To Find the Incidence of Insulin Resistance and Dyslipidaemia in Non-Alcoholic Fatty Liver Disease – A Cross Sectional Study from Amritsar, Punjab

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ABSTRACT

BACKGROUND

A high prevalence of non-alcoholic fatty liver disease (NAFLD) has been reported specially among patients with diabetes mellitus, however the prevalence of non-alcoholic fatty liver disease among non-diabetic individuals is also considerable. Some reports have proposed that NAFLD is more closely associated with insulin resistance rather than metabolic syndrome itself and fasting hyperinsulinemia is common in individuals with impaired glucose homeostasis and is widely accepted surrogate measure of insulin resistance. In this study, we wanted to find out the incidence of insulin resistance and dyslipidaemia in non-alcoholic fatty liver disease.

METHODS

This was a cross sectional study undertaken in Sri Guru Ram Das Institute of Medical Sciences and Research, a tertiary care hospital, conducted on 100 consecutive non diabetic patients with diagnosis of NAFLD on ultrasonography (USG) of whole abdomen. In all the patients, fasting plasma glucose, HbA1c, fasting plasma insulin levels and fasting lipid profile were measured. Insulin resistance (IR) using homeostatic model assessment (HOMA IR) formula was calculated and analysed.

RESULTS

29.2 % patients of grade 1, 36.6 % of grade 2 and 81.8 % of grade 3 fatty liver had raised serum cholesterol levels (P = 0.005). 31.3 % of grade 1, 56.1 % of grade 2 and 72.7 % of grade 3 fatty liver had raised serum triglyceride levels (P = 0.011). 33.3 % patients of grade 1, 48.8 % of grade 2 and 72.7 % of grade 3 fatty liver had raised serum LDL cholesterol levels (P = 0.043). 50.0 % of grade 1, 70.7 % of grade 2 and 81.8 % of grade 3 fatty liver low serum high density lipoproteins (HDL) cholesterol levels (P = 0.047). Insulin resistance was present in 39 % patients of NAFLD. 6.3 % patients of grade 1, 63.4 % of grade 2 and 90.9 % of grade 3 fatty liver had insulin resistance (HOMA-IR ≥ 1.8).

CONCLUSIONS

It was concluded that dyslipidaemia and insulin resistance had a significant relationship with NAFLD.

KEYWORDS

Non-Alcoholic Fatty Liver, Dyslipidemia, Insulin Resistance

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BACKGROUND

Non-alcoholic fatty liver disease is the most common cause of chronic liver disease in Western countries and is also predicted to become the most frequent indication for liver transplantation by 2030.[1] The definition of NAFLD includes evidence of hepatic steatosis, either by imaging or by histology and also there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders.[2]

Other aetiologies leading to similar hepatic histology must be ruled out including excessive alcohol consumption, chronic viral hepatitis, other chronic liver diseases e.g.: Wilson's disease, hemochromatosis, autoimmune hepatitis, cholestatic liver disease, conditions like starvation, lipodystrophy, celiac disease, Cushing's disease and medications (corticosteroids, methotrexate, diltiazem, oxaliplatin, amiodarone, isoniazid, highly active anti-retroviral therapy etc). Current guidelines recommend utilizing criteria requiring an alcohol exposure of less than 30 g/d for men and less than 20 g/d for women as a component of NAFLD diagnosis.[3] In the general adult population, overall NAFLD prevalence is higher in men than women (22 - 42 % in men vs. 13 - 24 % in women).[4]

The major risk factors for NAFLD are central obesity, type 2 diabetes mellitus, dyslipidaemia and insulin resistance, older age, elevated serum aminotransferases (≥ 2 times the upper limit of normal), body mass index (BMI) ≥ 28 kg/m^2 [8.] Patients with NAFLD may have hyperlipidaemia, hyperglycaemia, hyperinsulinemia, and reduced insulin sensitivity. Aminotransferases are often mildly or moderately increased, with aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio less than 1.[5]

