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Research Article

Cardiovascular disease risk assessment in diabetes and metabolic syndrome patients with and without non-alcoholic fatty liver disease

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ABSTRACT

Background: Recently non-alcoholic fatty liver disease (NAFLD) has been suggested as independent cardiovascular (CVD) risk factor and many studies have shown strong links between NAFLD and CVD but NAFLD has not been related to cardiovascular mortality independently on a long term follow up. Inflammation and oxidative stress is well recognized factors for NALFD which lead to many interrelated factors contributing to cardiovascular risk. Aim: To study the cardiovascular disease risk in diabetes and metabolic syndrome patients with and without NAFLD using different risk assessment calculators.
Methods: This was a single center, prospective cross sectional study. 62 patients with diabetes and metabolic syndrome attending the endocrinology & gastroenterology clinics of Osmania General Hospital were enrolled in to the study with 31 patients in group A (NAFLD) and 31 patients in group B (Non-NAFLD). Patients were diagnosed with fatty liver by ultrasound examination.
Results: The groups were individually evaluated for cardiovascular risk assessment by PROCAM risk score, atherosclerotic cardiovascular disease (ASCVD) score and atherosclerosis Index. The means ± standard(%) deviation of Procam risk score for NAFLD group was 6.00 ± 1.00 and for Non NAFLD group it was 10.00 ± 2.00 (p=0.039). ASCVD risk score shows 5.11 ± 1.12 for NAFLD and Non NAFLD group showed 8.25 ± 2.18 (p=0.235). The Atherosclerosis index for NAFLD group was 0.24 ± 0.03 and Non NAFLD 0.18 ± 0.04 (p=0.785). The QRsik2 score for NAFLD and Non-NAFLD patients was 13.16 ± 7.56 and 17.45 ± 10.36.
Conclusions: There was no difference in CVD risk assessment when assessed with different calculators in this population.

Keywords: Non-alcoholic fatty liver disease, Coronary artery disease, PROCAM risk score, Atherosclerosis index, QRisk2, ASCVD

INTRODUCTION

In past few decades, the incidence and prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) has been increasing in Western and Asian countries.[1,2] Fatty liver disease is condition where fat is deposited in liver which is abnormal and if associated with inflammation and liver damage (Steatohepatitis) not due to alcohol intake is known as non-alcoholic fatty liver disease and the extreme form of NAFLD is non-alcoholic steatohepatitis (NASH).[3,4]

The etiology of NAFLD is not clearly defined, although a close link with the 'metabolic syndrome' characterized by obesity, glucose intolerance, insulin resistance, hyperlipidemia and hypertension has been established.[5-8] Insulin resistance is thought to play a key role in development of NAFLD.[9]

Patients with Diabetes Mellitus (DM) and Metabolic Syndrome (MS) has a significantly higher prevalence of NAFLD compared to those without diabetes and metabolic syndrome.[6] Since NAFLD is more prevalent in patients with Diabetes and metabolic syndrome, patients seems to be at more risk of cardiovascular disease. NAFLD is associated with high risk of cardiovascular disease (CVD) and atherosclerosis such as carotid artery wall thickness and lower endothelial flow-mediated vasodilation independently of classical risk factors and components of the metabolic syndrome.[10]

Many of markers for cardiovascular disease are typically present in patients with NAFLD putting these patients at higher risk of cardiovascular events.[11] Most of the follow up studies on NAFLD patients shows cardiovascular mortality as second most common cause for deaths.[12] For our ease we defined cardiovascular disease as stroke, myocardial infarction, heart attack, angina and transient ischemic attack based on the definitions derived from these risk calculators QRisk2 and atherosclerotic cardiovascular disease (ASCVD). Treatment strategies for NAFLD involve diet and lifestyle modification for weight loss and pharmacotherapy which also improves the cardiovascular risk profile.[12-14]

In present study we intend to assess the cardiovascular disease risk in patient with and without non-alcoholic fatty liver disease by different cardiovascular risk assessment tools for 10 year CVD risk.

METHODS

The risk assessment analysis for cardiovascular disease was a part of a single center, prospective, observational study. 62 patients were enrolled in to the study with 31 patients in group A (NAFLD) and 31 patients in group B (Non NAFLD). Patients visiting to endocrinology and gastroenterology department of Osmania General Hospital were evaluated for Non Alcoholic Fatty liver Disease (NAFLD) by ultrasound.

