

Research Article

Estimation of adiponectin levels in diabetic, non-diabetic fatty liver diseases and healthy controls

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ABSTRACT

Background: Estimation of adiponectin levels in diabetic and non-diabetic fatty liver and healthy controls.

Methods: We studied 25 subjects for diabetic fatty liver, 25 subjects for non-diabetic fatty liver and 25 healthy controls. Clinical evaluation included anthropometric measurements, BMI, biochemical investigations and adiponectin estimation by ELISA.

Results: There were 15 males (60%) and 10 (40%) females subjects in the DFL group, 18 males (72%) and 7 females (28%) subjects in the NDFL group and 13 males (52%) and 12 females (48%) subjects in the control group. 80% (20) of the DFL patients and 72% (18) subjects of NDFL group had BMI >25kg/m². 80% (12 males and 8 females) of subjects in the DFL group and 68% (12 males and 5 females) had a waist circumference that indicated central obesity as per Indian cut-offs (>90 cm for females and >80 cm for males). The mean adiponectin (µg/ml) ± SD levels in DFL were 4.03 ± 0.43, NDFL was 5.01 ± 0.55 and in controls was 7.63 ± 0.66, the difference being statistically significant with P <0.001. The difference in the adiponectin levels was statistically significant between each of the three groups with P <0.001. There was no difference in serum adiponectin levels between males and females in all three groups.

Conclusion: The chief conclusion of this study are that serum adiponectin levels are lower in subjects with NAFLD than those without it; adiponectin levels are inversely related to the degree of steatosis in NAFLD, with the lowest levels in more severe forms of steatosis.

Keywords: Adiponectin, Fatty liver, Diabetes mellitus, Non-alcoholic fatty liver diseases

INTRODUCTION

Adiponectin, a protein normally produced by the adipose tissue, is considered a potent modulator of lipid and glucose metabolism. Adiponectin has been shown to have anti-inflammatory, anti-diabetic and anti-atherogenic properties. It plays an important role in the pathogenesis of metabolic diseases and therefore adiponectin levels inversely correlate with multiple metabolic and related disorders.¹ Adiponectin increases the sensitivity of

peripheral tissues like the adipose tissue and skeletal muscle to insulin and thus protects against inflammation and apoptosis. It is considered to be vital in the relationship between adiposity, insulin resistance and inflammation.

It is a desirable marker as it is readily detectable in blood, stable upon collection and relatively inert to the method of collection and diurnal changes.

In recent studies, serum adiponectin level has been shown to progressively decrease in accordance to the severity of obesity, insulin resistance, diabetes mellitus or cardiovascular diseases.²⁻⁴

Non-Alcoholic Fatty Liver Disease (NAFLD) is a common type of chronic liver injury. It is a condition characterized by findings of fat infiltration of the liver on radiological or biopsy examination, without history of significant alcohol consumption, medication intake leading to fatty liver, or other known causes. The spectrum of NAFLD includes simple steatosis, Non-Alcoholic Steato-Hepatitis (NASH), fibrosis, cirrhosis and hepato-cellular carcinoma. NAFLD is considered to be the hepatic manifestation of a metabolic syndrome and shows profound correlations with insulin resistance, obesity, type 2 diabetes, dyslipidemia and other conditions.⁵ Although the pathogenesis of NAFLD remains largely unknown, insulin resistance, oxidative stress and inflammation are known to play important roles in the development and progression of NAFLD.⁶

This study was undertaken to determine the serum levels of adiponectin in patients of fatty liver disease, with and without diabetes mellitus and study the role of adiponectin in NAFLD.

METHODS

A cross sectional case-control study was undertaken in the department of Endocrinology and Gastroenterology after obtaining ethical clearance from our institution between May 2013 and October 2013. The study involved 75 subjects in the age group of 18-50 years. The study population comprised of three groups- group 1: patients of fatty liver disease with diabetes mellitus, group 2: patients of fatty liver disease without diabetes mellitus attending gastroenterology and endocrinology OPD and group 3: healthy normal subjects coming to the diagnostic laboratory for routine health check-ups were included as controls. The controls had a normal ultrasonographic examination of liver and did not meet any of the five criteria required for a diagnosis of metabolic syndrome according to the updated AHA/NHLBI statement (Modified NCEP ATP III criteria).⁷

Presence or absence of fatty liver was confirmed by ultrasonography as was done in a study by Sargin H et al.^[15] though the gold standard for diagnosis of fatty liver is liver biopsy. Diagnosis of type 2 diabetes was made based on history and laboratory investigations [Fasting Blood Sugar (FBS), according to the WHO criteria (Fasting blood glucose ≥ 126 mg/dl)].⁸

Subjects on drugs reported to cause or improve steatosis (e.g.: steroids, estrogens, tamoxifen, amiodarone, valproic acid, oral contraceptives, diltiazem or methotrexate, metformin, pioglitazone, statins, or any herbal medicine in the past 3 months), patients with

kidney disease, viral hepatitis (positive for hepatitis B surface antigen and anti-hepatitis C virus), chronic liver disease, hepatocellular carcinoma, history of alcohol ingestion (>30 g/day for men and >20 g/day for women), and diabetics with cardiovascular or cerebrovascular complications were excluded from the study.

