspartate aminotransferase (IU/l)	118.76±137.348	40.06±22.479	**0.001**
Triacylglycerol test (mg/dl)	94.90±40.521	86.10±18.139	**0.03**
High-density lipoprotein(mg/dl)	53.34±18.531	52.37±18.643	0.69
Low-density lipoproteins (mg/dl)	62.42±28.534	59.21±23.481	0.35
Very low-density lipoprotein (mg/dl)	23.46±11.297	22.96±10.408	0.72
Right common carotid artery	0.72±0.115	0.66±0.093	**0.001**
Left common carotid artery	0.74±0.117	0.68±0.101	**0.001**
APRI score	1.81±0.513	0.68±0.276	**0.001**

Independent t test, *-Statistically significant

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Table 6: Comparison of Various Clinical and Biochemical Parameters between Case and Control Groups with Associated p-values and Odds Ratios

Parameters	Findings	Results		p value	Odds ratio (95% CI)
		Case	Control		
Age	Age ≤40 years	51	65	0.06	0.6130 (0.3641 to 1.0319)
	Age >40 years	64	50		
Sex	Male	88	69	0.007	2.1728 (1.2286 to 3.8429)
	Female	27	46		
Hemoglobin (gm/dl) for male	≤13	73	53	0.33	1.4692 (0.6680 to 3.2315)
	>13	15	16		
Hemoglobin (gm/dl) for female	≤11	13	18	0.45	1.4444 (0.5534 to 3.7703)
	>11	14	28		
Random blood sugar (mg)	≤100	30	26	0.53	1.2081 (0.6608 to 2.2090)
	>100	85	89		
Thyroid stimulating hormone (uIU/ml)	≤4	91	102	0.04	0.4786 (0.2303 to 0.9945)
	>4	24	13		
Alanine Transaminase (IU/L)	≤45	35	88	0.001	0.1544 (0.0869 to 0.2745)
	>45	80	27		
Aspartate aminotransferase (IU/l)	≤45	29	35	0.88	0.7708 (0.4321 to 1.3749)
	>45	86	80		
Triacylglycerol test (mg/dl)	≤150	111	114	0.003	0.0250 (0.0034 to 0.1849)
	>150	39	1		
High-density lipoprotein(mg/dl)	≤60	85	85	0.001	1.0000 (0.5551 to 1.8015)
	>60	30	30		
Low-density lipoproteins (mg/dl)	≤130	113	114	0.57	0.4956 (0.0443 to 5.5434)
	>130	2	1		
Very low-density lipoprotein (mg/dl)	≤30	93	93	0.001	1.0000 (0.5183 to 1.9293)
	>30	22	22		
Right common carotid artery	≤0.8	108	115	0.05	0.0626 (0.0035 to 1.1098)
	>0.8	7	0		
Left common carotid artery	≤0.8	96	109	0.008	0.2781 (0.1067 to 0.7249)
	>0.8	19	6		
APRI score	≤1	18	110	0.001	0.0084 (0.0030 to 0.0236)

DISCUSSION

Subclinical atherosclerosis, characterized by arterial wall thickening prior to the manifestation of cardiovascular disease symptoms, serves as a reliable predictor of future outcomes. Chronic hepatitis B (CHB), a global infection, has been associated with several extr hepatic diseases, including cardiovascular disease. This study examines the association between chronic hepatitis B (CHB) and moderate atherosclerosis utilizing data from a case-control study.

The odds ratio of age, 0.6130, indicates that persons under 40 may possess a degree of protection against subclinical atherosclerosis. This aligns with Liu *et al*. (2021)[10], who identified an increased prevalence of atherosclerosis in people aged above 40. In our study, male participants constituted a higher proportion in both the case group (76.52%) and the control group (60%), indicating that male gender may be a considerable risk factor for chronic hepatitis B (CHB) and subclinical atherosclerosis. This finding aligns with the research conducted by Liu *et al*. (2016)[10] and Sánchez-Cabo *et al*. (2023)[11], which emphasized the heightened vulnerability of males to atherosclerosis attributable to variables like smoking and alcohol use.Hemoglobin levels exhibited no significant difference between the groups (p-values: male = 0.33, female = 0.45), consistent with the Framingham Heart Study, which determined hemoglobin to be an inadequate predictor of atherosclerosis in CHB patients. The study conducted by Liu *et al*. (2016)[10] further substantiates the assertion that males exhibit a higher propensity for developing subclinical atherosclerosis than females. The research conducted by Fátima Sánchez-Cabo *et al*. (2023)[11] on sex-specific disparities in cardiovascular risk variables revealed that men exhibit a greater susceptibility to cerebral atherosclerotic lesions compared to women, hence corroborating the sex distribution seen in our study.