Diabetes and metabolic syndrome patients of age greater than 18 years with or without an alcohol intake of <21 units/week for men and <14 units/week[15] for women were included in the study and patients with cirrhosis or drug induced liver diseases were excluded. Metabolic syndrome was defined as per modified National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III criteria.[16] The modified waist circumference (>90 cm in men and >80 cm in women), increased TGs and low HDL cholesterol as defined above, high blood pressure (>130/85 mmHg; or on anti-hypertensive drugs), and high fasting blood glucose (FBG) (>110 mg/dL; or a known diabetic) were applied and MS was defined by the presence of three or more of these criteria. Patient's body mass index, waist hip circumference was calculated and biochemistry assessment was done.

Cardiovascular risk assessment was done by QRISK®2-2014 risk calculator, Procam risk score, ASCVD and Atherosclerosis index score which are available online, these risk calculators has been validated and hence used because of their popularity, and applicability to this population settings.

PROCAM score

Data from prospective cardiovascular munster study (PROCAM), was analyzed and a scoring system was developed for predicting global CHD risk.[17] A tailormade risk calculator was developed to study people for cardiovascular risk factors, mortality, and cardiovascular events (including MI and stroke).

Cardiovascular risk score was designed and validated based on variables like age, blood pressure, diabetes, cigarette smoking, total and low-density cholesterol, TGs and family history of myocardial infarction. PROCAM score has been regarded as a simple and accurate means of predicting risk of myocardial infarction in clinical practice.

QRisk2 score

The QRISK®2 algorithm was developed by doctors and academics working in the UK National Health Service, based on routinely collected data from many thousands of general practice's across the country. It is being used internationally and is a well-established CVD risk score. Risk factors included for calculation are self-assigned ethnicity, age, sex, smoking status, systolic blood pressure, ratio of total serum cholesterol: high density lipoprotein cholesterol, body mass index, family history of coronary heart disease in first degree relative under 60 years, townsend deprivation score, treated hypertension, type 2 diabetes, renal disease, atrial fibrillation, and rheumatoid arthritis. (http://www.clinrisk.co.uk/ClinRisk/QRISK2_overview.html)

Atherogenic index of plasma score

A significant predictor of atherosclerosis is a log (TG/HDL-C) used by some practitioners. Atherogenic dyslipidemia is a combination of low levels of HDL-Cholesterol and high levels of triglycerides. Atherogenic Index of Plasma (AIP) is based on the ratio of the values of triglycerides to high-density lipoprotein (HDL) levels, and is calculated according to the following formula (AIP=Log [TGs]/ [HDL]). The AIP has demonstrated

cardiovascular risk in several clinical trials the optimal value for AIP should be less than 0.1.[18,19]

ASCVD score

The ultimate goal of the new cholesterol practice guidelines is to reduce a person's risk of heart attack, stroke and death, atherosclerotic cardiovascular disease (ASCVD), defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke, based on the Pooled Cohort equations and lifetime risk prediction tools, heart attack and stroke are usually caused by atherosclerotic cardiovascular disease (ASCVD). ASCVD develops because of a build-up of sticky cholesterol-rich plaque. The information required to estimate ASCVD risk includes age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering medication use, diabetes status, and smoking status. (http://tools.cardiosource.org/ASCVD-Risk-Estimator/#page_about).[20]

The study was approved by the institutional ethics committee and has been registered at clinical trial registry of India (CTRI/2014/07/004725). The study was carried out in accordance with the "Ethical Guidelines for Biomedical Research on Human Participants, 2006" by the Indian Council of Medical Research and the Declaration of Helsinki, 2008. Written informed consent was obtained from all the participants.

Data analysis

Descriptive statistics was done using Microsoft excel 2013.

RESULTS

All results have been expressed as means ± Standard Deviation (SD) in Table 1. 62 patients were enrolled with diabetes and metabolic syndrome, mean age of men was (53.5 ± 9.1) and women were (48.2 ± 7.63). Patients were divided into two groups NAFLD and Non NAFLD based on ultrasound examinations. The mean age for NAFLD group was 47.87 ± 7.61 and Non NAFLD group was 50.25 ± 8.43. Cardiovascular risk assessment was done by PROCAM, ASCVD, atherosclerosis index and QRisk2. Means ± SD are mentioned in Table 2. Our results shows that patients with NAFLD are at high risk of cardiovascular disease than Non NAFLD by atherosclerosis index which takes triglycerides and HDL cholesterol for estimating risk which is more suitable for Indian population, however the Non NAFLD patients were at more risk compared to NAFLD group by PROCAM risk score, ASCVD and QRisk2 scores. There is wide variability in the cardiovascular risk assessment for these patients as assessed by different risk scores. The risk assessment is based on factors mostly related to diabetes and metabolic syndrome such as cholesterol, height, weight or BMI, age, and medical history.

