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To Study the Association Between Nonalcoholic Fatty Liver Disease and Metabolic Syndrome

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Abstract
The research had 100 patients in total, 48 (48%) of whome were male and 52 (52%) of whome were female. The maximum age range for research participants was 41-70 years, the prevalence of NAFLD in metabolic syndrome to be 85% in this study. Here among the 85 NAFLD subjects. The frequency of NASH/CIRRHOSIS in individuals with NAFLD of the 85 individuals diagnosed with NAFLD, 25 were also confirmed to have NASH. Dyslipidemia was seen in 87.1% of the NAFLD subjects and was present in 100% of the NASH group thus, we observed a significant positive correlation between components of metabolic blood glucose levels with NAFLD. It was shown that up to 85% of individuals with metabolic syndrome have NAFLD. Cirrhosis was a serious condition seen in as many as 29.41% of NAFLD patients (NASH). This research supported the idea that, in order to halt the disease's course and avoid target organ damage and cardiovascular consequences, all participants with metabolic syndrome and related co-morbidities should be evaluated for undiagnosed NAFLD.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is now the most prevalent cause of abnormal liver function tests due to the rising occurrence of obesity. When more than 5% of hepatocytes in people who do not drink excessively are steatosis, NAFLD is present[1].

Steatogenic medication treatment, including amiodarone, tamoxifen and steroids, may potentially be the secondary cause of fatty infiltration in theselivers. The disorders associated with metabolism the first step in identifying people at risk of NAFLD is to identify those who have one of the metabolic syndromes[2]. Any three or more of the characteristic characteristics may be present in the metabolic syndrome. More than 90% of NAFLD patients have at least one characteristic and around one-third have the whole metabolic syndrome. The NASH and fibrosis are more common in patients with higher metabolic risk factors and the severity of NAFLD is correlated with the severity of these metabolic syndromes. A crucial mediator that connects NAFLD and the metabolic syndrome is insulin resistance[3-5].

A liver biopsy is the last test for NAFLD and gives an evaluation of hepatic steatosis, hepatocellular damage, inflammation and fibrosis, even though it is usually not necessary for the diagnosis. The primary histological characteristic that separates NASH from simple steatosis is the existence of hepatocyte ballooning degeneration in the conjunction with steatosis. The most popular histological grading and staging approach for Non-alcoholic Fatty Liver Disease (NAFLD) is called the "NAFLD activity score" (NAS). The majority of patients with NAFLD may be appropriately identified and staged using non-invasive strategies, however the SAF scores, which include an evaluation of fibrosis (F), activity (A) and steatosis (S), may be more accurate in diagnosing NASH. When non-invasive staging is ambiguous or there is diagnostic uncertainty in a person, liver biopsy should be used[2-5]. The hepatic symptoms of Metabolic Syndromes (MS) have been recognized as NAFLD and previous observational studies have revealed a link between NAFLD and MS. There are many mechanisms that are similar between the development of MS and NAFLD. One such mechanism is that insulin resistance may be the pathophysiological foundation for both conditions[6].

