Correlation of Serum Adiponectin with Hepatic Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease

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Abstract

Objective: Nonalcoholic fatty liver disease (NAFLD) is a metabolic disorder characterized by excessive triglyceride accumulation in the hepatocytes. NAFLD describes a spectrum of clinicopathological changes extending from simple steatosis through non-alcoholic steatohepatitis (NASH) to fibrosis. Aim of the study was to assess the correlation of serum adiponectin with severity of NAFLD.

Methods: It was an observational, cross sectional study. Fifty patients who fulfilled the inclusion criteria of NAFLD were included in the study; they were studied with liver histology and serum adiponectin level. Correlation of serum adiponectin with non- NASH, NASH and stages of liver fibrosis was analyzed.

Result: Mean age was 38.0±9.4 years with range from 20 to 59 years with female predominance (62%). Serum adiponectin level was 9.09±3.68 microgram/mL in patients with non-NASH (n=17), and it was 4.90±2.34 microgram/mL in those with NASH (n=33). Serum adiponectin was 6.57±3.84 microgram/mL in 38 patients with fibrosis score 1; it was 5.51±1.84 microgram/mL in 10 patients with fibrosis score 2; and it was 5.59±1.08 microgram/mL in 2 patients with fibrosis score 3.

Conclusion: Serum adiponectin level decreased in patients with NASH than in patients not having NASH, and it is also reduced in patients with advanced hepatic fibrosis.

Keywords: NAFLD; NAS; Adiponectin; NASH

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a metabolic disorder characterized by excessive triglyceride accumulation in the hepatocytes. It is a hepatic manifestation of metabolic syndrome [1]. The prevalence of NAFLD in India above 20 years age was 18.9% [2]. The prevalence of NAFLD increased with increased age. Obesity, diabetes mellitus (DM), insulin resistance (IR) are predisposing factors for NAFLD. Although NAFLD is more common in subject with obesity and diabetes mellitus (DM), it also occurs in lean and non-diabetic subject [3,4,5]. Non obese was 25.6% among NAFLD patient in Bangladesh. About 53.1 % of non-obese NAFLD cases were NASH [6].

NAFLD consists of a wide spectrum of conditions, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) which can progress to cirrhosis and hepatocellular carcinoma (HCC). The prevalence of NASH is 42.4% among NAFLD patients in Bangladesh [7]. The contrasting clinical course of NASH vs non-NASH fatty liver (NNFL) indicates that these two conditions diverge early in the course of NAFLD. A progression to cirrhosis is usually preceded by longstanding histological NASH and is infrequent during NNFL. Overall, 37.5% of normal serum Alanine Aminotransferase (ALT) group had NASH or advanced fibrosis, whereas 53% of elevated ALT had NASH or advanced fibrosis [8].

NASH is a common cause of “cryptogenic” cirrhosis, which accounts for 10%-20% of all cirrhosis cases [9]. The pathogenesis of NAFLD is the “multi-hit hypothesis” with metabolic syndrome playing a major role, due to insulin resistance and the proinflammatory process mediated by different proteins and immune components [10]. Adiponectin also known as adipocyte
Adiponectin is a fat-derived hormone that circulates at relatively high concentrations in the serum [13] also derived from the placenta in pregnancy. This adipocytokine is believed to mediate insulin action in insulin-sensitive tissues, such as the liver and the muscles, in both humans and animals [14]. Especially in the liver, adiponectin stimulates glucose utilization and fatty acid oxidation by activating the adenosine monophosphate-activated protein kinase, thus mediating hepatic insulin action [15,16]. There are increasing data in the literature indicating that the serum adiponectin correlated with Homeostatic model assessment (HOMA) (Pearson correlation coefficient \( r = -0.544, P=0.001 \)).

Adiponectin concentration was negatively associated with higher stages of fibrosis (one-way analysis of variance, \( P=0.007 \)), and was not associated with NAFLD activity score. Low serum adiponectin levels in NAFLD patients are suggestive of advanced fibrosis. Therefore, assessment of serum adiponectin levels may be useful in clinical follow-up [17]. The pathological committee of the NASH clinical research network designed and validated a histological feature scoring system that address the spectrum of lesions of NAFLD and proposed Nonalcoholic fatty liver disease Activity Score (NAS) for use of clinical trial.

