A study on the altered glycemic and lipid parameters and prevalence of insulin resistance in nonalcoholic fatty liver disease

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ABSTRACT

Introduction: Nonalcoholic fatty liver disease (NAFLD) is a hepatic disorder that develops in the absence of alcohol intake. Obesity and diabetes are considered risk factors for the development of fatty liver; however, whether fatty liver is the cause or consequence of these conditions is not yet clear. Insulin resistance (IR) is found to be a common risk factor for the development of diabetes, obesity and fatty liver. **Aims and Objectives:** The aim and objective of this study is to determine the prevalence of undetected diabetes, dyslipidemia, and IR in subjects with NAFLD. **Materials and Methods:** In apparently healthy 100 subjects, with ultrasound diagnosis of fatty liver, fasting and postprandial blood sugar levels, fasting insulin levels, and fasting lipid profile were checked. IR value was estimated using homeostatic model assessment-IR formula. Appropriate statistical methods were adopted to analyze the data. **Results:** A total of 66 subjects out of the 100 had IR. It was noted that IR significantly correlated with raised fasting blood sugar and fasting plasma insulin values. There was no significant correlation between IR and lipid profile values. **Conclusion:** The chance of developing NAFLD was high if the subjects are having IR, or vice versa. There was an increased prevalence of prediabetes and diabetes in the subjects with NAFLD. Waist circumference, rather than body mass index, was found to be a strong predictor of central adiposity and IR.

Keywords: Dyslipidemia, insulin resistance, nonalcoholic fatty liver disease, obesity, type 2 diabetes mellitus

Introduction

Nonalcoholic fatty liver disease (NAFLD) refers to a condition where there is excess fat accumulation in the form of triglycerides (TGs) in liver. NAFLD is primarily considered disease of middle age group (40–49 years); although it is also found in pediatric and elderly age groups. A subgroup of the patients having NAFLD can have liver cell inflammation in addition to fat accumulation nonalcoholic steatohepatitis (NASH). NAFLD and NASH are asymptomatic conditions and are usually detected on routine ultrasound screening of apparently healthy population. There may be a mild elevation of liver transaminases (42%–90%). The only confirmatory test available for this condition is liver biopsy.

The prevalence of NAFLD has doubled during the last 20 years. Simple steatosis in NAFLD does not correlate with increased mortality or morbidity, but progression to NASH increases the risk of cirrhosis, liver failure, and hepatocellular carcinoma. Recently, liver disease has been recognized as a major complication of Type 2 diabetes with mortality rate for cirrhosis greater than that for cardiovascular disease.

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Materials and Methods

- Study area - Health check-up department of our hospital (outpatient basis)
- Study population - Apparently healthy individuals, aged between 20 and 60 years, coming for routine health check up to our hospital are included in the study
- Sample size - 100
- Study design - Cross-sectional study
- Study Duration - 6 months.

Methodology

Apparently healthy 100 individuals, aged between 20 and 60 years, coming for routine health check up to our hospital, within the study duration of 6 months were included in the study. They have their height, weight, body mass index (BMI), liver function tests, fasting blood sugars and postprandial blood sugars (FBSs and PPBSs), serology, fasting lipid profile, and ultrasound (USG) abdomen (along with other tests) done routinely as part of their periodic health assessment. Those with sonological evidence of fatty liver were further studied. The exclusion criteria were those with significant comorbidities, those who are chronic alcohol users (for occasional users, those who have consumed alcohol in the last 1 month were excluded), those using drugs causing either hepatic steatosis or toxicity. Patient who is already diabetic (on treatment) and those having viral hepatitis on serology were also excluded. Informed consent was taken from the eligible subject before recruiting in the study. The study was approved by the institutional scientific and ethics committee.

The prevalence of fatty liver can be made out by calculating the percentage between number of people having fatty liver change on USG (X) and total number of people who did USG as part of their health check-up (Y).

Prevalence of fatty liver = X/Y × 100

From those with fatty liver report, people with altered glucose and fat metabolism, i.e., FBS >110 mg/dl, PPBS >140 mg/dl, total cholesterol >200 mg/dl, TG->150 mg/dl, high-density lipoprotein (HDL)-<40, and <50 mg/dl in men and female, respectively, were found out.