The pathophysiology of non-alcoholic fatty liver disease is currently unclear. A normal metabolic response cannot be achieved with normal insulin concentrations and this state is known as insulin resistance. (a) Higher than normal insulin levels are required and (b) Normal insulin concentrations are insufficient to provide a normal metabolic response. Insulin is apleiotropic hormone that regulates gene expression, energy balance, enzymatic activity and the stimulation of nutrient transport into cells, among its many other roles. Insulin binds to its receptor in the plasma insulin-dependent cell membrane, phosphorylates the receptor and then activates the receptor through the phosphorylation of insulin receptor substrate proteins (IRS proteins)[7,8]. These proteins activate two major signaling pathways: the Ras-mitogen-activated protein kinase (MAPK) pathway, which controls some gene expression and works with the PI3K pathway to control cell growth and differentiation and the phosphatidylinositol 3-kinase (PI3K)-AKT/protein kinase B (PKB) pathway, which accounts for the majority of these metabolic actions of insulin. AKT/PKB is a kind of serine/threonine kinase that facilitates cell absorption of glucose by activating the translocation of glucose transporters (GLUT4) to the plasma membrane. GSK-3, or glycogen synthase kinase, is another target of AKT/PKB[10]. Increased glycogen synthesis results from GSK3 phosphorylation, which lowers the enzyme's activity toward glycogen synthase. By regulating the activity of the winged helix or fork head (FOX) family of these enzymes, AKT/PKB also controls the production of gluconeogenic and lipogenic enzymes of the transcriptional factor. Protein synthesis is regulated by the mTOR pathway, which is efficiently activated by AKT/PKB. Several exogenous factors, such as oxidative stress, free fatty acids, tumor necrosis factor-α, ceramide as an intracellular mediator, IKKβ (inhibitor of κβ kinase) and nuclear factor kappa Insulin signaling pathways have been shown to modify the cytochromes CYP2E1, PKC-δ (Protein Kinase C-θ), JNK1 (Jun N-Terminal Kinase-1) and SOCS (suppressors of cytokine signaling), which in turn causes insulin resistance. The "two-hit hypothesis" is the most commonly recognized explanation for how NAFLD develops and how mild steatosis progresses to NASH. Lipid buildup in the hepatocytes is the "first hit" and Hepatic steatosis is mostly caused by insulin resistance. The "second hit" causes fibrosis, inflammation and hepatocyte damage. Oxidative stress and the ensuing lipid peroxidation, proinflammatory cytokines, adipokines and mitochondrial dysfunctions are the factors that start the second hit.

The present Study aimed to assess the association between Nonalcoholic Fatty Liver Disease and Metabolic Syndrome.

MATERIALS AND METHODS

Study design: Prospective observational study.

Study sample: 100 patients with Metabolic Syndrome.

Study setting: attending General Medicine OPD in Dr. Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation, Chinna Avutapalli, Vijayawada.

Duration of study: from the time of approval to till 24 months duration was selected for this study after getting informed written consent in local language.

MATERIALS AND METHODS

Patients coming to the General Medicine OPD and admitted in General Medicine Wards who fulfill the inclusion and exclusion criteria was selected for this study.

Subjects who are above the age of 18 years who fulfill the inclusion (metabolic syndrome) and exclusion criteria was enrolled into the study after taking informed consent.

A detailed history, clinical examination and all the necessary investigations required for the study was carried out and the outcome were assessed.

Inclusion criteria: Subjects with metabolic syndrome (defined by IDF criteria) who are above the age of 18 years.

Exclusion criteria:

- Alcohol consumption greater than or equal to 20 g day^{-1} in women and 30 g day^{-1} in men
- Known hepatic diseases, HbsAg, HCV positive subjects
- Subjects on medications like corticosteroids amiodarone, tamoxifen, methotrexate or high dose estrogens, anti-HIV drugs
- Subjects who have undergone Jejunoileal bypass or extensive small bowel resections
- Pregnancy

Data was collected and the results on continuous measurements were presented on mean +/- SD and results on categorical measurements were in Number (%). Appropriate Statistical test were applied. The statistical significance of the association was calculated by setting the p-value as 0.05.

RESULTS

At a mean age of 51+/-9 years, the majority of the patients in this research were middle-aged. 19% of the participants were younger than 40, while 9% were older than 70. As a result, the maximum age range for research participants was 41-70 years, while actual patients ranged in age from 31-78 years.

In this study out of 100 subjects of metabolic syndrome, 85 subjects had Non-Alcoholic Fatty liver disease detected by the ultrasonography and 15 subjects had normal liver. Thus. making the prevalence of NAFLD in metabolic syndrome to be 85%. Here among the 85 NAFLD subjects 59 subjects (69.41%) had hypertension and in the 15 non-NAFLD subjects statistically significant.

The mean waist circumference of NAFLD was 114.18 +/- 10.98 and in the Non NAFLD was 109.24 +/- 9.42 which is statistically significantly (p = 0.01).