Grading	
Grade 1 (mild)	Steatosis: Up to 66 % Ballooning: Occasional in zone 3 Intralobular inflammation: Scattered polymorphs ± lymphocytes Portal inflammation: No or mild
Grade 2 (moderate)	Steatosis: Any degree Ballooning: Obvious, predominantly zone 3 Intralobular inflammation: Polymorphs and chronic inflammation Portal inflammation: Mild to moderate
Grade 3 (severe)	Steatosis: Panacinar Ballooning: Ballooning and disarray obvious, predominantly in zone 3 Intralobular inflammation: Scattered polymorphs ± mild chronic inflammation Portal inflammation: Mild or moderate

Histological Grading and Staging of NAFLD[24]

On ultrasound abdomen, steatosis is graded as follows:[6]

- Grade 0 - The echotexture of the liver is normal.
- Grade 1 - Slight and diffuse increase of liver echogenicity with normal visualization of the diaphragm and of the portal vein wall.
- Grade 2 - Moderate increase of liver echogenicity with slightly impaired appearance of the portal vein wall and the diaphragm.
- Grade 3 - Marked increase of liver echogenicity with poor or no visualization of portal vein wall, diaphragm and posterior part of the right liver lobe.

Dyslipidemia represents a key factor in NAFLD. It has been suggested that raised serum triglycerides, raised serum LDL cholesterol and low serum HDL cholesterol levels are the risk factors of NAFLD. Overweight and obese individuals with low serum HDL cholesterol levels or high diastolic blood pressure also have greater odds of having NAFLD.[7] HOMA-IR has been validated using the euglycemic hyperinsulinaemic clamp method, which is an expensive and invasive gold-standard method.

Previously identified anthropometric and metabolic parameters other than fasting plasma glucose in a non-diabetic population showed a significant correlation with HOMA-IR on multivariate analysis. Body mass index (BMI), serum triglyceride (TG) levels and systolic blood pressure (SBP) significantly correlated with insulin resistance in men and women. Serum high-density lipoprotein cholesterol (HDL-C) levels were found to be inversely correlated with insulin resistance by multiple logistic regression analysis in men.[52]

The prevalence of insulin resistance in NAFLD patients with hypercholesterolemia, low serum HDL cholesterol or increased serum LDL cholesterol is much higher than that of patients without dyslipidaemia. However, the prevalence rates of insulin resistance between patients with hypertriglyceridemia or normal serum triglyceride levels are similar.[8]

Thus, hepatic steatosis is epidemiologically associated with insulin resistance. By using gold standard measures of insulin action, it has been consistently shown that hepatic steatosis, independent of adiposity, is associated with impaired insulin action on liver, skeletal muscle, and adipose tissue in both lean individuals and nondiabetic individuals with obesity.[9]

Objectives

1. To assess insulin resistance by fasting plasma glucose and fasting insulin levels in patients with non-alcoholic fatty liver disease.
2. To estimate fasting plasma glucose, HbA1c, fasting insulin levels and fasting lipid profile in non-alcoholic fatty liver disease.
3. To find out relationship between fasting lipid profile and non-alcoholic fatty liver disease.

METHODS

The present cross-sectional study was conducted in a tertiary care hospital, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar from March 2019 to March 2020, among the patients who had palpable liver on physical examination and had history of alcohol consumption < 30 g/day for men and < 20 gm/day for women were sent for ultrasound whole abdomen which was done by the qualified radiologist in the department of radiology and those who satisfied the inclusion and exclusion criteria. 100 patients of NAFLD diagnosed on ultrasonography whole abdomen were taken for study, the prevalence of dyslipidaemia and insulin resistance by HOMA IR formula was calculated.

$$HOMA\ IR = \frac{HOMA - IR = fasting\ Plasma\ insulin\ (microU/L) \times fasting\ Plasma\ (nmol/L)}{22.5}$$

Value of HOMA IR more than 1.8 was considered insulin resistance

Inclusion Criteria

Patients above 18 years of age who had palpable liver on physical examination or who had history of alcohol consumption < 30 g/day for men and < 20 gm/day for women were sent for ultrasound whole abdomen which was done by the qualified radiologist in the department of radiology and diagnosed as NAFLD on ultrasound abdomen visiting out-patient department (OPD) or indoor of Department of Medicine in Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar

Exclusion Criteria

1. Patients with comorbidities (congestive heart failure, chronic kidney disease).
2. Patients who are chronic alcohol users.
3. Patients using drugs causing either hepatic steatosis or toxicity (amiodarone, valproate, tamoxifen, and methotrexate etc.)
4. Patients who are overt diabetic and already on anti-diabetic drugs.
5. Patients having viral hepatitis.
6. Patient who are hypothyroid or hyperthyroid.