The scoring system comprises steatosis (0-3), lobular inflammation (0-3), hepatocellular ballooning (0-2) and a separate fibrosis staging (0-4). The proposed NAS is the sum of steatosis, lobular inflammation and hepatocellular ballooning score. NAS of \( \geq 5 \) correlated with diagnosis of NASH and biopsy with scoring of 3-4 suggestive of NASH and less than 3 were diagnosed as non-NASH fatty liver [18]. Other pathological findings such as Mallory denk bodies or perisinusoidal fibrosis can make the diagnosis even stronger. Fibrosis Stage evaluated separately from NAS; Stages F0, F1, F2 were considered early fibrosis and Stage F3, F4 were considered to be advanced fibrosis [19]. As NASH, fibrosis and cirrhosis is a histological diagnosis, liver biopsy is needed to establish or rule it out definitively. However, it is not practical to do biopsy in every patient with suspected NAFLD. Therefore, a noninvasive marker that can signify the presence or absence of NASH and/or fibrosis is highly demanding.

**NAFLD and Adiponectin**

NAFLD has a multifactorial disorder associated with obesity, insulin resistance, type 2 diabetes and dyslipidemia. Moreover, genetic mutations also play a role in predisposition to the development and progression of NAFLD [20]. Especially in the liver, adiponectin stimulates glucose utilization and fatty acid oxidation by activating the adenosine monophosphate-activated protein kinase, thus mediating hepatic insulin action 15,16. Adiponectin also manifests anti-inflammatory action by neutralizing tumor necrosis factor-alpha13 and antifibrotic action by inhibiting hepatic stellate cell proliferation and migration [21]. It was found that serum adiponectin levels in patients with NAFLD ranged between 0.4 and 13.2 µg/mL, which is lower compared with normal values (5 to 30 µg/mL) and is consistent with the findings of other investigators in patients with NAFLD [22]. Objective of the study was to correlate serum adiponectin level with severity of nonalkoholic fatty liver disease (NAFLD).

**NAFLD**

It is reported that almost 10% to 20% of individuals with NAFLD have NASH and 10%-15% of individual with NASH progress to cirrhosis [23]. The prevalence of NASH is 42.4% among NAFLD patients in Bangladesh [7]. Longitudinal studies with serial biopsies have shown that approximately one-third of NASH patients develop advanced fibrosis (stage 3 or 4 fibrosis) over the course of 5-10 years from the time of the initial diagnosis [24,25]. Although it is usually relatively slow, the progression to cirrhosis can occur in as little as 2-3 years.

**NASH**

Is a common cause of “cryptogenic” cirrhosis, which accounts for 10%-20% of all cirrhosis cases [9]. Among patients diagnosed with NASH related cirrhosis, the risk of developing portal hypertension (a major complication) is 17%, 23% and 52% at 1, 3 and 10 years, respectively. Among the patients with early-stage of NASH, the overall mortality over 10-15 years is approximately 10%-12%, being significantly higher in the NASH vs the NNFL patients, compared to the general population. The risk of developing decompensated cirrhosis is 5%-10%, and that of hepatocellular cancer is 1%-2%. There is a ten-fold increased risk of deatrhosis relative to the general population [26].

| Item    | Score | Extent | Definition and comment                                      |
|---------|-------|--------|-------------------------------------------------------------|
| Steatosis | 0     | <5%    | Refers to amount of surface area involved by steatosis as evaluated on low to medium power examination; |
|         | 1     | 5-33%  |                                                              |
|         | 2     | >33-66%|                                                              |
|         | 3     | >66%   |                                                              |
**Methods**