A written informed consent was obtained from the subjects. A detailed history was taken. Blood pressure and anthropometric measurements and physical examination were carried out using standardized instruments and protocols.⁹ BMI was calculated using the formula: weight (kg)/height² (m²).¹⁰

All study subjects underwent an Oral Glucose Tolerance Test (OGTT) using 75gm glucose load, except self-reported diabetic subjects for whom fasting blood sugar was measured. Diagnosis of diabetes was based on WHO consulting group criteria, i.e., 2 hour post load blood glucose ≥ 200 mg/dl and/or fasting blood sugar ≥ 126 mg/dl or self-reported diabetic subjects on treatment by a physician. Normal glucose tolerance was diagnosed if 2 hour post load glucose was <140 mg/dl and / or FBS <100 mg/dl.¹¹ Three milliliters of fasting sample of blood was collected into a plain vacutainer using aseptic precautions from the all the study subjects after confirming no calorific intake for at least 8-10 hours. The blood samples were allowed to clot and after centrifugation, the following biochemical investigations were done on the separated serum: Fasting Blood Sugar (FBS) (by hexokinase method), total bilirubin (Diazo method), alanine transaminase (ALT) (modified IFCC method without PLP activation), alkaline phosphatase (ALP) (IFCC method), Gamma Glutamyl Transpeptidase (GGT) (Enzymatic colorimetric assay), complete lipid profile (serum total cholesterol-enzymatic colorimetric method using cholesterol oxidase, serum triglyceride-enzymatic colorimetric method using glycerol phosphate oxidase, serum high density lipoprotein HDL-enzymatic colorimetric method using cholesterol oxidase and esterase and low density lipoprotein LDL using Friedwalds equation) using kits supplied by Roche Diagnostics (Basel, Switzerland) on Cobas 6000 c501 RXL MAXTM, fully automated analyzer in the biochemistry laboratory. The intra and interassay coefficients of variation for the biochemical assays ranged between 3.1 and 7.6%. Glycated haemoglobin (HbA_{1c}) was done BioradD10 analyser using high performance liquid chromatography with the intra- and inter-assay co-efficient of variation being <10 per cent. Serum adiponectin was measured using Enzyme Linked Immune Assay (ELISA) using an ELISA kit obtained from Bio Vendor research and diagnostic products. Ultrasonography examination of liver was performed by an experienced radiologist, using a high-resolution B-mode ultrasonography system (Voluson 730 PRO; GE medical systems) with a convex transducer with a frequency of 3-5 MHz's. The radiologist was blinded to all clinical and biochemical characteristics of the subjects. The images obtained were recorded and saved

digitally. Fatty liver was defined as the presence of an echogenic “bright” liver with liver echogenicity greater than that of the renal parenchyma, vessel obscuration or blurring, and narrowing of the lumen of the hepatic veins in the absence of findings suggestive of chronic liver disease such as coarsened echo texture or surface nodularity.¹²

Only those subjects who denied consuming any alcohol were chosen. This ensured that patients with alcoholic fatty liver disease were excluded. NAFLD was defined as any degree of fatty liver in the absence of any alcohol intake. NAFLD, if present, was classified based on the severity of fatty liver based on standard criteria, grade 1 (mild steatosis) was defined as slightly increased liver echogenicity with normal vessels and absent posterior attenuation, grade 2 (moderate steatosis) was defined as moderately increased liver echogenicity with partial dimming of vessels and early posterior attenuation, grade 3 (severe steatosis) was defined as diffusely increased liver echogenicity with absence of visible vessels and heavy posterior attenuation.¹²

Statistical analysis

A descriptive and inferential statistical analysis was carried out in the present study. The data was collected in preformed questionnaires and then entered into Microsoft excel sheets. Statistical analysis was performed with SPSS version19 software package (SPSS, Inc. Chicago). Results on continuous measurements were presented on mean ± SD (Min-Max) and results on categorical measurements are presented in number (%). Significance was assessed at 5 % level of significance.