Statistical Analysis

The data collected was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then was exported to data editor page of Statistical Package for Social Sciences (SPSS version 20) (SPSS Inc., Chicago, Illinois, USA).

Descriptive statistics included computation of percentages, means and standard deviations. The statistical tests applied for analysis were Pearson's chi-square test, t-test, and one-way analysis of variance. For all tests, confidence interval and P value was set at 95 % and ≤ 0.05 respectively.

Sample Size

$$n = \frac{\left(Z_{1-\alpha/2}\right)^2 (\mathrm{p})(\mathrm{q})}{d^2}$$

$$n = \frac{(1.96)^2 (34)(66)}{10^2}$$

$$n = 86.20$$

$$n = 87$$

$$n = 87 + 8\ (considering\ 10\ \%\ dropout\ rate\ of\ subects)$$

$$sample\ size\ (n) = 94$$

Minimum sample size is 94, here in this study 100 samples have been taken.

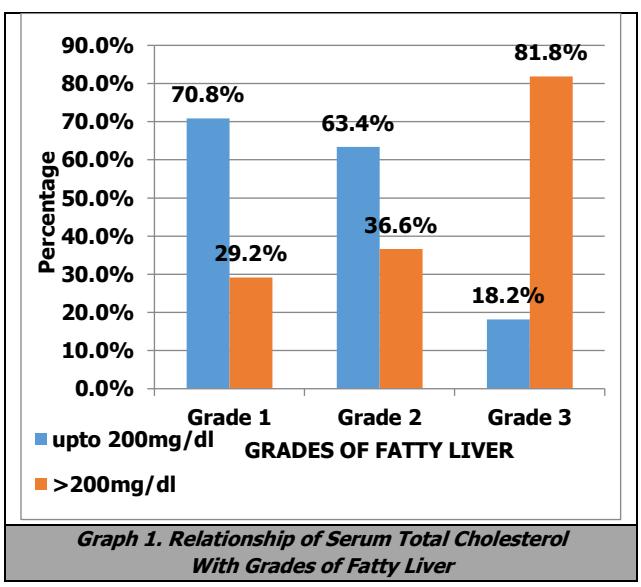
RESULTS

Most of the patients (36 %) belonged to 4th to 6th decade of life followed by 6th to 8th decade (31 %). Mean age was 53.7 ± 17.8 Years. Male to female ratio was 1.27:1.48 % patients were having fatty liver grade 1, 41 % were grade 2 and 11 % were having grade 3 fatty liver on USG abdomen. Maximum patients (57 %) belonged to overweight group with a mean value of 27.0 ± 3.0 Kg/m^2. Out of 48 patients of grade 1 fatty liver, 34 (70.8 %) patients had fasting serum total cholesterol levels within normal range of up to 200 mg/dl while only 14 (29.2 %) patients had raised levels of fasting serum total cholesterol (> 200 mg/dl).Out of 41 patients of grade 2 fatty liver, 26 (63.4 %) patients had normal levels of fasting serum total cholesterol levels while 15 (36.6 %) patients had raised levels of fasting serum total cholesterol levels (> 200 mg/dl). Out of 11 patients of grade 3 fatty liver, only 2 (18.2 %) patients had normal fasting serum total cholesterol levels of up to 200 mg/dl while majority of patients i.e. 11 (81.8 %) patients had raised fasting serum total cholesterol levels. Thus, with increasing grades of fatty liver, more percentage of patients had raised fasting serum total cholesterol levels and the relationship was significant (P = 0.005). Out of 48 patients of grade 1 fatty liver, 33 (68.8 %) patients had fasting serum triglyceride levels of up to 150 mg/dl while 15 (31.3 %) patients had raised fasting serum triglyceride levels of > 150 mg/dl.

