CORRELATIVE ANALYSIS OF ATHEROGENIC DYSLIPIDEMIA AMONG THE PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE VISITING TERTIARY CARE CENTER

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ABSTRACT

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most prominent causes of chronic liver disease. It is known that dyslipidemia in NAFLD patients may have more severe atherogenic potential with high triglyceride and low density lipoprotein (LDL) as well as less high density lipoprotein (HDL) level.

Objective

To determine the atherogenic dyslipidemia and associated factors among patients with NAFLD, Visiting Tertiary Care Center

Methodology

Prospective cross-sectional study was conducted at Dhulikhel Hospital-Kathmandu University Hospital (DH-KUH) from January, 2016 to December, 2016. All the patients (n= 973) diagnosed to have fatty liver during this study period were initially enrolled in this study. Patients were further asked to fill up the questioner. Out of total 973 cases, 169 patients were identified as NAFLD. Fasting blood sample and anthropometric measurements (BMI, WHR) were taken. After adjusting exclusion criteria, refusal to participate and dropout from the study, 101 patients and 92 apparently healthy age sex matched control group was selected for the study. Blood sugar level and lipid profile were analyzed to assess the risk of athrogenicity among the NAFLD.

Result

High total cholesterol was found in 64.4 %, High LDL was found in 20.8 %, Low HDL is present in 72.2% and high triglyceride is present in 65.8 % patients with NAFLD. Non-HDL cholesterol was higher in NAFLD compared to control group (116.75 ± 34.38 vs. 137.63 ± 39.76, p=0.00). Similarly, calculated cardiac risk ratio (TC/HDL) (4.15 ± 1.18 vs. 5.25 ± 1.78, p=0.00) and atherogenic index of plasma (AIP) was higher (0.30 ± 0.13 vs. 0.33 ± 0.19, p=0.37) in NAFLD compared to the control group.

Conclusion

NAFLD is significantly associated with atherogenic dyslipidemia. Calculated cardiac risk and AIP is higher in patients with NAFLD. Therefore it may be helpful to assess dyslipidemia among the patients with NAFLD to prevent cardiovascular events.

KEYWORDS

Atherogenic index of plasma, atherosclerosis, cardiovascular diseases, dyslipidemias, lipoproteins, non-alcoholic fatty liver disease

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most prominent cause of chronic liver disease affecting nearly 30% of population.[1,2] This is also associated with risk for development of cirrhosis and liver cancer, as it is estimated that NAFLD will be the leading cause of liver transplantation by 2030.[3] The development of NAFLD is strongly associated with metabolic syndrome (MetS) as reflected by the fact that approximately 90 % of patients with NAFLD have more than one feature of MetS and about 33% have three or more criteria like, abdominal obesity, elevated triglycerides, reduced HDL-C level, hypertension and impaired fasting glucose.[4] Besides chronic liver disease, recent evidences show NAFLD is strongly associated with cardiovascular diseases (CVD) [5] leading to globally death of nearly 18 million annually and out of that 80% are from low and middle income countries (LMICs).[6]

Study shows that prevalence of NAFLD in Nepal is increasing in hospital based studies,[7] but National prevalence of NAFLD of Nepal is not well documented. This alarming condition also rises the possibilities of higher prevalence of NAFLD associated CVD among Nepalese population.

In general NAFLD is an asymptomatic and progresses as a silent disease which can be identified after basic routine health examinations having some biochemical changes in liver enzymes without any other specific causes like, alcohol consumption, virus infection, effects of drugs and autoimmune diseases.[8] Most NAFLD patients have no signs or symptoms of liver disease at the time of diagnosis. However many patients report fatigue or malaise and a sensation of fullness or dull ache in the right upper abdomen and hepatomegaly is the only physical finding in most of the patients.[9] The diagnosis of NAFLD needs confirmation of hepatic steatosis based on either imaging studies or liver biopsy, together with the clinical examinations. [10]

Ultrasonographic fatty liver indicator (US-FLI) with semi quantitative grading system is acceptable tool for NAFLD screening.[11] Noninvasive, quick, cost effective and easily availability of ultrasonography in many hospitals is the choice to detect and grade NAFLD in Nepal.[7] However, studies show that ultrasound has moderate accuracy in the detection of NAFLD.[12] Several studies show there is a positive association between blood lipids and degree of NAFLD.[7,13,14] Therefore blood lipids could be measured in NAFLD.

Recent finding shows that prevalence of NAFLD increases 60 to 70% in obese and diabetic people, while NAFLD affecting about 15-30% of the general population[15] and cardiovascular disease is the leading cause of mortality in this group.[16,17] To identify and minimize the NAFLD associated CVD risk, it is essential to rule out every possible factor associated with CVD including dyslipidemia and their association with NAFLD in patients visiting hospital.