The following assumptions on data were made: 1. dependent variables are normally distributed, 2. samples drawn from the population, are random, cases of the samples are independent. Analysis of variance (ANOVA) was used to find the significance of study parameters between three or more groups of patients; Post-Hoc Tukey test has been used to find the pair wise significance, Chi-square/Fisher exact test was used to find the significance of study parameters on categorical scale between two or more groups. Pearson correlation was used between adiponectin with anthropometric, biochemical and lipid variables.

RESULTS

75 subjects were included in the present study with 25 each in each of the three groups - groups 1: Patients of fatty liver disease with diabetes mellitus (DFL), group 2: Patients of fatty liver disease without diabetes mellitus (NDFL) group 3: Healthy normal subjects (controls).

The mean age in year’s ± SD of the study subjects was 46.00 ± 10.12 years in DFL group, 41.28 ± 8.12 years in NDFL group and 41.24 ± 7.23 in the control group. There were 15 males (60%) and 10 (40%) females subjects in the DFL group, 18 males (72%) and 7 females (28%) subjects in the NDFL group and 13 males (52%) and 12 females (48%) subjects in the control group. 80% (20) of the DFL patients and 72% (18) subjects of NDFL group had BMI >25 kg/m². 80% (12 males and 8 females) of subjects in the DFL group and 68% (12 males and 5 females) had a waist circumference that indicated central obesity as per Indian cut-offs (>90 cm for females and >80 cm for males).¹³

Table 1: Comparison of anthropometric & biochemical variables in the three groups studied.

| Anthropometric variables | Results | | | P value | Pair wise significance | | |
|--|----------------|----------------|----------------|----------|------------------------|--------------|---------------|
| | DFL | NDFL | Controls | | DFL-NDFL | DFL-Controls | NDFL-Controls |
| Age in years | 46.00 ± 10.12 | 41.28 ± 8.12 | 41.24 ± 7.23 | 0.085 | 0.139 | 0.129 | 1.000 |
| BMI (kg/m ²) | 29.71 ± 3.11 | 27.46 ± 2.31 | 22.19 ± 1.02 | <0.001** | 0.003** | <0.001** | <0.001** |
| Waist circumference (cm) | 97.34 ± 10.27 | 91.60 ± 7.60 | 81.80 ± 6.14 | <0.001** | 0.041* | <0.001** | <0.001** |
| Fasting blood sugar (mg/dl) | 156.2 ± 43.64 | 110.76 ± 10.96 | 92.36 ± 7.65 | <0.001** | <0.001** | <0.001** | 0.042* |
| Glycated haemoglobin HbA _{1c} (%) | 7.48 ± 0.59 | 5.70 ± 0.15 | 5.24 ± 0.27 | <0.001** | <0.001** | <0.001** | <0.001** |
| Total bilirubin (mg/dl) | 0.88 ± 0.33 | 0.78 ± 0.26 | 0.61 ± 0.24 | 0.004** | 0.448 | 0.003** | 0.082+ |
| Alanine aminotransferase (U/L) | 45.04 ± 2.51 | 43.32 ± 8.17 | 19.12 ± 3.70 | <0.001** | 0.499 | <0.001** | <0.001** |
| Alkaline phosphatase (U/L) | 113.4 ± 25.31 | 90.20 ± 13.09 | 87.32 ± 17.67 | <0.001** | <0.001** | <0.001** | 0.859 |
| Gamma glutamyl transpeptidase (IU/L) | 38.12 ± 3.05 | 35.80 ± 2.40 | 21.96 ± 2.54 | <0.001** | 0.009** | <0.001** | <0.001** |
| Triglycerides (mg/dl) | 221.4 ± 48.34 | 183.0 ± 50.97 | 126.2 ± 24.63 | <0.001** | 0.007** | <0.001** | <0.001** |
| Total cholesterol (mg/dl) | 190.4 ± 36.59 | 185.3 ± 18.98 | 177.5 ± 29.33 | 0.297 | 0.812 | 0.270 | 0.614 |
| HDL (mg/dl) | 40.64 ± 9.28 | 32.32 ± 5.53 | 47.96 ± 5.88 | <0.001** | <0.001** | 0.001** | <0.001** |
| LDL (mg/dl) | 124.40 ± 25.30 | 98.44 ± 29.89 | 115.84 ± 28.04 | 0.005** | 0.004** | 0.524 | 0.076+ |
| Adiponectin (µg/ml) | 4.03 ± 0.43 | 5.01 ± 0.55 | 7.63 ± 0.66 | <0.001** | <0.001** | <0.001** | <0.001** |