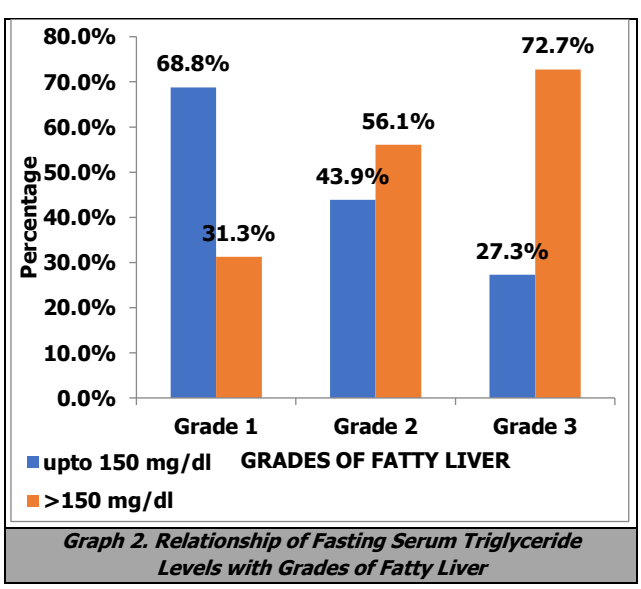
Out of 41 patients of grade 2 fatty liver, 18 (43.9 %) patients had normal range of fasting serum triglyceride levels while 23 (56.1 %) patients had raised fasting serum triglyceride levels (> 150 mg/dl).Out of 11 patients of grade 3 fatty liver, only 3 (27.3 %) patients had normal fasting serum triglyceride levels of up to 150 mg/dl, while 8(72.7 %) patients had raised fasting serum triglyceride levels (> 150 mg/dl). Thus, with increasing grades of fatty liver, more percentage of patients had raised fasting serum triglyceride levels and the relationship was significant (P = 0.011). Out of 48 patients of grade 1 fatty liver, 32 (66.7 %) patients had normal fasting serum LDL cholesterol levels while 16 (33.3 %) patients had raised fasting serum LDL cholesterol levels of > 99 mg/dl. Out of 41 patients of grade 2 fatty liver, 21 (51.2 %) patients had fasting serum LDL cholesterol levels of up to 99 mg/dl while 20 (48.8 %) patients had raised fasting serum LDL cholesterol levels of > 99 mg/dl. In grade 3 fatty liver, 3 (27.3 %) patients had normal fasting serum LDL cholesterol levels while 8 (72.7 %) patients of grade 3 fatty liver had raised fasting serum LDL cholesterol levels of > 99 mg/dl. Thus, with increasing grades of fatty liver, from grade 1 to grade 3, percentage of patients with raised levels of fasting serum LDL levels increased and this relationship was significant (P = 0.043). Out of 48 patients of grade 1 fatty liver, 24 (50 %) patients had normal fasting serum HDL cholesterol levels while 24 (50 %) patients had decreased fasting serum HDL cholesterol levels of < 40 mg/dl. Out of 41 patients of grade 2 fatty liver, 12 (29.3 %) patients had normal fasting serum HDL cholesterol levels while 29 (70.7 %) patients had decreased fasting serum HDL cholesterol levels of < 40 mg/dl. In grade 3 fatty liver, 2 (18.2 %) patients had normal fasting serum HDL cholesterol

levels while 9 (81.8 %) showed decreased fasting serum HDL cholesterol levels of < 40mg/dl. Thus, as the grades of fatty liver increased from grade 1 to 3, percentage of patients with decreased levels of fasting serum HDL cholesterol levels increased and this relationship was significant (P = 0.047). Out of 48 patients of grade 1 fatty liver, 45 (93.8 %) patients had HOMA IR of ≤ 1.8 thus had no insulin resistance and only 3 (6.3 %) patients had HOMA IR > 1.8 thus having insulin resistance.

