

Relationship of Adiponectin with Liver Enzymes in NAFLD Subjects

Charu Gunjal¹, Ankita Sharma², G.G. Kaushik³, Manjubala Maheriya¹

¹M.Sc. Student, ²Sr. Demonstrator, ³Sr. Professor,
Department of Biochemistry, J.L.N. Medical College, Ajmer.

Corresponding Author: Ankita Sharma

ABSTRACT

NAFLD is a complex metabolic condition in which excessive fat gets accumulated in the liver of patients in absence of immoderate alcohol consumption. The increased fat content of the liver correlates positively with the insulin resistance that characterizes metabolic syndrome. Adipokines are hormones secreted by visceral adipose tissue which are implicated in development of obesity and pathogenesis of Insulin resistance (IR). Recently, there is great enthusiasm in studying their potential role in the pathogenesis of NAFLD. The aim of this study was to determine the validity of adiponectin (non-invasive parameter) for Non-alcoholic fatty liver disease and to investigate the correlation between serum levels of this adipokine and liver enzymes in patients with Non-alcoholic fatty liver disease in Indian population. 84 USG proven NAFLD subjects and 84 healthy non-obese age and gender matched controls were studied. Serum concentrations of ALT, AST, GGT, ALP and Adiponectin levels were assessed. The study showed that serum adiponectin is statistically significantly lower in patients with NAFLD than in control group. Serum adiponectin and liver enzymes were significantly inversely correlated in NAFLD subjects. Hence, it is concluded that in addition to liver enzymes, adiponectin (non invasive parameter) can also be used as diagnostic measure for NAFLD subjects.

Keywords: Adiponectin, NAFLD, Liver Enzymes

INTRODUCTION

NAFLD is defined as the accumulation of excessive fat in the liver of patients without history of alcohol abuse or other causes of hepatic steatosis. ⁽¹⁾ The majority of patients with NAFLD are obese or even morbidly obese and have accompanying insulin resistance that plays a central role in the metabolic syndrome.

Adiponectin is a plasma protein secreted mainly by adipocytes. ^(2,3) It improves hepatic and peripheral insulin sensitivity ^(4,5) and has anti-inflammatory, antilipogenic and antiatherogenic properties. ⁽⁶⁾ It also protects hepatocytes from triglyceride accumulation. ^(5,7) Previous studies have suggested role of adipohormones (adiponectin, resistin, leptin, etc.) in pathogenesis of NAFLD and its

progression to NASH through their metabolic and pro or anti-inflammatory activity. ^(6,8) Its secretion is found to be decreased in obesity, insulin resistance, type 2 diabetes mellitus and other conditions associated with metabolic syndrome. ⁽⁶⁾ Recent data have shown hypo-adiponectinemia in patients with NASH. ^(2,3)

NAFLD is characterized by mild to moderate increase in aspartate transaminase (AST), alanine transaminase (ALT), or both. Aminotransferase levels may be elevated two to four times over the upper limit of normal, ⁽⁹⁾ with ALT being higher than AST, in contrast to alcoholic steatohepatitis. However, in the absence of advanced disease, routine liver function tests are either normal or typically show only mild elevations in aminotransferase levels, with

alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) levels 1.5 to 3 times the upper limit of normal. ⁽¹⁰⁾

Therefore, the present study was undertaken to determine the validity of adiponectin (non-invasive parameter) for Non-alcoholic fatty liver disease and to investigate the correlation between serum levels of this adipokine and liver function tests in subjects with Non-alcoholic fatty liver disease.

MATERIALS & METHODS

In this observational study, 84 USG proven NAFLD subjects and 84 healthy non-obese age and gender matched controls were enrolled. Diagnosis of NAFLD was based on presence of persistently elevated aminotransferase levels and USG finding of bright liver according to the criteria accepted by the American Gastroenterology association.