It was an observational cross-sectional study carried out in the department of Hepatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, during the period from July'2016 to August’2017. Ethical Clearance was approved by the Institutional Review Board (IRB). Sixty-five patients with ultrasonographic evidence of fatty infiltration of the liver attending the outpatient and inpatient department of Hepatology, BSMMU were initially selected. Those with significant alcohol intake (consumption of more than 14 units /week in women and more than 21 units /week in men), history of taking drugs that may cause fatty liver (e.g., tamoxifen, sodium valproate, amiodarone, MTX, corticosteroids), known or overt case of any other liver diseases (e.g., Chronic hepatitis B, chronic hepatitis C, Autoimmune liver disease, Haemochromatosis, Wilson’s disease, Primary biliary cirrhosis), pregnancy, and other co-morbid conditions (e.g., chronic obstructive pulmonary disease, chronic kidney disease, cardiac failure) were excluded from the study. Of the initially included patients, fifty patients (those who have given informed written consent, and those who fulfilled the inclusion criteria) of age 20 to 50 years, with Nonalcoholic fatty liver disease (NAFLD) were finally included.

**Study procedure**

Included patients were advised to do serum sampling for complete blood count (CBC), fasting blood sugar (FBS), blood sugar 2 hours after breakfast (BS 2hrs ABF), Bilirubin, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Prothrombin Time (PT), Thyroid Stimulating Hormone (TSH), Fasting lipid profile, HBsAg (ELISA), Anti HBc (Total) & Anti-HCV (ELISA), Serum ferritin, Serum ceruloplasmin, and antinuclear antibody (ANA). The degree of insulin resistance (IR) was determined by the homeostatic model assessment (HOMA) using the formula, HOMA-IR = (FPI × FPG)/22.5. Patients with HOMA >1.78 were considered insulin resistant [28].

They were hospitalized for liver biopsy after adequate counseling. Percutaneous liver biopsy was done for each patient following standard procedure. Following biopsy, liver tissue, preserved in 10% formal saline, was sent to a Pathologist for NAS & fibrosis score. On the morning of liver biopsy, 3 ml of venous blood sample was drawn to determine serum adiponectin level. Serum adiponectin levels were determined by an enzyme-linked immunosorbent assay (ELISA) kit (Quintikine) obtained from R&D Systems (Wiesbaden-Nordenstadt, Germany).

The histological diagnosis of NAFLD (NNFL & NASH) was based on NAFLD Activity Score (NAS), and stages of fibrosis were evaluated by fibrosis score. All other biochemical tests were performed using conventional automated analyzers within the Biochemistry Laboratory at BSMMU. All biochemical analyses were performed in a “blinded” manner.

**Data processing and data analysis**

Data were collected using structured questionnaire. The statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. Chi-Square test was used to analyze the categorical variables, shown with cross tabulation. Student t-test was used for continuous variables. ANOVA test was used to analyze the continuous variables, shown with mean and standard deviation. Pearson’s and spearman’s correlation coefficients were used to test the relationship between the groups. Sensitivity and
specificity were calculated by using the area under the receiver operating characteristic (ROC) curves. P value of <0.05 was taken as significant.