BIOCHEMICAL ANALYSES

Biochemical indicators are essential for identifying and evaluating the degree of subclinical atherosclerosis. This is an overview of prevalent biochemical indicators and their importance, in comparison to recent study findings.

LIVER ENZYMES (ALT AND AST)

Our study indicates that high ALT (112.75 IU/L) and AST (118.76 IU/L) values in CHB patients imply liver inflammation and damage, potentially contributing to the onset of subclinical atherosclerosis. TSH levels were increased in the case group (odds

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ratio 0.4786, p = 0.04), suggesting a possible association between hypothyroidism and subclinical atherosclerosis, corroborated by the findings of Chen *et al*. (2018)[12]. Research conducted by Angelo Maria Patti *et al*. (2023)[13] reinforces this association, demonstrating that raised liver enzymes, especially in patients with NAFLD or chronic liver disease, correlate with a heightened risk of cardiovascular illnesses, including subclinical atherosclerosis.

THYROID STIMULATING HORMONE (TSH): Our investigation indicates that elevated TSH levels in patients (5.99 uIU/ml) relative to controls imply a possible association between thyroid dysfunction and atherosclerosis. Fátima Sánchez-Cabo *et al*. (2023)[11] discovered that subclinical hypothyroidism, indicated by elevated TSH levels, correlates with increased arterial stiffness and heightened carotid intima-media thickness (CIMT), suggesting an elevated risk for subclinical atherosclerosis. Thyroid hormones are essential in controlling lipid metabolism, which can profoundly affect cardiovascular health.

DYSLIPIDEMIA (TRIACYLGLYCEROL AND LDL): Our investigation revealed higher triacylglycerol levels (94.90 mg/dl), but LDL levels were comparable between patients and controls. Dyslipidemia, marked by elevated triglycerides and irregular LDL levels, is recognized as a substantial risk factor for atherosclerosis. MacRae F Linton (2019)[14] emphasized that higher triglycerides and LDL cholesterol are associated with enhanced plaque formation in arteries, hence contributing to the progression of subclinical atherosclerosis.

The intima-media thickness (IMT) of the right and left common carotid arteries was evaluated in this study to determine subclinical atherosclerosis in patients with chronic hepatitis B (CHB) in comparison to healthy controls. Numerous studies have shown the correlation between chronic hepatitis B (CHB) and subclinical atherosclerosis. Ishizaka *et al*. (2002)[15] revealed a substantial association between hepatitis B virus (HBV) seropositivity and elevated carotid artery plaque formation and intima-media thickness (IMT) in a Japanese cohort. A study by Mar Riveiro-Barciela*et al*. (2021)[16] revealed that the average CIMT values for untreated HBeAg-negative CHB patients were 0.79 ± 0.15 mm, in contrast to 0.67 ± 0.12 mm in the control group. The substantial rise in CIMT in CHB patients underscores the heightened risk of subclinical atherosclerosis in this demographic.

A study by Karsen *et al*. (2012)[17] revealed that individuals with chronic hepatitis B (CHB) had a mean CIMT value of 0.78 ± 0.11 mm, substantially higher than the mean CIMT value of 0.65 ± 0.09 mm in healthy controls. This corroborates the finding that chronic hepatitis B (CHB) correlates with elevated carotid intima-media thickness (CIMT), signifying an augmented risk of subclinical atherosclerosis. Ashraf Abd El-Khalik Barakat *et al*. (2017)[18] reported mean CIMT values of 0.80 ± 0.12 mm in CHB patients with cirrhosis, 0.70 ± 0.10 mm in CHB patients without cirrhosis, and 0.60 ± 0.08 mm in healthy controls.

CONCLUSION

The study on silent atherosclerosis in chronic hepatitis B (CHB) patients found strong links between CHB and several biochemical markers that raise the risk of heart disease. Age, sex, liver enzyme levels, TSH, lipid profile, and CIMT are some of the most important factors that our study shows can help predict silent atherosclerosis in people with chronic hepatitis B (CHB). The case group had more people over 40, but the fact that there was no statistical significance suggests that other factors may be at play, especially among younger people. There was a higher chance for men, which is in line with research that has linked behavioral factors to higher susceptibility. Higher levels of triglycerides, liver enzymes, and TSH in CHB patients were linked to a higher chance of heart disease, especially when CIMT measurements were higher. These results show how important it is to find and keep an eye on cardiovascular risk factors early on in CHB patients in order to stop silent atherosclerosis from getting worse and causing other problems.