Patients with Inflammatory diseases, viral hepatitis and autoimmune hepatitis, Haemochromatosis, Wilson's disease were excluded. Patients with daily alcohol intake exceeding 20g/day and patients having BMI < 25Kg/m² and BMI > 35 Kg/m² were also excluded. Subjects using steroids, corticosteroids, oral contraceptives and lipid-lowering agents were also excluded from the study. An informed consent was obtained from all the participants prior to enrolment.

All subjects included in the study were subjected to detailed history taking, complete clinical examination including anthropometric evaluation (weight, height,

body mass index (BMI). Laboratory investigations included liver function tests i.e. ALT, AST, GGT and ALP. Serum Adiponectin levels were measured using the ELISA technique.

Statistical Analysis

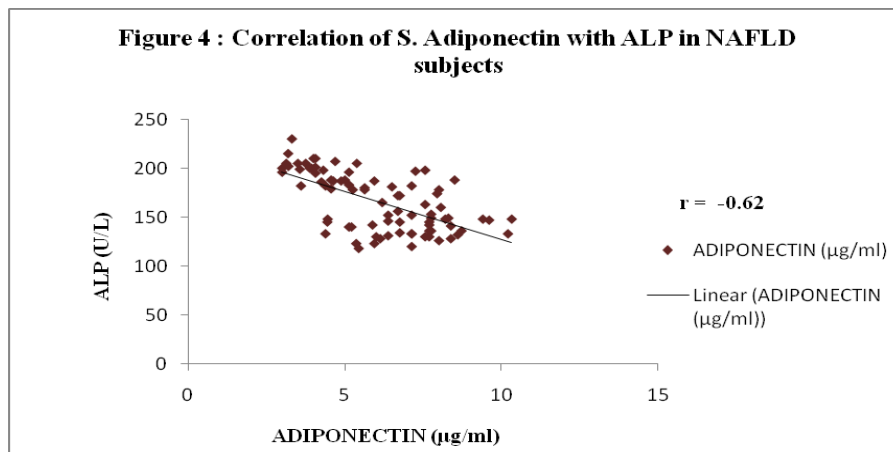
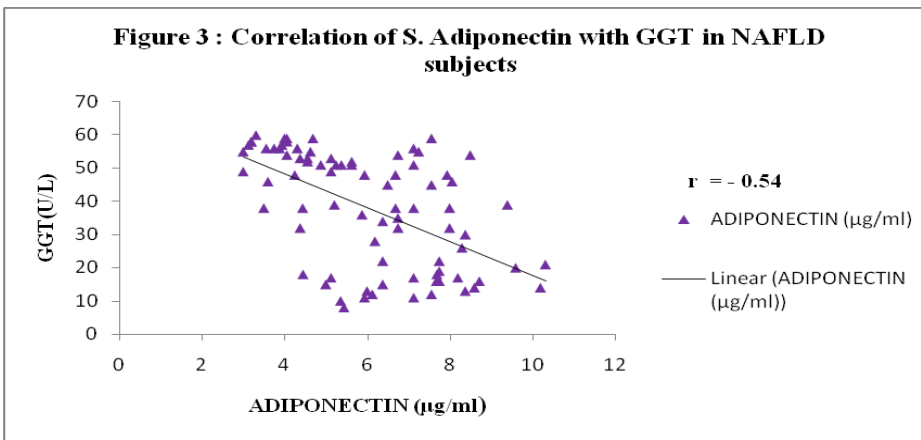
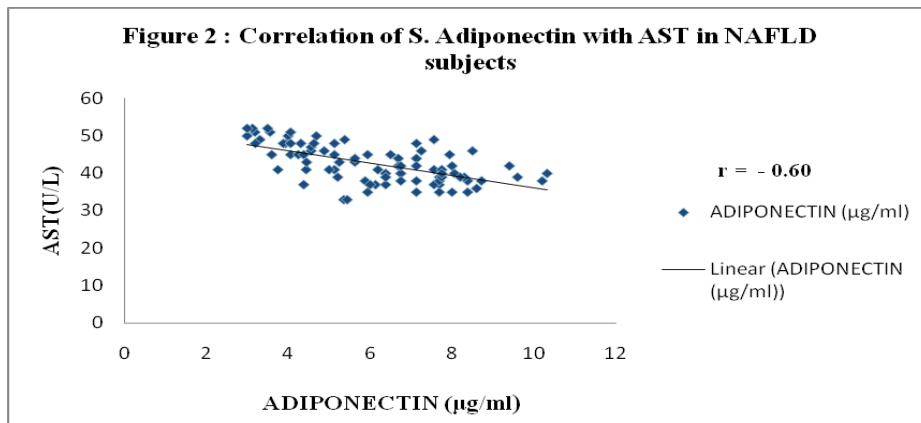
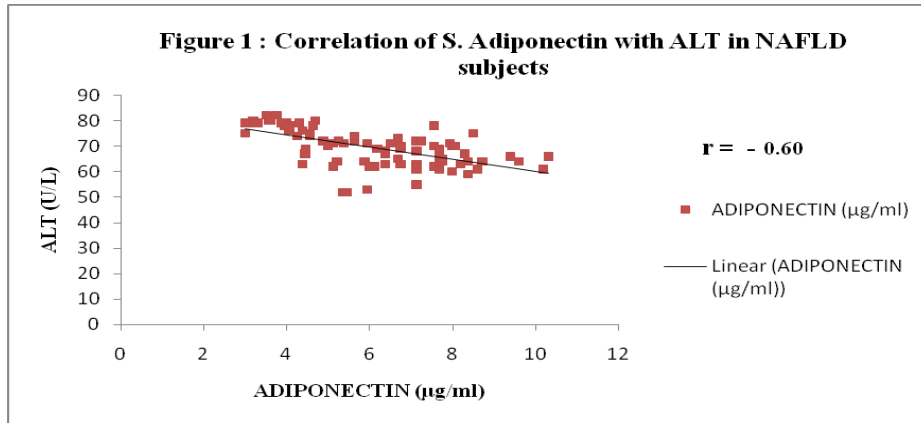
Data were recorded in a predesigned performa as mean±SD. Comparison of physical and biochemical parameters between NAFLD subjects and Healthy controls were performed using student t-test and statistical significance was seen by p value <0.05. The association between serum liver enzymes and adipokines were examined using correlation coefficient (r).

