ORIGINAL ARTICLE

HYPERCHOLESTEROLEMIA AS A CAUSATIVE RISK FACTOR FOR NON-ALCOHOLIC FATTY LIVER DISEASE

Sarwat Abbasi[1], Saadia Sadiq[2], Nadia Haleem[1], Salma Shazia[3], Sara Jadoon[4], Muhammad Israr[5]

[1]Department of Biochemistry, [3]Department of Forensic Medicine, [4]Department of Anatomy, Ayub Medical College, Abbottabad-Pakistan
[2]Department of Biochemistry, Abbottabad International Medical College, Abbottabad-Pakistan
[5]Department of Biochemistry, Bacha Khan Medical College, Mardan-Pakistan

Background: Increased serum Cholesterol level is a known risk factor for cardiovascular diseases. Derangements in serum Cholesterol levels will affect normal hepatic Cholesterol homeostasis resulting in hypercholesterolemia. Non-Alcoholic fatty liver disease (NAFLD) initially asymptomatic but can lead to cirrhosis and hepatocellular carcinoma from mild steatosis to non-alcoholic steatohepatitis. The objective of this study is to find out hypercholesterolemia as a causative risk factor in NAFLD patients. This will help to prevent the development and progression of the disease. **Methods:** This cross-sectional study was conducted from 16th August 2021 to 16th August 2022 at Ayub Medical institute Abbottabad. Random sampling technique was used. Sample size was 100, in which 50 were diagnosed cases of liver disease and 50 normal subjects diagnosed on ultrasound. A questionnaire was designed. Subjects between 40–65 years age group were selected after informed consent and confidentiality. Data was collected from the out-patient department of medical and surgical unit and analysed with the help of SPSS-22.00. Chi-square test was used. Enzymatic kit method was used for serum cholesterol and triglycerides estimation. BMI was derived from the mass (weight) and height of the person. **Results:** It was found that 48% study subjects with NAFLD shows high serum Cholesterol levels while 52% subjects with NAFLD were found within normal limits but 10% individuals with no fatty infiltration had high serum Cholesterol levels while 90% without NAFLD had shown normal serum Cholesterol levels. Significant *p*-value of <0.001 was found between presence of NAFLD and high serum Cholesterol levels. Significant association was also found among serum Cholesterol and serum Triglyceride levels showing strong association of serum cholesterol levels with NAFLD and raised serum triglycerides levels with *p*-value 0.001. Similarly, significant association was found between serum cholesterol levels and BMI with *p*-value <0.001. **Conclusion:** Highly significant association was found between Hypercholesterolemia and non-alcoholic fatty liver disease. It suggests hypercholesterolemia as a causative risk factor for NAFLD.

Keywords: Hypercholesterolemia; Hepatic Disorder; Non-Alcoholic Fatty Liver Disease (NAFLD).

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the emerging problems across the world. Scientists from all over the world are trying to identify the factors that are responsible for its development and progression. The disease is asymptomatic in early stages but it can lead to serious outcomes. Main cause of fatty liver is suggested as high intake of alcohol which can affect the hepatic tissues of an individual. However, the disease is progressing amongst Muslim countries where alcohol consumption is strictly prohibited. Exact cause is not known however, it is suggested that high cholesterol levels especially high LDL levels and low HDL levels are responsible in the development of NAFLD. The disease is found to be a risk factor for obesity, hyperlipidaemias, Insulin resistance and type 2 Diabetes Mellitus.[1] It is considered as a lipid related metabolic disorder. The disease progresses from asymptomatic condition, i.e., benign steatosis to non-alcoholic steatohepatitis (NASH) characterized by insulin resistance, hepatic inflammation and then fibrosis. NASH may lead to hepatic cirrhosis and hepatocellular carcinoma.[2] Exact pathogenesis and progression of the disease is not well known however, abnormal hepatic lipid metabolism seems to have a key role.[3] It is found that NAFLD is associated with the risk of ischemic cardiac disease, stroke and congestive heart failure.[4]

It is proven scientifically that high cholesterol level is major risk factor for ischemic heart disease.[5] Unhealthy diet, sedentary life styles, no physical activities, obesity, smoking etc. are different factors that are responsible of hypercholesterolemia. With advancing age and any liver pathology, hepatic tissue becomes less able to remove LDL cholesterol

resulting in hypercholesterolemia and hence became risk factor for atherosclerosis leading to ischemic heart disease and myocardial infarction, a major cause of majority of cardiovascular deaths.[4]