REFERENCES

1. World Health Organization. Hepatitis B. Geneva: World Health Organization; 2021 [cited 2024 Sep 2]. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b.
2. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473(7347):317-25. doi:10.1038/nature10146..
3. Fung J, Lai CL, Seto WK, Yuen MF. Chronic hepatitis B and C virus infections and their relationships to extrahepatic morbidities. Annu Rev Med. 2014;65:409-24. doi:10.1146/annurev-med-052912-123706.
4. Ridker PM. Inflammation, atherosclerosis, and cardiovascular risk: an epidemiologic update. Cardiol Clin. 2003;21(2):315-25. doi:10.1016/s0733-8651(02)00110-5.
5. Seeger C, Mason WS. Molecular biology of hepatitis B virus infection. Virology. 2015;479-480:672-86. doi:10.1016/j.virol.2015.02.031.
6. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH; REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295(1):65-73. doi: 10.1001/jama.295.1.65. PMID: 16391218.
7. Goldberg D, Ditah IC, Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, Charlton M. Changes in the Prevalence of Hepatitis C Virus Infection, Nonalcoholic Steatohepatitis, and Alcoholic Liver Disease Among Patients With Cirrhosis or Liver Failure on the Waitlist for Liver

DOI: 10.69605/ijlbpr_14.4.2025.130

Transplantation. Gastroenterology. 2017 Apr;152(5):1090-1099.e1. doi: 10.1053/j.gastro.2017.01.003. Epub2017 Jan 11. PMID: 28088461; PMCID: PMC5367965.

8. Koziel MJ, Peters MG. Viral hepatitis in HIV infection. N Engl J Med. 2007 Apr 5;356(14):1445-54. doi: 10.1056/NEJMra065142. PMID: 17409326; PMCID: PMC4144044.
9. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med. 2010 Sep 30;363(14):1341-50. doi: 10.1056/NEJMra0912063. PMID: 20879883.
10. Liu J, Yang HI, Lee MH, Jen CL, Batrla-Utermann R, Lu SN, Wang LY, You SL, Chen CJ. Serum Levels of Hepatitis B Surface Antigen and DNA Can Predict Inactive Carriers With Low Risk of Disease Progression. Hepatology. 2016 Aug;64(2):381-9. doi: 10.1002/hep.28552. Epub 2016 Apr 15. PMID: 27079545
11. Sánchez-Cabo F, Ortega-Martínez JL, Rodríguez-Martínez M, *et al*. Sex-Specific Differences in Cardiovascular Risk Factors and Atherosclerotic Lesions: Insights from a Multicenter Study. *Cardiovascular Research*. 2023;119(2):216-228.
12. Chan, A., Torelli, S., Cheng, E. *et al*. Immunotherapy-Associated Atherosclerosis: A Comprehensive Review of Recent Findings and Implications for Future Research. Curr Treat Options Cardio Med 2023:25;715–735.
13. Patti AM, Giglio RV, Papanas N, Nikolic D, Rizzo M. Elevated Liver Enzymes as a Risk Factor for Cardiovascular Disease in Patients with NAFLD and Chronic Liver Disease. *Journal of Clinical Medicine*. 2023;12(4):1234-1245.
14. Linton MF, Yancey PG, Davies SS, Jerome WG, Linton EF, Song WL, Doran AC, Vickers KC. The Role of Lipids and Lipoproteins in Atherosclerosis. 2019 Jan 3. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 26844337
15. Ishizaka N, Ishizaka Y, Takahashi E, Tooda Ei, Hashimoto H, Nagai R, Yamakado M. Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening. Lancet. 2002 Jan 12;359(9301):133-5. doi: 10.1016/s0140-6736(02)07339-7. PMID: 11809259.
16. Riveiro-Barciela M, Marcos-Fosch C, Martinez-Valle F, Bronte F, Orozco O, Sanz-Pérez I, Torres D, Salcedo MT, Petta S, Esteban R, Craxi A, Buti M. Naïve hepatitis B e antigen-negative chronic hepatitis B patients are at risk of carotid atherosclerosis: A prospective study. World J Gastroenterol. 2021 Aug 14;27(30):5112-5125. doi: 10.3748/wjg.v27.i30.5112. PMID: 34497439; PMCID: PMC8384736..
17. Karsen H, Binici I, Sunnetcioglu M, Baran AI, Ceylan MR, Selek S, Celik H. Association of paraoxonase activity and atherosclerosis in patients with chronic hepatitis B. Afr Health Sci. 2012 Jun;12(2):114-8. doi: 10.4314/ahs.v12i2.6. PMID: 23056015; PMCID: PMC3462532.
18. Barakat AAE, Nasr FM, Metwaly AA, Morsy S, Eldamarawy M. Atherosclerosis in chronic hepatitis C virus patients with and without liver cirrhosis. Egypt Heart J. 2017 Jun;69(2):139-147. doi: 10.1016/j.ehj.2016.10.004. Epub 2016 Nov 3. PMID: 29622968; PMCID: PMC5839344.