The mean FBS of NAFLD group was 169.03 +/- 13.61 and in the Non NAFLD was 105.42 +/-11.63 which is statistically significantly (p<0.02).

The mean triglycerides values of NAFLD was 174.92+/-14.38 in the Non NAFLDwas 112.51+/-13.88 which is statistically significantly. (p = -0.02).The mean value of HDL of NAFLD was 39.82 +/-3.11 and in the Non NAFLD was 33.25+/-3.28 which is statistically significantly (p = 0.02).

Thus, we observed a significant positive correlation between Components of metabolic syndrome namely waist circumference, triglyceride levels and fasting blood glucose levels with NAFLD.

The frequency of NASH/CIRRHOSIS in individuals with NAFLD. Of the 85 individuals diagnosed with NAFLD, 25 were also confirmed to have NASH. Consequently, NASH/cirrhosis was present in 29.41% of the NAFLD participants.

The mean waist circumference of NAFLD was 110.22 +/- 10.23 and in the NASH was 102.36 +/- 10.91 which is statistically significantly (p = 0.02). The mean FBS of NAFLD group was 156.11 +/-12.62 and in the NASH was 142.84 +/-12.83 which is statistically significantly (p<0.001). The mean triglycerides values of NAFLD was 169.26+/-14.58 and in the NASH was 162.42+/-14.51 which is statistically significantly. (p = 0.002). The mean value of HDL of NAFLD was 36.58 +/-3.63 and in the NASH was 31.42+/-3.72 which is statistically significantly (p = 0.002).

The mean value of AST and ALT were34.556+/-14.666 and 4 1.056+/25.213 respectively in NASH subjects, the mean difference of which was not statistically significant but noticeably ALT was higher in NASH patients. The mean value of TP was 7.506+/-0.375 in NAFLD subjects and was 6.172+/-0.714 in NASH group which showed statistically significant difference between the two groups with NASH having lower levels of Total protein. (Mean diff- 1.334 and p = -0.03). Thus, showing positive correlation between the synthesis of total protein and severity of NAFLD. The mean value of S. Albumin was 3.767+/-0.017 in NAFLD group and was 2.467+/- 0.490in NASH subjects which showed statisticallysignificant lower values in the NASH/cirrhosis group (p = -0.001). Again, showing positive correlation between the low serum albumin levels and the severity of NAFLD.

In this study, It was found that type 2 DM was found in 81.4% of the NAFLD subjects and 94.4 % of the NASH subjects which showed high prevalence in NAFLD subjects but showed higher prevalence in NASH subjects thus showing a positive correlation with the severity of NAFLD but wasn't statistically significant.

Hypertension showed higher prevalence in NAFLD and was found in 75.7% of the (non- NASH) NAFLD subjects and in 66.7% of NASH/cirrhosis subjects and did not show any positive correlation with the severity of NAFLD. Hypothyroidism was present in 14.3% of the NAFLD subjects and 33.3% of the NASH subjects and was more prevalent in NASH subjects. No statistical significance was seen between hypothyroidism and severity of NAFLD. IHD was seen in 21.4% of the NAFLD subjects and 11.1% of the NASH subjects and was more common in the non-NASH NAFLD group and showed no statistical significance. CKD was found in 8.6% of the NAFLD subjects and was not found in any of the NASH study subjects here in this study COPD was found in as few as 10% subjects in NAFLD and 11.1% of the NASH subjects but no statistical correlation could be derived between COPD and severity of NAFLD.CVA was seen in 4.3% of the NAFLD subjects and 11.1% of the NASH subjects and was markedly more common in NASH as compared to NAFLD subjects as a vascular complication but the correlation of CVA with severity showed no statistical significance. Dyslipidemia was seen in 87.1% of the NAFLD subjects and was present in 100% of the NASH group thus more prevalent in NASH group but p value was 0.11 making it statistically not significant OSA was present in 7.1% of the NAFLD subjects and 5.6% of the NASH subjects and showed no correlation between OSA and severity of NAFLD.Dilated cardiomyopathy was seen in 2.9% of NAFLD subjects and 11.1% of the NASH subjects and was more prevalent in NASH subjects as a cardiovascular complication but statistical significance wasn't found.