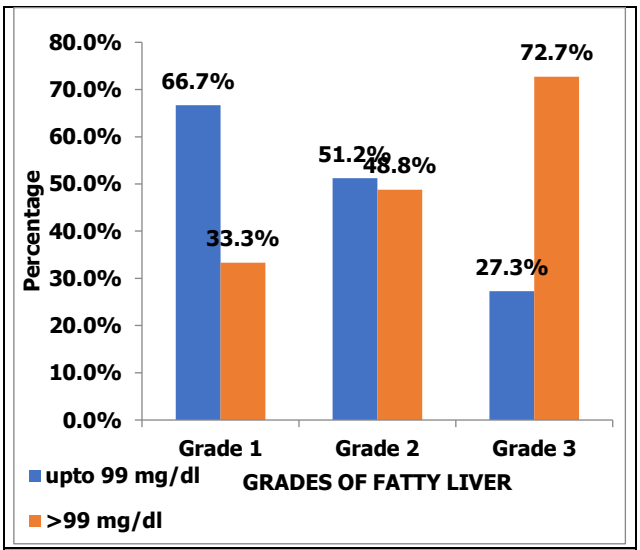
Among 41 patients of grade 2 fatty liver, 15 (36.6 %) had HOMA IR ≤ 1.8 and had no insulin resistance while 26 (63.4 %) had HOMA IR > 1.8 and thus had insulin resistance. While in 11 patients with grade 3 fatty liver, only 1 (9.1 %) had HOMA IR ≤ 1.8 and had no insulin resistance and 10 (90.9 %) had HOMA IR > 1.8 value and thus had insulin resistance. As such in patients with grade 1 fatty liver, only 6.3 % had insulin resistance, in grade 2 fatty liver 63.4 % patients had insulin resistance while in grade 3 fatty liver, 90.9 % patients had insulin resistance. Thus, patients with increasing grades of fatty liver, higher percentage of patients had insulin resistance and the relationship was significant (P = 0.0001).



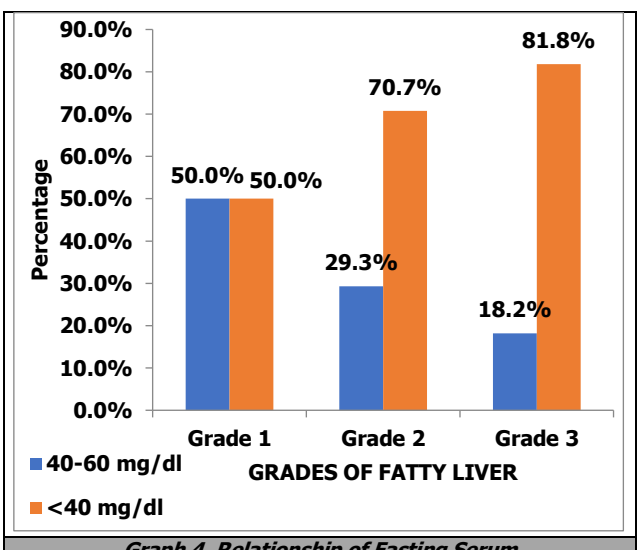
Graph 1. Relationship of Serum Total Cholesterol With Grades of Fatty Liver



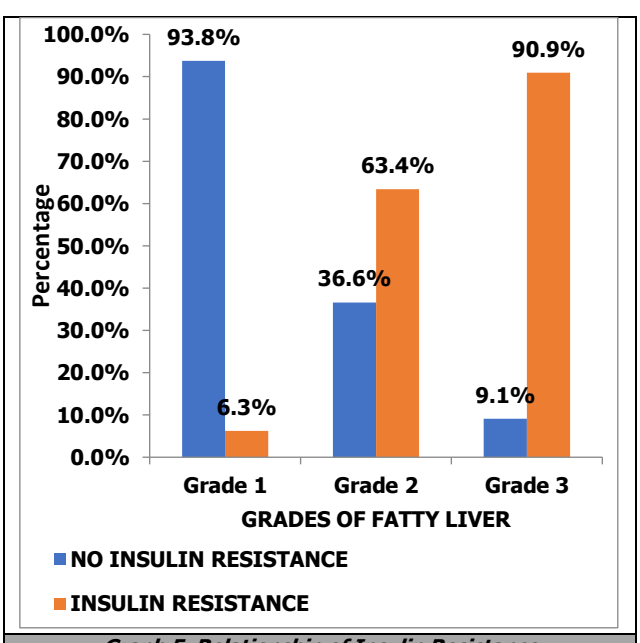
Graph 2. Relationship of Fasting Serum Triglyceride Levels with Grades of Fatty Liver



Graph 3. Relationship of Fasting Serum LDL Cholesterol Levels with Grades of Fatty Liver



Graph 4. Relationship of Fasting Serum HDL Cholesterol Levels with Grades of Fatty Liver