Fasting insulin level is tested in those with fatty liver (cost of the test was funded by hospital research foundation). From this fasting insulin value, insulin resistance (IR) is calculated with the homeostatic model assessment (HOMA) formula:

$$HOMA = \frac{Fasting\ Insulin \times Fasting\ Glucose}{22.5}$$

If the above value is >1.8–2.0, it suggests that person has IR.

The prevalence of obesity was calculated from abdominal waist circumference (WC) and from BMI values. The WC was measured using a nonstretchable fiber measuring tape at the point midway between the costal margins and the iliac crests at full expiration.

Abdominal WC (for considering obesity) is (Asians).

For men >90 cm and females, it is >80 cm.

BMI is calculated by taking measurements of height and weight of the subjects.

$$BMI = \frac{weight\ in\ kg}{\left(Height\ in\ metre\right)^2}$$

Person is considered obese if his BMI >25(Asian guidelines).

Statistical method used

1. Software used is SPSS version 17.0 (233 South Wacker Drive, 11th Floor Chicago, IL 60606-6412, USA.)
2. Association between categorical variable can be found out by Chi-square test
3. The cutoff for *P* = 0.05 (<0.05-signifiacant).

Results

The present study was a cross-sectional study of asymptomatic, apparently healthy controls in the middle age group, who came for periodic health assessment and later found to have ultrasound diagnosis of NAFLD. Among the 1931 subjects who underwent USG in the 6 months study period as part of their routine health check-up, 591 participants (30.6%) had NAFLD; thus making the prevalence of NAFLD as 30.6%.Out of 591,100 samples were taken for the present study after considering exclusion and inclusion criteria. Majority of subjects were in the age group 41–50 years. Among 100 samples, 73 were male, and 27 were female with male:female ratio of 2.7:1.

Out of 100, 66 subjects had IR (IR >2.5), indicating the data that IR plays a central role in the pathogenesis of NAFLD. It was also observed that NAFLD was found in 34% of subjects without IR.

In the study subjects, 16% had raised FBS values, and 14% had raised PPBS values. Blood sugar values were in diabetic range for 5% of those with high FBS and 3% of those with high PPBS (though not detected previously). About 94% of subjects with raised FBS and 78% of subjects with raised PPBS value had IR.

About 60% of subjects with NAFLD had raised total cholesterol values. TG was found increased in 43% of subjects, and low-density lipoprotein (LDL) was high in 44% of subjects. It was found that 46.6% of males and 59.26% of females were having HDL values. There was no significant association found between lipid profile variables and IR.

Majority of the subjects in the study group were obese (78%). In the remaining group, 11% were overweight, and 11% were of normal weight. None were underweight. About 90.4% of

male subjects and 85.2% of female subjects had raised WC. $P = 0.063$ was found while testing the association between IR and BMI, indicating that there was a marginal association between these two variables. It was observed that >60% of subjects who were either obese/overweight had high IR. Among those with normal BMI, IR was seen in 36%. It was found that there was a significant association between WC and IR. In those subjects with high WC, IR was found high in 74.2% of men and 73.9% of females, respectively. None of the subjects with low or normal WC had high IR.

Fasting plasma insulin (FPI) was found high in 74% of the subjects. More than half of those who were overweight and more than three-fourth of those who were obese had high FPI levels ($P = 0.005$).

Discussion

NAFLD is a liver disorder that develops in the absence of alcohol intake emergence of NAFLD poses a major health burden as its prevalence is steadily increasing. It behaves like any other chronic liver disease and may progress on to cirrhosis and hepatocellular carcinoma. NAFLD is usually associated with IR and obesity. There is increased risk of cardiovascular disease when accompanied by diabetes and components of metabolic syndrome. An additional feature is that it remains asymptomatic till features of chronic liver disease appear. The mechanisms underlying the development of NAFLD are not completely understood but likely involve a combination of increased free fatty acids and possibly decreased lipid oxidation in the liver as a result of IR. Currently, there are no recommended treatment guidelines for NAFLD. Various drugs tried are insulin-sensitizing agents, lipid-lowering drugs, antioxidants, and cytoprotectives. Preventive measures taken are low-calorie diet, high fiber intake, regular exercise and weight reduction and to avoid overindulgence in alcohol.