Table 1: Baseline parameters.

Variable (Mean ± SD)	Group A NAFLD patients (N=31)	Group B Non-NAFLD patients (N=31)
Age (years)	47.87 ± 7.61	50.25 ± 8.43
Height (cm)	153.87 ± 6.88	149.70 ± 7.14
Weight (Kg)	76.00 ± 11.91	66.41 ± 10.43
Waist (cm)	107.03 ± 12.07	99.90 ± 8.28
Hip (cm)	107.09 ± 9.23	97.93 ± 7.67
WHR	1.00 ± 0.08	1.02 ± 0.05
BMI (kg/m^2)	32.83 ± 4.96	29.41 ± 3.61
SBP (mmHg)	122.48 ± 14.34	139.64 ± 21.15
DBP (mmHg)	79.70 ± 10.52	82.41 ± 10.89
FBG	156.87 ± 47.45	162.09 ±61.22
Creatinine	1.03 ± 0.23	1.03 ± 0.31
HbA1C (%)	8.56 ± 1.66	9.23 ± 2.21
Total cholesterol	172.88 ± 38.74	169.65 ± 39.13
LDL	96.36 ± 34.11	101.81 ± 37.98
HDL	44.25 ± 7.79	40.60 ± 8.80
Triglycerides	149.92 ± 64.54	149.94 ± 78.15

Table 2: Cardiovascular risk assessment.

Risk score (Means ± SD)	Group A NAFLD patients (N=31)	Group B Non-NAFLD patients (N=31)
PROCAM risk score (%)	6 ± 4	10 ± 11
ASCVD (%)	5.11 ± 5.84	8.25 ± 10.23
Atherosclerosis index	0.236 ± 0.20	0.18 ± 0.23
QRisk2 score (%)	13.16 ± 7.56	17.45 ± 10.36

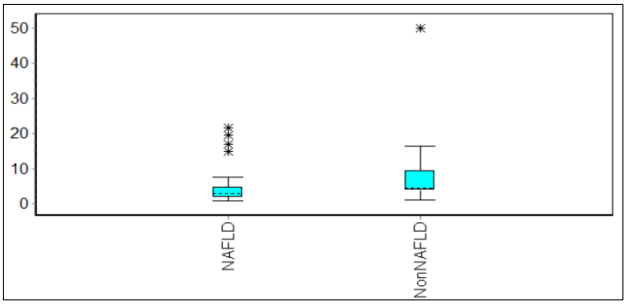

Figure 1: Box plot for ASCVD score.

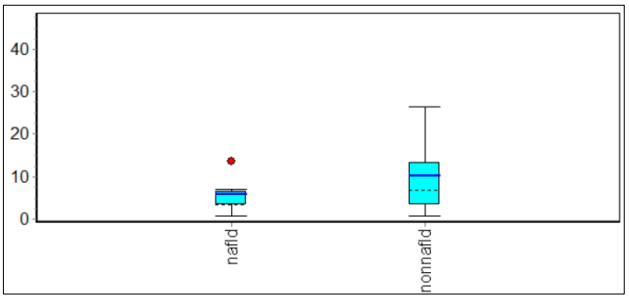

Figure 2: Box plot for PROCAM risk score.

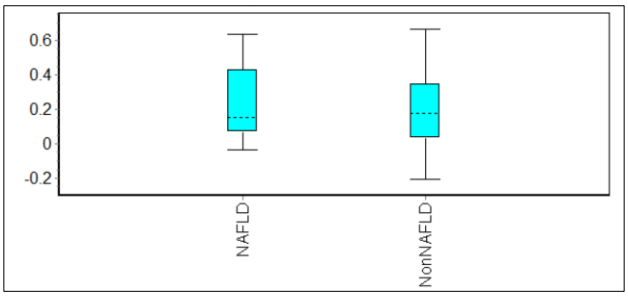

Figure 3: Box plot for atherogenic index of plasma score.