METHODOLOGY

Ethical clearance was obtained from Institutional Review Committee (IRC) of Kathmandu University School of Medical Sciences (KUSMS) Prospective cross sectional study was conducted among patients attending Dhulikhel Hospital-Kathmandu University Hospital (DH-KUH) from January, 2016 to December, 2016 who were referred for abdominal ultrasonogram. During this study period, 973 patients found to have fatty liver were initially included in this study. Fatty liver was graded according to the standard criteria accepted by American Gastroenterological Association.[18] Patients were asked for history of alcohol consumption, viral hepatitis, biliary cirrhosis, any other known liver disease including using any medicine for dyslipidemia and nephrotic syndrome. History of alcohol consumption more than 20 gram per day and other above mentioned diseases was excluded. After exclusion, 169 patients diagnosed as NAFLD were asked to give fasting blood samples and anthropometric measurement was done. After adjusting exclusion criteria, refusal to participate and dropout from the study, 101 patients and 92 apparently healthy age and sex matched control group was enrolled in the study.

Five milliliters of overnight fasting blood samples were collected via sterile venepuncture in a serum separator tube and processed in the Department of Clinical Biochemistry Laboratory of DH-KUH. Total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, Triacylglycerol and blood glucose was analyzed in fully automatic biochemistry analyzer (BA 400 Biosystems, Spain) after validation of internal quality control. Serum cholesterol > 200mg/dl, triaclyglycerol >150 mg/dl, LDL >100 mg/dl and HDL < 40mg/dl were considered abnormal.[19] Cardiac risk ratio (TC/HDL), non HDL cholesterol was calculated using standard formula. AIP was calculated as the logarithmically transformed ratio of TG to HDL-C [log (TG/HDL-C)] measured in mmol/L.

All the information collected from participants were entered in Microsoft Excel 2013 and all data were analyzed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive analysis along with Pearson correlation was analyzed to unfold correlation coefficient with blood lipids.

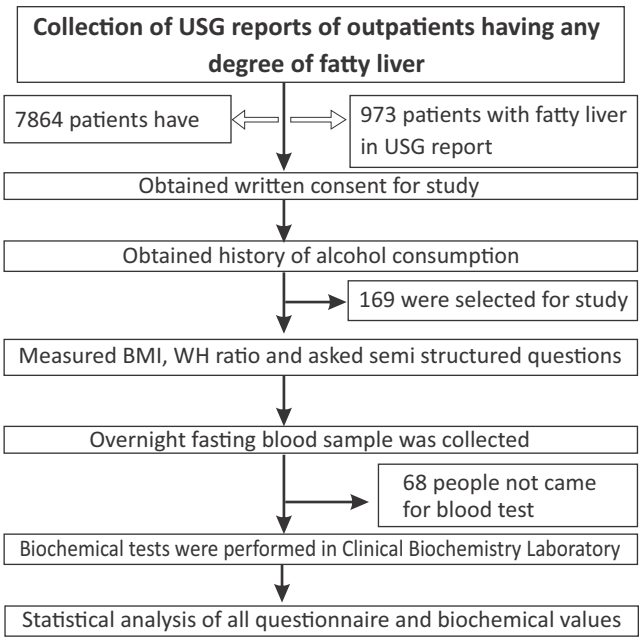

Figure 1: Flow chart of study process

RESULT

NAFLD was seen in 50 cases between the age group 40-59 years, hypertension was seen in 22 and diabetes was seen in 7 cases with NAFLD. Similarly, only 35 cases with NAFLD were having normal BMI (table 1).

Table 1: Characteristics of NAFLD cases enrolled in the study

Variables		NAFLD (n)
Age Group (years)	>30	18
	40-49	24
	50-59	26
	60-69	17
	>70	16
Gender	Male	50
	Female	51
Ethnicity	Hill Brahmin	33
	Hill Xetri	18
	Hill/Mountain Janjati	11
	Newar	27
	Hill Dalit	05
	Tarai/Madhesi	07
Blood Pressure	Normal	79
	High	22
Dietary Habit	Vegetarian	21
	Non-vegetarian	80
Diabetic History	Diabetic	07
	Non-diabetic	94
BMI Category	Normal	35
	Over Weight	48
	Obese	18
NAFLD	Grade I	60
	Grade II	35
	Grade III	06

As can be seen in figure 2, 59.4% cases are having NAFLD grade I. Grade III is seen only in 6 cases. Out of 60 grade I, 50% are hill Brahmin and 25% are Newar. Similarly in NAFLD grade II, 34.2% are hill Brahmin and 25.7% are Newar.