The present study was a hospital-based cross-sectional study. In the present study, among the 1931 subjects who underwent ultrasonogram as part of their routine health check-up, 591 subjects (30.6%) had NAFLD. The prevalence of NAFLD in Indian population ranges from 5% to 28%, which is comparable to the West.[1] A study from coastal regions of India found that 39 (24.5%) of 159 healthy attendants of patients had evidence of fatty liver on ultrasound (USG).[2] These data show that the prevalence of nonalcoholic fatty liver in asymptomatic healthy individuals is increasing.

Insulin resistance and nonalcoholic fatty liver disease

The present study showed that 66 subjects of the total 100 asymptomatic NAFLD subjects had high IR (>2.5) as measured by HOMA-IR (IR cutoff of 2.5 was taken as per suggestion of Institutional Scientific Committee). The rest 34 subjects had NAFLD with normal IR (<2.5) [Figure 1]. The presences of IR have become recognized as the most common
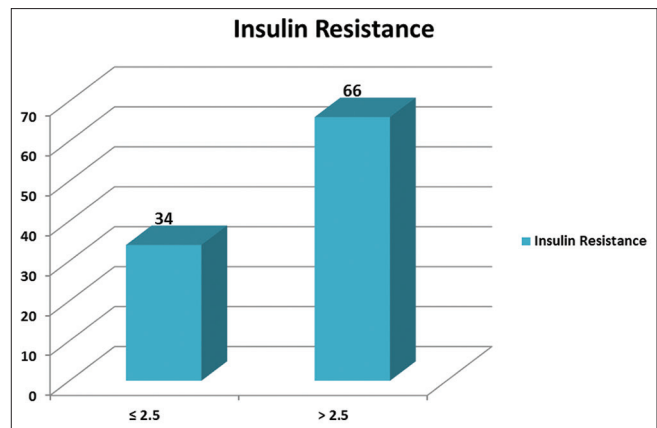

Figure 1: Examination of cell frequency showed that the majority of the study group (66%) had abnormally high-insulin resistance. It was also observed that nonalcoholic fatty liver disease was found in 34% of subjects without insulin resistance (insulin resistance cut off of 2.5 taken as per suggestion of scientific committee)

underlying risk factor for the development of NASH.[3] In fact, few studies have suggested that the presence of fatty liver is a very early and sensitive indicator of IR. NAFLD is strongly associated with both hepatic and adipose tissue IR as well as reduced whole-body insulin sensitivity.[4]

Mean age of the study population was 42.1 years (standard deviation +8.66). Majority of the subjects were in the age group of 41–50 years (42 out of 100). This was comparable to the global data that highest prevalence of NAFLD is in the age group of 40–49 years. The prevalence of NAFLD appears to increase with age, especially through the fourth to sixth decade of life.[5] The present study showed that IR was independent of age group. Every decade of age contains >50% patients with high IR levels.

There were 73 males and 27 females in the study group (Male-to-Female ratio of 2.70:1). Recent literature review suggests that NAFLD occurs equally in men and females. The Dionysos study supports that gender was not a risk factor for NAFLD in general population.[6] In the present study, gender difference had no association with IR in NAFLD, i.e., >60% of both gender groups had high IR value. In the present study, 21% of subjects had raised serum glutamic-oxaloacetic transaminase (SGOT) aspartate aminotransferase (AST), and 78% had raised serum glutamic-pyruvic transaminase SGPT alanine transaminase values. In addition, majority of subjects with raised SGOT and SGPT had high IR. An AST greater than twice the upper limit of normal was independently predictive of portal or bridging fibrosis in an Asian study of 60 patients with NAFLD.[7]