MATERIAL AND METHODS

This cross-sectional study was conducted at Ayub Medical institute Abbottabad which is a tertiary level health care centre giving full health care facilities to outdoor and indoor patients. Random sampling technique was used. Out-patient department of Medical and surgical unit were the areas for sample collection. Duration of the study was one year from 16th August 2021 to 16th August 2022. In accordance with fatty liver disease, two groups of individuals were selected. "A" group was composed of individuals with fatty liver disease and group "B" was those who were free of hepatic fatty infiltration. Age group was amongst 40–65 years. Individuals were selected randomly in the out-patient department. After taking approval from the ethical committee, study was conducted on the selected subjects. Informed consent was taken and assurance of confidentiality was given to the study subjects. Data was collected and then analyzed with the help of SPSS version 22.00. Subjects with fatty liver were diagnosed ultrasonographically by specialist ultrasonologist using the criteria of diffuse enhancement of the echogenicity of hepatic tissue, intrahepatic duct structure visibility, Hepatomegaly of mild to moderate type with blunt leading edge. Body mass index was calculated after measuring height and weight of the individuals. Serum total cholesterol and serum triglyceride was measured after taking 5ml blood with disposable syringe. Proper labelling of the samples was done. Serum Cholesterol was determined by Mindray B.S 400 fully automatic chemistry analyzer. The kit used for the determination of serum Cholesterol was Ecocline diagnostic made up of Germany. The method used is called enzymatic photometric test "CHOD-PAP". Serum triglyceride levels were detected by using reagents obtained from Innoline diagnostic kit by enzymatic splitting method.

Both male and female between age group 40–65 years, non-alcoholics, individuals with demographic, laboratory and liver ultrasound and without having history of any chronic liver disease were included in this study. Age below 40 and above 65, those without demographic, laboratory and liver ultrasound, alcoholics, pregnant ladies and individuals with history of viral hepatitis, autoimmune hepatitis or any other chronic liver disease were excluded from this study.

RESULTS

A total of 100 individuals were selected. 50 out of them were diagnosed with fatty liver and 50 were found normal ultrasonographically. Youngest participant was 40-year-old and while the eldest one was 65-year-old. Amongst these individuals 29% individuals had high serum cholesterol levels while 71% individuals had serum cholesterol levels within normal limits. Serum triglyceride levels were found high in 61% of individuals while 39% were found with normal serum triglyceride levels. According to BMI individuals were classified in normal, overweight and very obese individuals. Amongst them 44% were found with normal BMI, 29% were overweight and 27% were found in very obese group (Table-1). Chi- square test was applied by cross-tabulating NAFLD with serum Cholesterol.

Amongst Individuals with fatty liver 48% had high serum Cholesterol level while 52% were found with normal cholesterol estimation. Amongst individuals with no fatty changes in hepatic tissue, only 10% had high serum cholesterol levels while 90% had normal serum Cholesterol measurements (Table-2). Chi-square test shows significant association of NAFLD with hypercholesterolemia. It was also found that 24% individuals have both hypercholesterolemia and hypertriglyceridemia where as 37% with normal serum cholesterol level have high triglyceride level while 34% have both normal serum cholesterol and serum triglyceride level (Table-3). When we considered BMI, 7% normal, 8% overweight and 14% very obese have high serum cholesterol levels. Whereas 37% normal, 21% overweight and 13% very obese have normal serum cholesterol levels (Table-4). These results have shown significant association of hypercholesterolemia with NAFLD, serum triglyceride levels and BMI with *p*-value <0.001.

Table-1: Frequencies of serum cholesterol, triglycerides and BMI in study population (n=100)

		Frequency	Percent
Serum Cholesterol	High	29	29.0
	Normal	71	71.0
	Total	100	100.0
Serum Triglycerides	High	61	61.0
	Normal	39	39.0
	Total	100	100.0
BMI	Normal	44	44.0
	Overweight	29	29.0
	Very Obese	27	27.0
	Total	**100**	**100.0**

Table-2: Association between serum cholesterol levels & NAFLD

		Serum cholesterol		Total	*p*-value
		Normal	High		
NAFLD	Yes	26	24	50	<0.001
	No	45	5	50	
	Total	**71**	**29**	**100**	

Cholesterol level below 200 is recommended by "The American Heart Association"

Table-3: Association between serum cholesterol and triglyceride levels

		Serum Triglycerides			*p*-value
		Normal	High		
Serum Cholesterol	High	5	24	29	<0.001
	Normal	34	37	71	
	Total	**39**	**61**	**100**	