DISCUSSION

The research had 100 patients in total, 48% of whom were male and 52% of whom were female. At a mean age of 51+/-9 years, the majority of the patients in this research were middle-aged. In this instance, 41% of the individuals were in the 51-60 age range, 10% were in the 61-70 age range and 21% were in the 41-50 age range. Merely 19% of the participants were younger than 40, while 9% were older than 70. As a result, the maximum age range for research participants was 41-70 years.

Out of the 100 participants in this research who had metabolic syndrome, 85 had non-alcoholic fatty liver disease as shown by ultrasonography and the remaining 15 had normal livers. Consequently resulting in an 85% incidence of NAFLD in the metabolic syndrome in our investigation. Here, 59 individuals (69.41%) with NAFLD and 15 non-NAFLD patients exhibited statistically significant hypertension. The statistically significant difference between the mean waist circumferences of NAFLD patients, 114.18 +/- 10.98 and non-NAFLD patients, 109.24 +/- 9.42, was observed. p-value is 0.01). The statistically significant difference between the mean FBS of the NAFLD group (169.03 +/-13.61) and the non-NAFLD group (105.42 +/-11.63) was observed. (P=0.02).The statistically significant difference between the mean triglyceride readings of NAFLD (174.92+/-14.38) and non-NAFLD (112.51+/-13.88) was observed (p = 0.02). The HDL mean values for NAFLD and non-NAFLD were 39.82 +/- 3.11 and 33.25 +/-3.28, indicating statistical significance. (p-value: 0.02). Hence, we found a strong positive association between NAFLD and the metabolic syndrome's three components: lipid levels, waist circumference and fasting blood glucose levels. The frequency of NASH/CIRRHOSIS in individuals with NAFLD. Among the 85 cases diagnosed with NAFLD, 25 were also confirmed to have NASH. Consequently, NASH/cirrhosis was present in 29.4% of the NAFLD participants.

The mean waist circumference in the NASH was 102.36 +/- 10.91, which is statistically significant, while in the NAFLD it was 110.22 +/- 10.23. (p-value: 0.02). The statistically significant mean FBS values for the NAFLD group were 156.11 +/-12.62 and the NASH group was 142.84 +/-12.83 (p = 0.001). The statistically significant mean triglyceride readings for NAFLD were 169.26+/-14.58, whereas the NASH values were 162.42+/-14.51 (p = 0.002). The statistically significant mean HDL values for NAFLD and NASH were 36.58 +/-3.63 and 31.42 +/-3.72 (p = 0.002). Hence, we found a strong positive association between NAFLD and the metabolic syndrome's three components: Lipid levels, waist circumference and fasting blood glucose levels.

According to a different research conducted on the Japanese population, the prevalence of NAFLD rose to 43% in people with impaired glucose tolerance and 62% in those with type 2 diabetes. NAFLD is highly correlated with hyperlipidemia, namely high triglyceride and low HDL cholesterol levels. In NAFLD patients, hypertriglyceridemia and low HDL cholesterol are seen in 64% and 30×42% of cases. The prevalence of fatty liver was more than twice as high in 55 non-obese, non-diabetic individuals with primary hypertension as it was in the control group[10,11].

CONCLUSION

It was shown that up to 85% of individuals with metabolic syndrome have NAFLD. Cirrhosis was a serious condition seen in as many as 29.41% of NAFLD patients (NASH). This research demonstrated a strong relationship between the severity of NAFLD and the elements of the metabolic syndrome. This research supported the idea that, in order to halt the disease's

course and avoid target organ damage and cardiovascular consequences, all participants with metabolic syndrome and related co-morbidities should be evaluated for undiagnosed NAFLD.

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