Association nonalcoholic fatty liver disease with altered glucose metabolism

Overall 45% of subjects with NAFLD had a positive family history of diabetes. A study by Loomba *et al.* showed that family history of diabetes was associated with the presence of NASH and fibrosis

in patients with NAFLD. Majority of subjects in the study group had normal blood sugar levels. Sixteen percent of the subjects had high FBS values, and 14% had high PPBS when normal values of FBS and PPBS were taken as 110 mg/dl and 140 mg/dl, respectively [Figure 2]. Among them, 5% had their FBS, and 3% had their PPBS values in the diabetic range, respectively. Study by Singh *et al.* in 515 NAFLD patients concluded that the prevalence of diabetes and prediabetes was high in NAFLD patients.[8]

In the present study, FPI levels were raised in 74% of the subjects when normal value of FPI taken as ≤10. The rest 26% had normal FPI value. High FPI percentage was found in both hyperglycemics and nonhyperglycemics pointing that their association was not statistically significant. Fasting hyperinsulinemia was common in individuals with impaired glucose homeostasis, predicts the development of diabetes in various populations, and was a widely accepted surrogate measure of IR. The present study showed that IR was significantly correlated to raised FBS and FPI levels. More than 60% of the subjects had raised IR irrespective of their PPBS values.

Association with altered fat metabolism

The present study shows that the majority of subjects with NAFLD do not have a positive family history of dyslipidemia. When looked into the lipid profiles, among the 100 samples, 60 (60%) had raised total cholesterol values. Raised LDL values were found in 44% of subjects. TGs were raised in 43% of subjects when cutoff taken is >150 mg/dl. More than 50% of subjects with NAFLD had normal TG levels. About 46.6% of males and nearly 60% of females had low HDL values (normal taken cut off value-Male <40mg/dl and Female <50 mg/dl). The presence of dyslipidemia (hypercholesterolemia, hypertriglyceridemia, or both) had been reported in 20% to 80% of cases associated with NAFLD.[9] Studies by Chatrath *et al.* showed that dyslipidemia in NAFLD was typically characterized by increased serum TG levels, increased small, dense LDL particles, and decreased HDL cholesterol.[10]
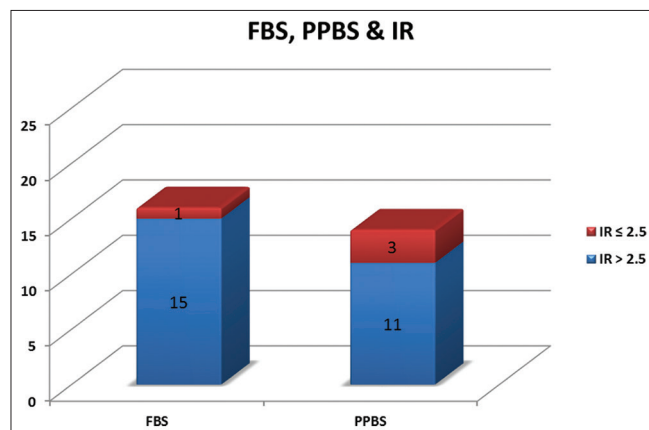
There was no significant correlation between IR and lipid profile values in the present study group. FPI levels were found to be marginally significant with TG values. High FPI was found in 83.7% of the subjects with raised TG levels.

Prevalence of obesity in nonalcoholic fatty liver disease

Obesity prevalence was calculated using two parameters- (1) BMI and (2) WC. The cutoff taken for BMI and WC in the study group was as per the revised WHO guidelines for the Asian population. In the present study group, 11 were of normal weight, 11 were overweight. Obesity was found in 78 subjects (as per new Asian guidelines). None of the subjects with NAFLD were underweight. When assessed with WC, 90.4% of male subjects and 85.2% of female subjects had high values, i.e., 89% of the study group had raised WC [Figure 3].

In the present study, it was observed that >60% of the subjects who were either obese/overweight had high IR showing that there was significant association between these two variables. Among those with normal BMI and NAFLD, IR was seen in 36%. IR was high in >70% of those with raised WC, irrespective of gender. None of the subjects with low or normal WC had high IR. In addition, it was concluded from the present study that FPI levels were significantly associated with BMI.

