Short communication

Evaluation of hepcidin and its relationship with iron in non-alcoholic fatty liver disease

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ABSTRACT

Introduction and Aim: There is an increase in the incidence of non-alcoholic fatty liver disease (NAFLD) in obese people, type 2 diabetes and metabolic syndrome. Iron leads to the development of NAFLD. Hence serum hepcidin played a vital role in the development of liver cirrhosis. This study was undertaken to evaluate the role of hepcidin and iron and their relationship with NAFLD.

Materials and Methods: This cross-sectional hospital-based study involved 50 patients. Plasma was evaluated for hepcidin by ELISA, and iron by semi-autoanalyzer. Hepcidin and iron were correlated using Spearman’s correlation.

Results: There was a positive correlation between hepcidin and iron in NAFLD patients. We observed that patients with lower BMI were prone to develop NAFLD. Positive correlation of hepcidin with iron has led to diminished ability to inhibit iron.

Conclusion: Further studies related to the altered lipid metabolism its link with iron, or change in the genes responsible for maintenance of iron balance, or a blend of both results in overload of iron in NAFLD patients. Dysmetabolic iron overload syndrome (DIOS) in the development of NAFLD iron played a vital role hence could be used as a target for treatment. Therefore, this evidence-based study may result in new treatment modalities in NAFLD.

Keywords: Non-alcoholic fatty liver disease (NAFLD); hepcidin; iron.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a group of disorders that includes the deposition of ectopic fat in the liver to more progressive steatohepatitis (1). The occurrence of NAFLD is increasing worldwide every year and ranges from 6-35% (2). However, there is a rise in incidence of NAFLD in overweight individuals, type 2 diabetes mellitus and metabolic syndrome. Liver steatosis occurs as a consequence of accumulation of free fatty acids which are predominantly produced from lipolysis in the adipose tissue (3). Free fatty acids promote oxidative stress and possibly play a crucial role in the progress of NAFLD (4). Iron, a vital nutrient, has been widely linked to the development of NAFLD. Iron is vital for erythropoiesis and various metabolic functions at cellular level and its level in excess leads to the production of reactive oxygen species and further it can cause cellular damage (5). Dysmetabolic iron overload syndrome (DIOS) is seen in NAFLD patients with increased serum ferritin and iron stores in liver. The basis for DIOS is unknown. Non-alcoholic steatohepatitis (NASH), which is the more severe form of NAFLD, excessive iron stores result in hepatocyte ballooning that further leads to inflammation in the hepatocyte and ultimately fibrosis occurs. Hepcidin is a peptide containing 25 amino acids that impedes iron uptake in the gut and recycles iron from macrophages thereby regulating the balance of iron in the body (4). Hence serum hepcidin played a vital role in the development of liver cirrhosis. The association of iron stores in the body with hepcidin synthesis, in NAFLD patients, has not yet been well ascertained. As a result, this study was undertaken to evaluate the role of hepcidin and iron and their relationship with NAFLD. Therefore, this evidence based study may result in new treatment modalities in NAFLD (6).

MATERIALS AND METHODS

Study setting

This study was conducted in Kasturba Medical College Hospital, Ambedkar Circle, (KMCHAC), Kasturba Medical College Hospital, Attavar (KMCHAT), and Department of Biochemistry, Centre for Basic Sciences, Bejai, Mangalore. The protocol of the study was approved by the institutional ethical committee.

Study design

50 patients diagnosed with NAFLD by upper abdomen ultrasound were included in the study. The subjects were approached regarding their wish for study and an informed written consent was taken from the subjects. Both clinical and anthropometric data was being taken from the subjects.
Inclusion criteria
1. Patient with non-alcoholic fatty liver disease
2. Age group 30-50 years
3. Gender both male and female

Exclusion criteria
1. Patient with alcoholic fatty liver disease
2. Viral hepatitis, hepatobiliary disease, malignancies, inflammatory bowel disease, current medication with lipid lowering drugs, chronic cardiac, renal, and respiratory diseases, pregnant women.

Biochemical measurement
The patients who came for routine health check and diagnosed with NAFLD by abdominal ultrasound were included in the study. The same patients who have also been subjected to routine blood tests and their left over serum/plasma was collected from the lab and used for the biochemical measurements for the study. The blood sample was immediately stored at -80 degrees until analysis.

Methods
Serum hepcidin was estimated by enzyme linked immuno sorbent assay (ELISA) based ion sandwich method (7). Serum iron was estimated by ferrozine method (8).

Statistical analysis
Data was analyzed in SPSS version 17.0. Descriptive statistics of different parameters, were tabulated. Correlation of hepcidin with iron in NAFLD patients was done using Spearman’s correlation. p<0.05 was considered as significant.