**Table 1: Baseline characteristics of the study population (n=50).**

| Baseline characteristics                          | Non-NASH (n=17) | NASH (n=33) | P value |
|--------------------------------------------------|-----------------|-------------|---------|
| Age (years)                                      | 39.9±8.63       | 36.9±9.80   | 0.292 **|
| Sex (male/female)                                | 99              | 11/22       | 0.344 **|
| Occupation (Housewife/others)                    | 99              | 15/18       | 0.914 **|
| Symptomatic                                      | 14              | 22          | 0.203 **|
| BMI (kg/m²)                                      | 25.06±3.79      | 26.65±3.49  | 0.145 **|
| Waist circumference (cm)                         | 76.88±6.33      | 79.85±10.65 | 0.297 **|
| Systolic BP (mmHg)                               | 120.29±21.54    | 119.76±19.33| 0.930 **|
| Diastolic BP (mmHg)                              | 76.76±7.49      | 77.27±8.93  | 0.841 **|
| Platelet count (x10⁹/L)                          | 273.2±62.17     | 291.79±70.04| 0.035 **|
| Fasting blood sugar (mmol/L)                     | 6.3±2.62        | 5.7±1.81    | 0.207 **|
| BS 2hrs ABF (mmol/L)                             | 9.99±4.15       | 9.33±4.32   | 0.607 **|
| TSH (µIU/ml)                                     | 2.23±1.17       | 2.2±1.14    | 0.960 **|
| Total cholesterol (mg/dl)                        | 193.76±42.97    | 200.58±52.39| 0.606 **|
| LDL (mg/dl)                                      | 121.12±35.8     | 120.84±41.6 | 0.981 **|
| HDL (mg/dl)                                      | 38.53±8.66      | 36.9±9.3    | 0.776 **|
| TG (mg/dl)                                       | 175.41±58.98    | 240.97±140.14| 0.084 **|
| AST (U/L)                                        | 34.82±25.67     | 46.79±37.39 | 0.243 **|
| ALT (U/L)                                        | 42.71±26.26     | 45.06±23.69 | 0.750 **|
| INR                                              | 0.99±0.06       | 1.0±0.03    | 0.434 **|
| HOMA-IR                                          | 2.52±1.70       | 2.53±1.66   | 0.985 **|
| GGT (U/L)                                        | 43.47±48.67     | 43.24±23.61 | 0.982 **|

s= significant, ns=not significant

*P value reaches from unpaired t-test

bP value reaches from chi square test

The mean age was found 38.0±9.4 years with range from 20 to 59 years. Regarding sex distribution of the study patients, it was observed that 31(62.0%) patients were female and 19(38.0%) patients were male. Complaints of the study patients, it was observed that 36(72.0%) patients had symptomatic, 29(58.0%) had pain in right upper abdomen (RUA), 27(54.0%) had nausea, 5(10.0%) had mass in RUA and 5(10.0%) had weight gain. Body Mass Index (BMI) was 26.1±3.6 kg/m², systolic blood pressure (BP) was 119.9±19.9 mmHg and diastolic BP was 77.1±8.4 mmHg. The hematological and biochemical parameters were as follows: platelet count was 285.5±67.4 x10⁹/L, FBS was 5.9±2.1 mmol/L, BS 2hrs ABF was 9.6±4.2 mmol/L, total cholesterol was 198.3±49.1 mg/dl, high density lipoprotein (HDL) was 38.0±9.3 mg/dl, triglyceride (TG) was 218.7±127.2 mg/dl, AST/ALT ratio was 1.0±0.8, ALP was 112.1±60.9 µL, gamma glutamyl transpeptidase (GGT) was 43.3±33.7U/L, INR was 1.0±0.45, HOMA-IR was 2.52±1.79, serum albumin was 4.6±0.3 g/dl, and serum bilirubin was 0.6±0.3 mg/dl. It was observed that the mean platelet count was statistically significant between non-NASH and NASH group but other baseline characteristics were not statistically significant in non-NASH and NASH group and stages of fibrosis.

Association between serum adiponectin with NAFLD: Table-2

**Table 2: Association between serum adiponectin with NAFLD (n=50).**

| NAFLD | Serum adiponectin (microgram/mL) | P value |
|-------|----------------------------------|---------|
|       | n | Mean±SD | Min±SD | 0.001s |
| Non-NASH (≤4) | 17 | 9.09±3.68 | 3.38-16.46 | |
| NASH (≥5) | 33 | 4.9±2.34 | 1.2-9.54 | |

Seventeen patients were found to have non-NASH and their serum adiponectin was 9.09±3.68 microgram/mL. Thirty three patients were found to have NASH and their serum adiponectin was 4.9±2.34 microgram/mL. The mean difference was statistically significant (p<0.05) between two groups. About two thirds of patients were in NASH group.
Association between serum adiponectin with fibrosis score:

Table 3: Association between serum adiponectin with fibrosis score (n=50).