Table 1 shows a comparison of the three groups in terms of anthropometric and biochemical variables. Statistically significant differences were found amongst the three groups with respect to weight, BMI, waist circumference, waist hip ratio, FBS, HbA_{1c}, total bilirubin, ALT, ALP, GGT, triglycerides, total cholesterol, HDL, LDL and adiponectin levels. The mean adiponectin (µg/ml) ± SD levels in DFL were 4.03 ± 0.43, NDFL was 5.01 ± 0.55 and in controls was 7.63 ± 0.66, the difference being statistically significant with P <0.001. The difference in the adiponectin levels was statistically significant between each of the three groups with P <0.001. There was no difference in serum adiponectin levels between males and females in all the three groups.

Adiponectin correlated negatively with a few anthropometric parameters like BMI in NDFL group (r = -0.282, P <0.01) and controls (r = -0.26, P <0.05) but not in patients of diabetic fatty liver (r = -0.043, P = 0.31). There was a significant negative correlation between adiponectin and waist circumference only in the NDFL (r = -0.412, P = 0.041) and control group (r = -0.316, P <0.05) but not in the DFL group (r = -0.067, P = 0.751). A significant negative correlation was also seen between adiponectin and waist-hip ratio in all the three groups DFL (r = -0.604, P = 0.001), NDFL (r = -0.540, P = 0.005) and controls (r = -0.6, P = 0.04).

There was a significant positive correlation between adiponectin levels and HDL levels in all the three groups DFL (r = 0.607, P = 0.001), NDFL (r = 0.590, P = 0.002), controls (r = 0.37, P = 0.04). There was no significant correlation between adiponectin and total bilirubin, ALT, ALP, GGT or any other lipid profile in any of the three study groups. Based on ultrasonography findings, in DFL group, 10 subjects (40%) had moderate steatosis and 15 (60%) had severe hepatic steatosis. 1 (4%) subject had mild steatosis, 13 (52%) subjects had moderate steatosis and 11 (44%) subjects had severe steatosis in the NDFL group. Adiponectin levels were found to be inversely correlated to the degree of hepatic steatosis as shown in Table 2 (P <0.001). Figure 1 shows the serum adiponectin levels in the different grades of hepatic steatosis.

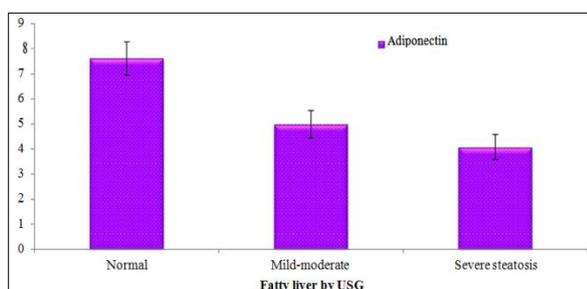


Figure 1: Serum adiponectin levels in the different grades of hepatic steatosis.

F=261.070; P <0.001**

Table 2: Comparison of adiponectin according to degree of steatosis in each three groups studied.

| Fatty liver by USG | Adiponectin | | |
|--------------------|------------------|--------------------|------------------|
| | Min-Max | Mean ± SD | 95%CI |
| Normal | 6.40-8.80 | 7.62 ± 0.66 | 7.35-7.90 |
| Mild-moderate | 4.20-6.20 | 4.99 ± 0.55 | 4.77-5.23 |
| Severe steatosis | 3.20-4.90 | 4.08 ± 0.50 | 3.88-4.28 |
| Total | 3.20-8.80 | 5.56 ± 1.62 | 5.18-5.93 |

DISCUSSION

A cross sectional study was undertaken in order to determine the serum levels of adiponectin in patients of fatty liver disease with and without diabetes mellitus and study the role of adiponectin in NAFLD.

The mean adiponectin levels in our study were lowest in patients of fatty liver with diabetes mellitus (DFL group) (4.03 ± 0.43 µg/ml). This was significantly lower than adiponectin levels in patients of fatty liver without diabetes mellitus (NDFL group) (5.01 ± 0.55 µg/ml) and in healthy normoglycemic subjects (controls) (7.63 ± 0.66 µg/ml). This finding is in accordance with previous studies in both western and Asian populations.¹⁴⁻¹⁶ Adiponectin concentrations are 20-60% lower in patients with NAFLD than in healthy persons.¹⁷