RESULTS
Table 1 shows A total of 50 participants with NAFLD were enrolled. Men accounted for 70% of the study population. Participants mean age was 43.0 ± 5.7 years. NAFLD was found in patients with a lower BMI (27.4 ±4.2 kg/m²) as depicted in Table 1. The serum HDL, LDL Triglycerides were found to be 49.7 ± 35.2 mg/dl, 142.3 ±41mg/dl, 79.71±56.84mg/dl which were higher in patients with NAFLD. The hepcidin and iron were 22.6 (1.96, 479.7) ng/dl 263.8(60.4,1341) mg/dl respectively.

Table 2: Correlation of hepcidin with iron in NAFLD patients

<table>
<thead>
<tr>
<th>Correlation</th>
<th>N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>r</td>
</tr>
<tr>
<td>p</td>
<td>0.010**</td>
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</table>

Table 2 shows the correlation analysis between hepcidin and iron in NAFLD patients. Hepcidin positively correlated with iron in NAFLD patients.

DISCUSSION
NAFLD is more common in males than in females. Due to the presence of estrogens, pre-menopausal women appear to be spared. However, the disease develops approximately 10 years at a later stage in post-menopausal women (9). In our hospital-based study it was found that occurrence of NAFLD in the middle-aged population but globally it has been reported at 60 -69 years of age (10). The difference observed between males and females with regards to the occurrence of NAFLD is due to difference in the functions of endocrine glands and distribution of fat (10).

In Western countries, obesity and its related diseases are considered as a major problem. However, in the past two decades, per capita economic enhancement in many Asian countries has led to a sedentary lifestyle and over nutrition- this sets the stage for development of obesity (9). Body mass index (BMI) is considered as the most reliable index to assess obesity. A BMI of 30–32.5 kg/m² had a higher risk of developing NAFLD/NASH as opposed to patients having a BMI of 20–22.5 kg/m² (11).

As per the present study, with respect to NAFLD/NASH, it has been noted that relative risks are higher for those at a lower BMI. A hospital-based study conducted at Delhi, documented a higher proportion of NAFLD among normal-weight children than those with obesity (12).

In the current study, it has been observed that serum LDL, serum triglyceride levels are significantly higher in subjects with NAFLD. The pathogenesis of NAFLD has not been very well understood since the mechanisms behind it are not yet known. A difference, either in the distribution of body-fat or...
antioxidant systems and genetic factors, are directly related to a net accumulation of lipids, mostly in the form of triglycerides within hepatocytes. The development of non-alcoholic fatty liver disease might be the result of insulin resistance which leads to alterations in the process of uptake, synthesis, degradation, and secretion during metabolism of lipids in the liver. Mahaling et al., has documented that insulin resistance plays an important role in the progress of non-alcoholic fatty liver disease (13).

The present study shows a positive association between hepcidin and iron levels: some other preceding studies have presented contradictory results. Barisani et al., concluded that production of hepcidin was lower in NAFLD patients, in comparison to controls (14). In the study done by Asma Siddique et al., it has been reported that an increased hepcidin level as a result of inflammatory process contributes to iron deficiency in NAFLD patients. Others have documented hepcidin levels correlated with iron parameters in NAFLD, which agrees with the present study, suggesting the inability of hepcidin to inhibit iron absorption. This could be due to hepcidin resistance in DIOS associated with NAFLD (15). It seems that rise in hepcidin levels in NASH is a result of inflammation in the liver or due to increased iron, which, in turn, stimulates hepcidin secretion that occurs prior to the development of NASH. In the setting of NAFLD and type II diabetes, insulin stimulates the release of hepcidin thus resulting in iron overload. Furthermore, it has been observed in obesity that, hepcidin increases as it is released from adipose tissue. This is another probable cause that may explain elevated serum hepcidin in NASH may be due to release of hepcidin from adipose tissue to the serum hepcidin pool. These findings implicate that the relation between iron and lipid metabolism is multi-dimensional. It can be concluded that excessive iron may result in altered lipid metabolism (8).

Briton et al., has documented a probable role for iron in the progress of disease in NASH: iron overload seen in NASH may be due to variations in dietary iron intake. Although there is no link between dietary intake of iron and the cause of NASH, it has been documented that red meat consumption can lead to insulin resistance and type II diabetes (5).

Additional studies are needed for better understanding into the intricacies related to the altered lipid metabolism its link with iron, or change in the genes responsible for maintenance of iron balance, or a blend of both which results in overload of iron in NAFLD patients.

CONCLUSION

Our cross-sectional hospital-based study included 50 patients diagnosed with NAFLD by history and upper abdomen ultra-sonogram. In the current study it was found that the possibility of NAFLD rises with increase in age. Our study also observed that patients with lower BMI were prone to develop NAFLD. It could be ascertained that positive correlation of hepcidin with iron has led to diminished ability to inhibit iron Additional studies are needed for better understanding into the intricacies related to the altered lipid metabolism its link with iron, or change in the genes responsible for maintenance of iron balance, or a blend of both which results in overload of iron in NAFLD patients. In the development of NAFLD iron played a vital role hence could be used as a target for treatment. Therefore, this evidence based study may lead to new treatment modalities in NAFLD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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