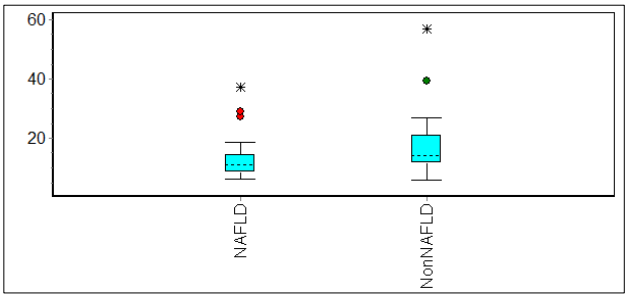

Figure 4: QRisk2 score.

DISCUSSION

The prevalence of NAFLD and NASH in general population is increasing, in obese populations, NAFLD may be present in 75% of subjects. Indeed, in the morbidly obese, steatosis (NAFLD) has been found in almost all subjects, with NASH being present in 25-70% of these individuals. Current basic and epidemiologic data reveal that the spectrum of NAFLD is closely associated with obesity, diabetes, and hyperlipidemia, a constellation of clinical problems that arise from insulin resistance[21] and also shows a strong association of NAFLD with many CVD risk factors.

Atherogenic dyslipidaemia is strongly linked to adverse CV outcome, such as ischemic heart disease, stroke, and peripheral vascular disease. TG/HDL cholesterol ratio of >4 seems to be an independent predictor of Coronary Artery Disease (CAD) development. This ratio is an attractive surrogate index of the atherogenicity of the plasma lipid profile.[22] This has been a strong predictor of cardiovascular risk in our study comparing to other risk assessments calculators.

Increase in ALT has been linked to increase in risk of CVD, the Hoorn Study showed that the association between ALT and CHD events is significant,[23] suggesting that NAFLD is associated with CHD independently of other features of the metabolic syndrome.[10]

The other cardiovascular risk assessment tools used in our study has showed mild to moderate risk for cardiovascular disease without any statistical significance on average, in these patients based on the classical risk factor, however there is need for an assessment tool to predict the risk of cardiovascular disease in patients with NAFLD with factors contributing to NAFLD only. Considering the patient medical history of Myocardial Infarction (MI), incidence was found to be much higher in NAFLD group (67.74%) than in non-NAFLD Group (38.71%).

The first step in cardiovascular risk management is targeted towards management of lipids which are considered to be strong predictor of coronary heart diseases.[24] Weight reduction with diet changes are typically suggested as the first step in the treatment of patients with this condition.[25] Treatment of NAFLD requires a consideration of which patients require treatment. Because not all cases progress to advanced liver disease, and because the goal of treatment is to improve liver-related outcomes from a liver standpoint efforts should be focused on patients with steatohepatitis and not simple steatosis. Several approaches have been used to differentiate simple steatosis and steatohepatitis. The clinical presentation of patients with simple steatosis is similar to the presentation in NASH, therefore clinical presentation cannot reliably distinguish between the two. Demographic and clinical parameters like age, gender, race, body mass index, dyslipidemia, or diabetes cannot reliably differentiate between simple steatosis and steatohepatitis.[26]

To date, no large reliable clinical trials have demonstrated efficacy in altering the natural history of NAFLD. Based on current understanding of the pathogenesis of NAFLD, investigational therapy has been targeted at reducing intrahepatic oxidant stresses and improving insulin resistance.

The risk assessment by different risk calculators is variable, however NAFLD patients are at higher risk of atherosclerosis as measured by AIP index. These risk are based on classical factors for CVD and more studies needs to be explored to find the actual cause and effect for NAFLD in progression towards cardiovascular disease. There are question being raised as to whether CVD events will occur prior to the development of liver failure in NAFLD patients, and important treatment modality for all patients with NAFLD is aggressive treatment of CVD risk factors. Irrespective of the pathophysiological mechanism, treatment should be aimed to reduce overall risk factors contributing for cardiovascular deaths. Also these variations in assessment of CVD risk by different methods also need to be standardize including specific symptoms of NAFLD.

Studies have shown strong association of NAFLD with CVD risk independently[27] but has not significantly increased the cardiovascular mortality or risk during the follow up in population with diabetes[28] and metabolic syndrome[29] which are in consistent with our findings.

CONCLUSION

We tried to estimate CVD risk in diabetic and metabolic syndrome patients with NAFLD and without NAFLD using different calculators and noticed that presence of NAFLD does not seem to have any major effect on CVD risk as estimated by different CVD risk calculators in our study population although diabetes itself is a high risk factor for cardiovascular disease. Large studies with longer follow up for CVD events are required in these patients to see an effect for cardiovascular risk contributed by NAFLD independently in addition to other risk factors.

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