| Fibrosis score | Serum adiponectin (microgram/mL) | P value |
|----------------|----------------------------------|---------|
| n              | Mean±SD                          | Min-max |
| 138            | 6.57±3.84                        | 1.2-16.46 |
| 210            | 5.5±1.84                         | 2.7-7.66 |
| 32             | 5.59±1.08                        | 4.82-6.36 |

Thirty-eight patients were found fibrosis score 1 and their serum adiponectin was 6.57±3.84 microgram/mL. Ten patients were found to have fibrosis score 2 and their serum adiponectin was 5.5±1.84 microgram/mL. Two patients were found to have fibrosis score 3 and their serum adiponectin was 5.59±1.08 microgram/mL. The mean difference was not statistically significant (p>0.05) between two groups. Very negligible number of patient were in significant fibrosis group (F2,3) and majority of patients in F1 group.

Association between serum adiponectin with BMI

Eighteen patients were found to have BMI ≤25.0 kg/m² and their serum adiponectin was 6.94±4.30 microgram/mL. Thirty-two patients were found BMI >25.0 kg/m² and their serum adiponectin were 5.97±2.92 microgram/mL. The mean difference was not statistically significant (p>0.05) between two groups.

Correlation between NAFLD Activity Score and serum adiponectin level

In this figure it was observed that negative correlation between serum adiponectin levels with NAFLD Activity Score. Correlation coefficient was (r=-0.644) that signify moderate negative correlation and that was statistically significant(p<0.001).

Receiver-operator characteristic (ROC) curve of serum adiponectin for prediction of NASH

It was observed in univariate analysis that obesity and serum adiponectin level were significantly associated with NASH but other variables were not associated with development of NASH.

Risk factors analysis for NASH (Multivariate logistic regression analysis)

A subject with serum adiponectin (<5 microgram/mL) vs serum adiponectin (≥5 microgram/mL) had 4.68 (95% CI 0.54 to 40.0) times increase in odds having NASH. Also, a subject with obese vs non-obese had 11.0 (95% CI 0.01 to 46.18) times increase in odds having NASH. Serum adiponectin level and obesity were significantly associated with NASH.

Discussion

This cross-sectional study was carried out including 50 NFALD patients to assess the correlation of serum adiponectin level with severity of nonalcoholic fatty liver disease (non-NASH fatty liver, NASH, and stages of fibrosis).

In the present study, it was observed that, two third of patients were below 40 years of age. It is probably due to altered food, and inadequate physical work habit. In 2016 a study by Jamali et al [27] showed the mean age was 37.02±9.82. Another study by Pandey...
et al. in 2015 [29] also showed alike observation; they showed the mean age in year’s ± SD of the study subjects was 46.00 ± 10.12 years in diabetic fatty liver disease group, 41.28 ± 8.12 years in non diabetic fatty liver disease group and 41.24 ± 7.23 in the control group. Wang Z et al. 2015 [30] observed prevalence of NAFLD 27.8% in women aged more than 55 years, the age prevalence is not consistent with our study.

Regarding sex distribution of the study patients, it was observed female were predominant. Female predominant observation probably due to sedentary life style. A study by Balmer et al. 2010 [31] showed 136 (58.62%) men and 96 (41.37%) women, which is inconsistent with our observation. In a study in 2013, Alam et al [7] found that NAFLD is more prevalent in female among Bangladeshi population; our observation is similar with this finding.

In this study we observed that the mean difference of HOMA-IR was not statistically significant (p=0.05) between non NASH and NASH groups. There are increasing data in the literature indicating that the serum adiponectin correlated with HOMA-IR (Pearson correlation coefficient r= -0.544, P=0.001). But, finding in a study by Esteghamati et al. in 2010 [28] is inconsistent with the finding in the current study.

In this study it was observed that two third of the patient were NASH group. As most of the patient were high BMI group they were more prone to develop NASH. Study by Savvidou et al. in 2009 [17] had similar observation that, 20 (60.6%) patients had “definite” NASH (NAS≥5), 10 patients had features suggestive of NASH (NAS=3 to 4), and 3 patients had simple steatosis (NAS<3).