Table-4: Association between serum cholesterol and BMI

		BMI				
		Normal	Overweight	Very obese	Total	*p*-value
Serum Cholesterol	High	7	8	14	29	<0.001
	Normal	37	21	13	71	
	Total	**44**	**29**	**27**	**100**	

DISCUSSION

Our study shows association between NAFLD and hypercholesterolemia. Liver is the main organ responsible for the synthesis and metabolism of lipoproteins and cholesterol.[6] Derangements in lipid metabolism disturbs normal hepatic homeostasis ultimately leads to hypercholesterolemia with hepatic fat accumulation.[7,8]

This is well documented that high serum remnant cholesterol levels increase the risk of coronary artery diseases, type 2 Diabetes Mellitus, NAFLD and metabolic syndrome.[9–12] Several studies suggested that serum Cholesterol increases the risk of NAFLD in the general population, non-obese individuals and adults that is consistent with our study which reflect the association of serum cholesterol levels with NAFLD.[13–15] Makri *et al.* also reported 2.8-fold increased risk of disease development in individuals with highest quartile of remnant cholesterol levels found during 5 years follow up study.[16] Mortality and morbidity due to cardiovascular involvement or hepatic cause increases with the development and progression of the disease. Early detection of the disease is helpful in preventing serious consequences of the disease as the clinical outcome depends upon the severity of the disease.[17] Furthermore, Stürzebecher PE in his study documented the association of remnant cholesterol with cardiovascular disease,[18] whereas Huang *et al.* in another study observed that higher cholesterol levels increase the risk of more severe NAFLD.[19]

Our study also shows that overweight and obese people have high values of serum cholesterol. Whatever is the cause of obesity, hypercholesterolemia is associated with obesity which in turn can develop cardiovascular and cerebrovascular diseases. It is documented that hyper-leptinaemia in obesity induces hyperglycaemia which in turn increases cholesterol level. This increases the risk of atherosclerosis leading to heart attack and stroke.[20] Obesity is a well-known risk factor for non-communicable diseases like undiagnosed diabetes mellitus, hypertension and hypercholesterolemia.[21] By reducing weight through life style changes can effectively revert back these non-communicable diseases.[22] It is also noticed that early detection and treatment is necessary through weight loss as undiagnosed Diabetes Mellitus, hypertension and hypercholesterolemia remain silent for years.[23] Previous studies also documented that NAFLD is closely related to obesity and diabetes. The risk for the development of complications due to diabetes and cardiac issues are increased with advancing age in the people with NAFLD.[24] Other's noticed that development of NAFLD results from increased HDL cholesterol, triglycerides and Apo B ectopic deposition, inflammation, lipid peroxidation and endocytosis of triglycerides.[25–27] The American Heart Association's atherosclerotic Cardiovascular disease (ASCVD) score mentioned Diabetes, cholesterol, blood pressure and use of tobacco as a risk of developing ASVD in 10 years and guides prophylactic treatment plan. All these factors correlate with the metabolic syndrome and are considered as risk for the development of NAFLD and Coronary Heart diseases. There is a significant association between these two

conditions and the individuals suffering from one condition are prone to develop the second one.[28]

CONCLUSION

In conclusion, hypercholesterolemia is associated with NAFLD development and its progression, suggesting it as a causative risk factor for this disease. However, by taking preventive measures like reducing weight by increasing physical activities, regular exercises, healthy balanced diet with less saturated fats and carbohydrates with the addition of fibers, regular follow up check-ups for controlling blood pressure and measuring blood sugar levels and Cholesterol levels and avoiding use of tobacco will prevent liver tissue from the development and progression of the disease.

Limitations of the study:

Limitations of the study include small no of the patients and lack of dietary analysis.

Recommendations: Advanced techniques required for early detection and prevention for the development and progression of the disease.

Conflict of interest: None

AUTHORS' CONTRIBUTION

SA: Conceptualization of the study design, data collection, literature search and write-up. SS: Conceptualization of the study design, data collection and analysis. NH: Data analysis, data interpretation and write-up. SS: Data analysis, data interpretation. SJ, MI: Data interpretation and proofreading.

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Address for Correspondence:

Nadia Haleem, Department of Biochemistry, Ayub Medical College, Abbottabad-Pakistan
Cell: +92 322 910 0036
Email: nadiahaleem@myself.com