Graph 5. Relationship of Insulin Resistance with Grades of Fatty Liver

DISCUSSION

NAFLD is the leading cause of chronic liver disease in Western countries and is currently an emerging disease in the developing countries also. NAFLD is the hepatic manifestation of the metabolic syndrome and frequently coexists with obesity, dyslipidaemia and insulin resistance. It is generally assumed that the incidence and the prevalence of NAFLD is rising proportionately. NAFLD is now a global public health problem that requires the attention and management in countries where the prevalence is increasing and now affects > 20 – 25 % of the adult population. Insulin resistance is an almost universal finding in non-alcoholic fatty liver disease. Insulin resistance in NAFLD is characterized by reduction in whole-body, hepatic and adipose tissue insulin sensitivity. Insulin resistance contributes to the development of fatty liver by impairing the ability of insulin to suppress lipolysis, leading to increased delivery of free fatty acids (FFAs) to the liver.

In the present study, 27 % patients were having normal BMI, 57 % were overweight and 16 % were obese. In a study by Jain V et al. a high prevalence of NAFLD (62.5 %) was observed in the overweight/obese adolescents. BMI was positively associated with a higher risk of NAFLD.[10,11] In the present study, out of 100 patients, patients having high serum total cholesterol, high serum triglyceride, high serum LDL cholesterol and low serum HDL cholesterol levels were 38 %, 46 %,44 % and 62 % respectively. In relationship with grades of fatty liver, percentage of patients having abnormal serum total cholesterol levels increased from grade 1 (29.2 %) to grade 3 fatty liver (81.8 %) (P = 0.005). 46 % patients had serum triglycerides levels >150 mg/dl. 31.3 % patients of grade 1 fatty liver, 56.1 % of grade 2 fatty liver and 72.7 % of grade 3 fatty liver had high levels of serum triglycerides (P = 0.011).33.3 % patients of grade1, 48.8 % of grade 2 and 72.7 % of grade 3 fatty liver had raised serum LDL cholesterol levels and the relationship was significant (P = 0.043). Out of 100 patients, 62 % patients have low serum HDL cholesterol levels. 50 % patients with grade 1 fatty liver, 70.7 % with grade 2 fatty liver and 81.8 % with grade 3 fatty liver had low serum HDL cholesterol levels and the relationship was significant with increasing grades of fatty liver (P = 0.047).

Peng K et al. studied the prevalence of NAFLD in patients with abnormal serum lipid indicators. Subjects with elevated total serum cholesterol, serum triglycerides and serum LDL cholesterol and reduced serum HDL cholesterol in mild and moderate to severe NAFLD group were analysed and concluded that these parameters were significantly related with NAFLD (P = 0.001). This study demonstrated that dyslipidaemia was more prominently associated with NAFLD and 2 or more abnormal serum lipid indexes were independently associated with NAFLD occurrence.[12,13]

Marchesini G et al. studied total serum cholesterol levels, high serum triglycerides and low serum HDL cholesterol levels along with waist circumference, waist hip ratio and BMI in 120 patients of NAFLD. They concluded that hypertriglyceridemia was present in 64 % (P = 0.002) and low HDL cholesterol level was present in 42 % patients. This study concluded that abnormally high levels of serum triglycerides and low serum HDL cholesterol levels (mean ± SD = 169 ± 106) had a significant relationship with NAFLD (P = 0.06 and 0.019 respectively).[14] Sun DQ et al. studied the relationship between serum LDL cholesterol and NAFLD. Their results suggested that patients with higher serum LDL cholesterol levels were more likely to develop NAFLD than subjects with lower serum LDL cholesterol levels and demonstrated that increased levels of serum LDL cholesterol within the normal range have an independent relationship with an elevated risk of NAFLD (P < 0.001). Thus, the serum LDL cholesterol levels within the normal range appear to play a significant role on the prevalence and incidence of NAFLD.[15]

Trojak A et al. analysed and studied relationship of NAFLD with alanine transaminases, serum HDL cholesterol levels, waist circumference and serum total cholesterol and concluded that there was significantly higher values of alanine transaminase (P = 0.033), lower values of serum HDL cholesterol (P < 0.001), waist circumference above normal (P = 0.007) and total serum cholesterol (P = 0.0079). These parameters were considered as positive predictors of NAFLD except serum HDL cholesterol (P = 0.0032) which was a negative predictor of NAFLD. Low concentrations of serum HDL cholesterol and higher concentrations of serum triglycerides were significant.[16] The present study showed that raised serum total cholesterol levels, serum triglyceride levels, serum LDL cholesterol levels and low serum HDL cholesterol levels i.e. all lipid indexes were associated with increasing grades of fatty liver. The relationship was significant and was comparable to the above-mentioned studies.