The mean difference of serum adiponectin between non-NASH and NASH group was statistically significant (p=0.001). As about half of the patient had high ALT and more than half of the patient had high AST and ALT ratio, also two third patient had high BMI they may present with significant inflammatory change in liver. Savvidou et al. 2009 [17] observed comparison of means after logarithmic transformation of adiponectin concentration revealed lower serum levels of this cytokine as NAS increased. However, the difference did not reach statistical significance (one-way ANOVA, P=0.316). Similar study by Arvaniti et al. 2008 [32] observed patients with confirmed NASH had lower serum adiponectin levels in comparison to non-NASH; it was 6.6±4.7 microgram/mL vs 9.2±4.8 microgram/mL, p = 0.01 that are consistent with this study. Another study Shimada et al. 2007 [33] reported that the serum adiponectin level was found to be significantly lower with NAS group (3.6 μg/mL) than in the simple steatosis (non-NASH) group (6.0 μg/mL) (P < 0.001).

In this study we observed that the mean difference of serum adiponectin and stages of fibrosis was not statistically significant (p=0.05); this may be because very negligible number of patient were in significant fibrosis group (F2, 3) and majority of patients in F1 groups. Bugianesi et al. in 2005 [34] found in a study that, adiponectin is related to hepatic fat content and not to necroinflammatory activity and fibrosis stage that were similar to current study. A study by Savvidou et al. in 2009 [17] observed that adiponectin was normally distributed after logarithmic transformation; this is not consistent with our observation. Comparison of means with one-way ANOVA revealed that serum adiponectin levels differed significantly among different stages of hepatic fibrosis (F=4.18 with P=0.007). Musso et al. in 2005 [22] in a study found that adiponectin could predict patients with higher necroinflammatory grade and fibrosis stage from those with milder histological findings that were not identical to this study.

Negative correlation between serum adiponectin levels with NAFLD Activity Score (NAS) (r=-0.644; p=0.001) was observed that was statistically significant. In 2006, Targher et al. [35] in a study showed that after logistic regression analysis, low adiponectin levels independently predicted hepatic steatosis and necroinflammation but not fibrosis after adjustment for age, sex, BMI, HOMA-IR and Metabolic syndrome (MetS) components those were consistent with the present study.

In this series also negative correlation (r = -0.086; p=0.533, negligible) between hepatic fibrosis score and serum adiponectin level was observed but not statistically significant. In a study by Savvidou et al. in 2009 [17] explored that the correlation between adiponectin levels and fibrosis stage revealed a negative correlation (r= -0.551 P=0.00048); the finding is consistent with the present study. Based on the receiver-operator characteristic (ROC) curves serum adiponectin level had area under curve 0.167. ROC was constructed by using serum adiponectin, which gave a cut off value <4.8 microgram/mL, with 51.5% sensitivity and 11.8% specificity for prediction of NASH. In the study by Shimada et al. in 2007, the AUC was high (0.765) in the early-stage NASH group, and it was also the highest among all other markers. The sensitivity of the serum adiponectin level in the diagnosis of early-stage NASH was 68% which was higher than for any other factors, while its specificity was 79% that were inconsistent with the current study.

After multivariable logistic regression analysis, serum adiponectin (<5 microgram/mL) vs serum adiponectin (≥5 microgram/mL) level were not associated with early fibrosis (F1) and significant fibrosis (≥F2) but a subject with serum adiponectin (<5 microgram/mL) vs serum adiponectin (≥5 microgram/mL) also had 4.68 (95% CI 0.54 to 40.0) times increase in odds having NASH. Targher et al. in 2006 [35] in a study showed that logistic regression analysis, low adiponectin levels independently predicted hepatic steatosis and necroinflammation but not fibrosis which was approximately similar with this study.

Conclusion

Serum adiponectin level decreased in patients with NASH than in patients not having NASH, and it is also reduced in patients with advanced hepatic fibrosis. Serum adiponectin could be a marker to differentiate between non-NASH & NASH.

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Conflict of Interest

No author has any relationship, either financial or otherwise with this work. So, there does not exist any conflict of interest.

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