The present study indicates that 80% of the DFL patients and 72% of subjects of NDFL group have BMI >25 kg/m² and 80% of subjects in the DFL group and 68% of the subjects in the NDFL group have a waist circumference that indicates central obesity as per Asian cut-offs.¹³ His observation is similar to that of Kumar R et.al.¹⁸ Who showed that 61.7% of the Indian NAFLD subjects were obese and 62% had central obesity. We also found that serum adiponectin levels correlated negatively with a few anthropometric parameters like BMI (in NDFL group and controls), waist circumference (in NDFL and control group) and waist hip ratio (in all the three groups). Many studies have described a similar significant negative correlation between serum adiponectin levels and BMI, percent body fat, waist-to-hip ratio and intra-abdominal fat.^{15,19,20} A few studies have found no correlation between serum adiponectin levels and anthropometric parameters.^{18, 21} Contradictory findings regarding the association between adiponectin and BMI are possibly the result of the different composition of the respective study collective with respect to the degree of overweight and the relative proportions of subcutaneous and visceral adipose tissue. In the present study, a negative correlation between BMI and serum levels of adiponectin could be because of the fact that obesity leads to adipose tissue dysfunction. Despite a lower BMI, Indians have a greater degree of adiposity and higher body fat percentage than their Caucasian counterparts.²² The total adipose tissue in an individual might have an upper limit or capacity for

storing fat optimally. Once this capacity is exceeded, any further nutrient excess will result in metabolic disturbance such as insulin resistance and inflammation.²³ It is likely that our study subjects have a lower capacity for fat storage and thus an excess caloric intake may result in greater metabolic perturbations. Hypoadiponectinemia may represent dysfunction of adipose tissue in obesity.²¹

The present study essentially shows that NAFLD patients have reduced circulating adiponectin and this reduction is greater in patients of diabetes mellitus with NAFLD than in patients with NAFLD without diabetes mellitus.

The pathogenesis of NAFLD appears to involve multiple-hit process. The first hit is the steatosis which is believed to be triggered by insulin resistance²⁴ and the second hit, which involves cytokines alteration and oxidative stress, results in disease progression.²⁵ A prominent feature in most patients with NAFLD is insulin resistance. A non-diabetic population may exhibit insulin resistance and genetic predisposition to insulin resistance is also seen, even in the absence of frank diabetes. These type of subjects may have been present in the NDFL & control subjects of our study. Patients of type 2 diabetes mellitus with NAFLD will have a relatively greater degree insulin deficiency or insulin resistance.¹⁹

Indians are known to have a relatively unfavorable risk profiles for type 2 diabetes and cardiovascular disease.¹⁹ There is a strong association between insulin resistance, obesity and NAFLD. Evidence suggests that insulin resistance affects hepatic fat accumulation by increasing release of free fatty acids from adipose tissue, increasing fatty acid and triglycerides synthesis in the liver, reducing fatty acid oxidation and reducing Very Low-Density Lipoprotein (VLDL) production.²⁷ Insulin resistance and hyperinsulinemia are also associated with the inflammatory and fibrotic reaction that complicates advanced stages of NAFLD.⁵ It has now been recognized that adipocytes play an important role in energy homeostasis because they secrete important cell signaling proteins like adipokines that regulate metabolism. It is believed that adiponectin, released from white adipose tissue, attenuates liver inflammation and fibrosis, possibly through a reduction in the hepatic and insulin resistance. Adiponectin is considered to have insulin sensitizing, antifibrogenic, antiapoptotic, and anti-inflammatory properties on a number of different cell types beside its peripheral effects, adiponectin acts in the brain to increase energy expenditure and cause weight loss.³⁰ Adiponectin release from adipocytes is down-regulated under adverse metabolic conditions, resulting in decreased adiponectin serum concentrations.³⁰ Various hormones associated with insulin resistance and obesity including catecholamines, insulin, glucocorticoids, TNF α and IL-6 down-regulate adiponectin expression and secretion in fat cells in vitro.³¹

In the present study, it was observed that adiponectin concentrations decline inversely to the degree of steatosis. This observation corresponds to findings of Flechtner-Mors et al. and Pisto et al. in which an increase in hepatic fat content, estimated by sonographic assessment of brightness into levels 0, 1 and 2, was associated with a decrease in adiponectin concentrations.^{32,33}

The main drawback of the present study was its cross sectional study design, with a small sample size and that Insulin resistance was not measured among study subjects. With reference to the shortcomings of the study, prospective follow up studies may be needed to determine the exact role played by low adiponectin levels in the pathogenesis of NAFLD.

CONCLUSION

The chief conclusions of the study are that serum adiponectin levels are lower in subjects with NAFLD than those without it; adiponectin levels are inversely related to the degree of steatosis in NAFLD, with the lowest levels in more severe forms of steatosis.

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Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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