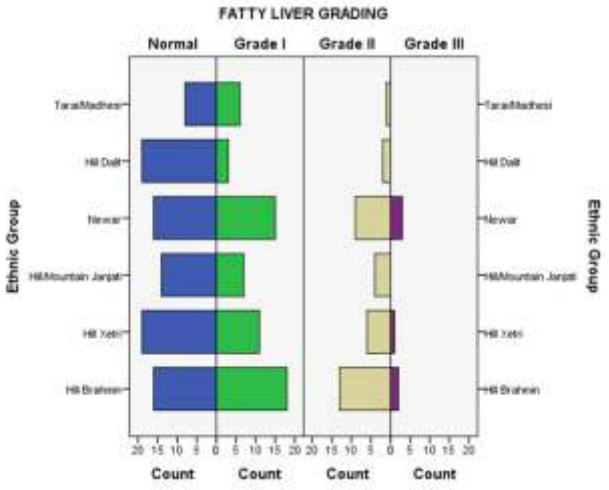

Figure 2: Distribution of NAFLD with grading among different ethnic groups

In the comparison of high-low-close chart (Figure 3) of BMI and waist-hip ratio against NAFLD, it is observed that, waist–hip ratio increases with degree of NAFLD in linear fashion while BMI of apparently normal and grade I NAFLD patients seems very close. However in NAFLD grade II onwards BMI also increase in a similar way to waist-hip ratio.

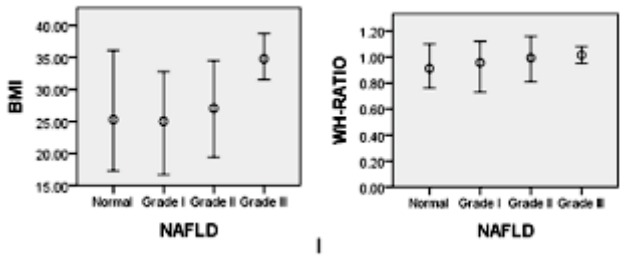

Figure 3: High-Low-Close chart of BMI and Waist Hip Ratio against NAFLD Respectively

When a simple dropbox plot was generated against the degree of NAFLD, it shows that, median of calculated cardiac risk is below 4.0 in apparently healthy controls but the median of grade I, II and III NAFLD patients is nearly 4.5, 5.0 and 6.5 respectively (figure 4). On similar analysis for atherogenic index of plasma against NAFLD, the median of AIP is between 0.25 to 0.35, which is not remarkably different in normal, grade I and grade II NAFLD patients. However, the median of grade III NAFLD is around 0.65.

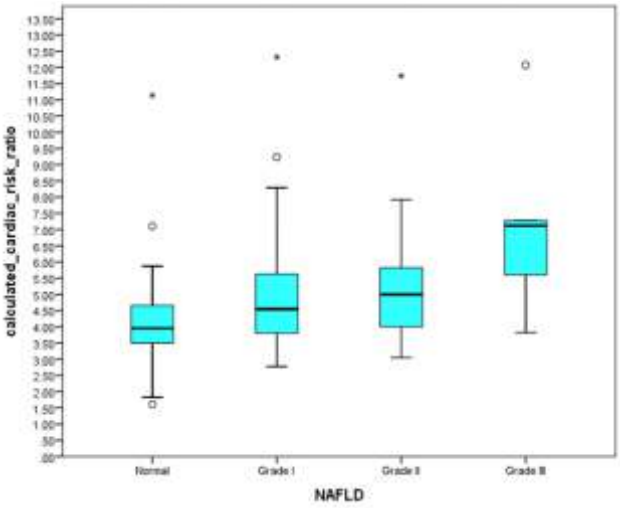

Figure 4: Drop box plot of calculated ratio of Total cholesterol to HDL (cardiac risk ratio) against NAFLD.

As seen in table 2, Total cholesterol (155.14±34.85vs 171.97±41.46, p=0.03) and LDL (81.93±20.79 vs. 105.55±27.64, p=0.00) are significantly higher in NAFLD compared to control, whereas HDL (38.39±7.51 vs. 34.34±8.03, p= 0.00) is significantly lower in NAFLD group compared to control. Non-HDL cholesterol is significantly higher in NAFLD compared to the control (116.75±34.38 vs. 137.63±39.76, p= 0.00). Similarly, calculated cardiac risk ratio (TC/HDL) is significant higher (4.15±1.18 vs. 5.25±1.78, p = 0.00) where as AIP is higher (0.30±0.13 vs. 0.33±0.19, p = 0.37) but not significant statistically.