RESULT

The study was undertaken in two groups viz group-I and group-II i.e. 84 normal healthy controls and 84 NAFLD subjects respectively. The anthropometric parameters viz, BMI mean ± SD in kg/m² in the group-I and group-II was (22.98 ± 5.03), (30.01±3.01) respectively. The mean serum ALT level and serum AST levels were found to be significantly high in NAFLD subjects (group-II) as compared to healthy controls (group-I) (p < 0.0001). A similar trend was observed in mean serum GGT level and serum ALP level [Table 1]. The mean serum adiponectin level in NAFLD subjects (6.07 ± 1.85 µg/ml) is found lower than healthy controls (9.59 ± 2.08 µg/ml; p<0.0001) [Table 1]. A negative correlation was found between serum adiponectin level and liver enzymes viz ALT (r = - 0.60), AST (r = -0.60), GGT (r = -0.54) and ALP (r = -0.62) (in NAFLD subjects) [Fig. 1-4].

Table 1: Anthropometric and Biochemical parameters of NAFLD subjects and Healthy subjects

Parameters	GROUP I Healthy Subjects Mean ± SD (n=84)	GROUP II NAFLD subjects Mean ± SD (n=84)
AGE (Years)	48.46 ± 8.42	49.42 ± 9.05
BMI (Kg/m ²)	22.98 ± 5.03	30.01 ± 3.01
Alanine aminotransferase (U/L)	33.58 ± 3.47	69.34 ± 7.27
Aspartate aminotransferase (U/L)	25.98 ± 6.57	42.58 ± 5.04
Gamma-Glutamyl Transferase (U/L)	24.41 ± 6.65	37.53 ± 17.22
Alkaline phosphatase (U/L)	121.26 ± 19.54	165.75 ± 29.24
S. Adiponectin (µg/ml)	9.59 ± 2.08	6.07 ± 1.85



DISCUSSION

Several studies have demonstrated the association between hypo adiponectinemia and NAFLD. Our finding is in accordance with recent report by Gad H. 2018, ⁽¹¹⁾ Jamali et al. 2016, ⁽¹²⁾ Amin MA et al. 2015 ⁽¹³⁾ who reported lower adiponectin level in patients with NAFLD than in control group. And this reduction was associated with insulin resistance. The strong association between insulin resistance and NAFLD has been extensively demonstrated. Gad H. 2018, ⁽¹¹⁾ Pagano et al. 2005, ⁽¹⁴⁾ Bugianesi et al. (2005) ⁽¹⁵⁾ revealed that fasting serum insulin and insulin resistance levels (HOMA test) were significantly higher in NAFLD subjects as compared to control group.

It is assumed that adiponectin might be able to preserve hepatic function by preventing the accumulation of lipids in hepatocytes. The possible mechanism could be through the activation of AMPK by adiponectin. Activation of AMPK is brought by the binding of APPL1 (Adaptor protein, phosphotyrosine interaction, PH domain and leucine zipper containing 1) to both adipoR1 and adipoR2 which causes its phosphorylation. ^(16,17)

AMPK activation reduces lipid synthesis by decreasing the activity of acetyl coenzyme A carboxylase (ACC). AMPK activation also enhances fatty acid oxidation by blocking the production of malonyl-CoA which allosterically inhibits carnitine palmitoyl transferase 1, the rate-limiting enzyme in fatty acid oxidation. In addition, activation of AMPK downregulates the expression of sterol regulatory element-binding protein 1c (SREB- P1c) which in turn results in downregulation of genes involved in lipogenesis i.e. ACC, fatty acid synthase, and glycerol-3-phosphate acyltransferase and hence regulates cholesterol and lipid synthesis. ⁽¹⁸⁾

Further, adiponectin also stimulate PPAR- α which controls the transcription of a panel of genes encoding fatty acid oxidation. ⁽¹⁹⁾ Therefore, adiponectin-mediated signaling pathways lead to

enhanced fat oxidation and reduced lipid synthesis thereby preventing accumulation of lipids in liver.

Previous studies have shown that serum adiponectin levels paradoxically decreases with the onset of obesity while weight loss induces adiponectin production. ⁽²⁰⁾ In the present study as the subjects were also overweight /obese therefore decrease in serum adiponectin level in NAFLD subjects might be due to obesity.

In this study, Serum adiponectin and liver enzymes were significantly inversely correlated in NAFLD subjects. Similar to this present study, Mohamed et al. (2014) demonstrated a weak negative correlation between adiponectin and the liver enzymes. ⁽²¹⁾ Kim SG et al. (2005) found inverse correlation of adiponectin with serum ALT and GGT levels before and after adjustment for age, BMI & HOMA value whereas no correlation was observed between AST, ALP and adiponectin level. ⁽²²⁾ A study by Sargin et al. (2005) conducted on 35 non-diabetic patients with NAFLD also found a significant correlation between adiponectin and liver function tests. Therefore, it is suggested that adiponectin has a greater role in maintenance of liver integrity. ⁽²³⁾

CONCLUSION

Serum adiponectin is statistically significantly lower in patients with NAFLD and is significantly associated with liver enzymes. Hence, in addition to liver enzymes, adiponectin can also be used as diagnostic measure as well as therapeutic target for NAFLD subjects. Further studies are needed as it might become an independent non invasive parameter for early diagnosis of NAFLD.

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