Obesity, more specifically central obesity, characterized by abdominal fat accumulation is definitely associated with NAFLD. WC is an effective indicator that can be used to screen central adiposity and IR. BMI is an independent predictor of the degree of fat infiltration of the liver and the likelihood of developing NASH increases with the severity of obesity. In the study by Das *et al.*, it was found that individuals with normal BMI (18.5–24.9 kg/m²) had 2-fold increases in risk for NAFLD than those with a BMI <18.5 kg/m². Evidence suggests that obesity and IR were major risk factors that contribute to the development of NAFLD.
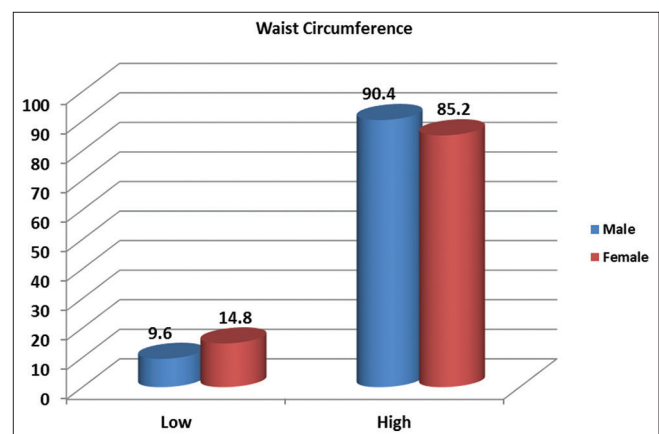

Figure 2: Majority of subjects in the study group had normal blood sugar levels. Sixteen percent of the subjects had high fasting blood sugar values, and 14% had high postprandial blood sugar values. 94% of subjects with raised fasting blood sugar values and 78% of subjects with raised postprandial blood sugar values had high-insulin resistance

Figure 3: Examination of cell frequency showed that 90.4% of male subjects and 85.2% of female subjects had raised waist circumference. Majority of patients had raised waist circumference (89%), and this was observed irrespective of their gender

Conclusion

The prevalence of NAFLD is steadily increasing. The present study concluded that the chance of developing NAFLD was high if the subjects are having IR, or vice versa. There was an increased prevalence of prediabetes and diabetes in the subjects with NAFLD. It was noted that NAFLD can occur in the absence of raised TG values. It was found that obese/overweight and IR was significantly associated. WC rather than BMI was found to be a strong predictor of central adiposity and IR. In summary, ultrasound diagnosis of fatty liver should be taken seriously as a predictor of metabolic syndrome. NAFLD can be an indirect predictor of IR. Exercise, diet control, and weight reduction are considered effective treatment for the progression of NAFLD.

Limitations of the study

1. Small sample size
2. Cross-sectional nature of the study does not allow for cause-effect conclusions to be made definitively
3. Not all criteria of metabolic syndrome were included.

What the present study adds to?

1. This study adds to the existing data on prevalence of nonalcoholic fatty liver and IR in South Indian (Kerala) population
2. Significant IR was found in majority of apparently asymptomatic middle aged individuals, who came for routine health assessment
3. Routine assessment of WC can be used as an effective indicator of central adiposity and hence IR
4. Individuals with nonalcoholic fatty liver should be screened for metabolic syndrome and necessary preventive measures can be taken
5. Calculation of IR should be added to routine health assessment protocol.

Recommendations of the study

Further, population-based studies are needed to determine the impact of nonalcoholic fatty liver disease on public health in the long-term

1. More follow-up studies are needed to assess the extent to which preventing the development of metabolic syndrome would prevent nonalcoholic fatty liver development and the reduction in liver-related morbidity and mortality
2. Further studies are needed to assess the cause-effect relation between IR and nonalcoholic fatty liver
3. More data from various regions are needed to accurately determine the extent of the disease, difference in occurrence with age and ethnicity and the impact on children
4. Considering the invasive nature and inconveniences associated with liver biopsy, ultrasound abdomen (which is less expensive, noninvasive, and easily accessible) should be considered as the next best screening tool of nonalcoholic fatty liver.

Conflicts of interest

There are no conflicts of interest.

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