Table 2: Biochemical parameters, in study group and control group

Parameters	Control group	NAFLD	*P* Value
Total Cholesterol	155.14±34.85	171.97±41.46	0.003
HDL-Cholesterol	38.39±7.51	34.34±8.03	0.000
LDL-Cholesterol	81.93±20.79	105.55±27.64	0.000
Triacylglycerol	157.35±35.99	171.56±61.57	0.055
Non-HDL-Cholesterol	116.75±34.38	137.63±39.76	0.000
Cardiac Risk Ratio (TC/HDL)	4.15±1.18	5.25±1.78	0.000
Atherogenic index of plasma	0.30±0.13	0.33±0.19	0.373

DISCUSSION

Increase prevalence of obesity, type 2 diabetes mellitus and other factors may have increased the incidence of NAFLD in Nepal, which should be verified by more studies. Furthermore, altered lipid metabolism in NAFLD that may increases the risk of CVD has to be studied. Very few study have been done so far to see dyslipidemia among NAFLD, therefore this study mainly analyzed dyslipidemia among NAFLD diagnosed by ultrasound.

This study found that majority of the case was found to be NAFLD grade I. Altogether, more that 95% case was found to be under grade I and II. Regarding the ethnicity, majorities were hill Brahmins and Newars in both grade I and II. We also found that WHR linearly increases among NAFLD, starting from grade I but, the BMI increases linearly among grade II onwards. The finding is supported by studies conducted in China and Iran.[20, 21] Zheng RD et al. has shown that, compared with the control group, the BMI, and WHR were significantly higher in patients with NAFLD. Further, BMI and WHR has been shown to be effective prognostic factors of NAFLD in the logistic regression analysis.[20] Mansour-Ghanaei R et al. also found that there was significant relationship between BMI (OR= 8.41; 95% CI = 5.59-12.75), and WHR (OR= 3.84; 95% CI = 2.26-6.52), and NAFLD (P<0.001).[21]

This study found that the degree of severity and prevalence of NAFLD is very high among hill Brahmin and Newar compared to the other community in this study. This may be due to the higher number of Hill Brahmin and Newar ethnic groups in this study and this finding also highlights the need for larger studies to evaluate Nepalese ethnic differences in NAFLD. Meanwhile, genetic susceptibility to NAFLD, life style and dietary habits among Brahmin and Newar ethnic groups cannot be ruled out and therefore clinicians need to be aware while evaluating NAFLD in different ethnic groups.

It is known that dyslipidemia in NAFLD patients may have a more severe atherogenic potential with high Total cholesterol, triacylglycerol and LDL and low HDL level. In this study, raised total cholesterol and triglycerides was seen in majority of the cases (>60%) and low HDL-C was seen in 72.2% patients with NAFLD. Almost similar finding has been shown by Pardhe BD et al in Nepal and Mahaling DU et al in India. [7,9] Pardhe BD et al showed increased triglycerides in 60.27% and decreased HDL in 69.8%, similarly Mahaling DU et al showed increased triglycerides in 67.14% and increased LDL in 34.28%, where as decreased HDL was shown in 62.85% of the NAFLD.

As shown in table 2, Lipid profile analysis showed significant increase in total cholesterol and LDL in NAFLD compared with normal group. Similarly, Triacylglycerol was higher in NAFLD but was not significant statistically. Whereas HDL was significantly lower in NAFLD compared to the control group. In the similar study done by Maharjan P et al[14] all the lipid profile parameters except HDL were significantly higher. In another study done by T.M.J. Santhosha kumari et al[13] all the parameters of lipid profile were significantly higher in the NAFLD compared with the control group except for HDL which was lower but not statistically significant. This little difference among the studies may be due to the differences in the sample size and difference in body-fat distribution, in the context of a genetic predisposition among various ethnic groups.

Non-HDL cholesterol, which better correlates with small dense LDL particles and is a best predictor of all cholesterol measures of coronary artery disease event[22,23] was also calculated in this study and was found to be significantly higher in NAFLD compared with the control groups. Similarly another calculated marker which can predict ischemic heart disease like cardiac risk ratio (TC/HDL)[24] was also higher among NAFLD compared to the control group. Therefore, this study suggests that NAFLD patients in Nepal could be at higher risk of CVD, but further detail clinical and radiological assessment is required to confirm the diagnosis.

Recently, AIP has been shown to correlate strongly with small low-density lipoprotein particle size and a strong marker to predict the risk of atherosclerosis and coronary heart disease.[25-27] In this study, AIP was found to be higher among NAFLD compared to the control group but was not statistically significant. In a study done by Wang Q et al, AIP was shown to correlate strongly with NAFLD and has suggested using AIP as a regular monitoring index of NAFLD in clinical practice.[28]

CONCLUSION

Obesity and dyslipidemia is more common among the cases of NAFLD compared to the control group. Blood lipids along with their calculated ratios are significantly increased in the NAFLD. To prevent any possible cardiovascular events in NAFLD, it is essential to perform lipid profile tests more frequently.

LIMITATIONS OF THE STUDY

The study was conducted in small sample size therefore larger studies are required to support the present findings

FINANCIAL DISCLOSURE

None

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