Hypertriglyceridemia was as high as 64 % (P = .002), a low HDL-cholesterol level was present in 30 % to 42 % of cases and the arterial pressure criteria were fulfilled in 34 % to 83 % of cases. In study by Kathleen E. Corey, MD, MPH1, Raj Vuppalanchi, MD2, Laura A. Wilson, ScM3, Oscar W. Cummings, MD2, and Naga Chalasani, MBBS2 for the NASH CRN. The dyslipidaemia of NAFLD and NASH has previously been characterized by hypertriglyceridemia, elevated LDL, elevated total cholesterol and low HDL. Our study confirms these findings and demonstrates that in addition to these parameters, non-HDL-C is the most common lipid abnormality seen in patients with NASH in the PIVENS trial. In fact, the present study found that while LDL was less frequently elevated in those with NASH.

In the present study, in patients with grade 1 fatty liver only 6.3 % had insulin resistance and in patients grade 2 fatty liver, 63.4 % had insulin resistance while in grade 3 fatty liver, 90.9 % patients had insulin resistance. Therefore, the insulin resistance increased with increase in grade of fatty liver and it was significant (P = 0.0001). Li M et al. studied prevalence of insulin resistance in 600 patients of NAFLD and concluded that the prevalence of insulin resistance in NAFLD patients with hypercholesterolemia, low serum HDL cholesterol or increased serum LDL cholesterol was much higher than that of patients without dyslipidaemia (P = 0.05). The prevalence of insulin resistance (HOMA IR = 2.6 ± 1.6) in the NAFLD groups was 37.8 % and thus insulin resistance was accepted as playing a key role in the development and progression of NAFLD.[8,10]

Suresh S et al. studied altered glycaemic and lipid parameters and prevalence of insulin resistance in non-alcoholic fatty liver disease on 100 patients of NAFLD. About 60 % of subjects with NAFLD had raised serum total cholesterol values. Serum triglyceride levels were found to be increased in 43 % of subjects, and serum low-density lipoprotein cholesterol was high in 44 % of subjects. It was found that 46.6 % of males and 59.26 % of females were having abnormal serum HDL cholesterol values and also concluded that 66 subjects had insulin resistance (IR) (IR > 2.5), indicating the data that insulin resistance plays a central role in the pathogenesis of NAFLD.[11,17]

In a study by Alkassabany YM et al. insulin resistance and hyperinsulinaemia were recognised as essential components in the development of NAFLD. In this study, HOMA-IR was significantly associated with NAFLD. Interestingly, their study showed that odds ratio of NAFLD increased with increasing percentile of HOMA-IR which consequently confirms the strong association and linear relationship between insulin resistance and NAFLD. Value ranged in cases from 1.0 to 10.3 with a median of 2.8 with (mean ± SD = 2.4 ± 1.3).[13,18] Present study also showed that the insulin resistance had a significant relationship with NAFLD (P = 0.0001) and the results are comparable to these studies.

CONCLUSIONS

1. There was a strong association between low serum HDL cholesterol levels (62 %), raised fasting serum triglyceride levels (46 %), raised fasting serum LDL cholesterol levels (44 %), raised fasting serum total cholesterol levels (38 %) and NAFLD.
2. Insulin resistance was present in 39 % patients and there was strong association and linear relationship between insulin resistance and increasing grades of NAFLD.
3. Patients with NAFLD especially with grade 2 and grade 3 fatty liver should be assessed for dyslipidaemia, insulin resistance and other aspects of metabolic syndrome.

Limitations of the Study

a) All criteria of metabolic syndrome were not included.
b) HOMA-IR was used as an index of insulin resistance. It may sometimes fail to show a close relationship with the whole-body insulin resistance which can be assessed by using the euglycemic clamp method.
c) Liver biopsy was not done for the diagnosis of NAFLD.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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