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Correlation between Anthropometric Measures, Lipid Profile and Serum Adiponectin and Steatosis in Nondiabetic Nonalcoholic Fatty Liver Disease

Hasan S. Mahmoud[1*], Mohamad M. Helal[1], Mohammed H. Hassan[2] and Mahmoud F. Sherif[3]

[1]Department of Tropical Medicine and Gastroenterology, Qena Faculty of Medicine, South Valley University, Qena, Egypt.
[2]Department of Medical Biochemistry, Qena Faculty of Medicine, South Valley University, Qena, Egypt.
[3]Department of Pathology, Assiut Faculty of Medicine, Assiut University, Egypt.

Authors' contributions

This work was carried out in collaboration between all authors. Author HSM designed and supervised the whole study, wrote the protocol, revised the manuscript. Author MMH wrote the protocol, carried out the work in hospital and wrote the first draft of the manuscript. Author MHH managed the laboratory process. Author MFS managed the histopathological process. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To assess the relation between the grade of steatosis and anthropometric measures, lipid profile and serum adiponectin in non-diabetic patients with nonalcoholic fatty liver.
Study Design: Cross sectional study.
Place and Duration of Study: Department of Tropical Medicine and Gastroenterology, Qena faculty of medicine, South Valley University.
Methodology: Fifty patients with US evidence suggestive of fatty liver disease and normal fasting and post-prandial serum glucose were included. No past or current history of alcohol consumption.

**Corresponding author: Email: hasan_sedeek@yahoo.com;*

Blood samples were taken to detect liver function tests, fasting lipogram, complete blood count and serum adiponectin. Body mass index (BMI) and waist circumferences (WC) were measured for all patients. Liver biopsy was done to detect the presence and the degree of steatosis.
Results: The mean age of patients was 40+/-12 years. Patients with steatosis showed significantly higher value for BMI and WC than those without (*P* value =0.000). Cholesterol, triglyceride and Low density lipoprotein-cholesterol (LDL-C) also were significantly higher in patients with steatosis (*P* value =0.00). High density lipoprotein-cholesterol (HDL-C) and serum adiponectin were significantly lower in patients with steatosis (*P* value =0.00). Patients with severe steatosis showed significantly higher values for BMI and WC, cholesterol, triglyceride, LDL-C and lower values for HDL-C and adiponectin (*P* value = 0.05) than those with mild or moderate steatosis. Positive correlations were detected between the age, BMI and WC, cholesterol, triglyceride, LDL-C and the grade of steatosis and negative correlations with HDL-C and adiponectin.
Conclusion: Anthropometric measures, lipogram and serum adiponectin are associated with progression of steatosis in nondiabetic patients with NAFLD. So their detection is important for evaluation and management.

Keywords: Anthropometric measures; lipogram; serum adiponectin; NAFLD.

1. INTRODUCTION

NAFLD has the potential for major economic impact on healthcare costs because of liver-related morbidity and mortality [1]. NAFLD is a condition defined by significant lipid accumulation (5–10%) in hepatic tissue in the absence of significant chronic alcohol consumption. Most patients with NAFLD have increased liver fat content alone (simple steatosis), but others develop increasing hepatic inflammation known as nonalcoholic steatohepatitis (NASH), and up to 20% of patients reveal progressive hepatic fibrosis and may eventually develop cirrhosis or liver failure and even hepatocellular carcinoma [2].The hallmark feature of the pathogenesis of NAFLD, both histologically and metabolically, is the accumulation of triacylglycerol (TAG) in the liver [3].

Excess liver fat is extremely common and prevalence of NAFLD has been increasing mainly because of the increased prevalence of obesity [4]. NAFLD occurs in 60% - 95% of people with obesity [5]. Truncal obesity seems to be an important risk factor for NAFLD, even in patients with a normal body mass index (BMI) [6].

Most patients with NAFLD, including adults and children with either NAFL or NASH are asymptomatic at presentation. When present, clinical symptoms and physical findings are nonspecific and unreliable in assessing disease severity in patients with compensated liver disease. The most common signs and symptoms are fatigue, right upper quadrant pain and hepatomegaly, as well as acanthosis nigricans, which tend to be seen more frequently in the pediatric population [7].

Adipose tissue is considered an endocrine organ regulating body metabolism [8]. The imbalanced production of pro- and anti-inflammatory adipokines secreted from fat contributes to the pathogenesis of NAFLD. Adiponectin is an important adipokine specifically secreted by adipocytes that circulates at relatively high levels in the bloodstream. It is made outside the liver and appeared to protect against liver damage [9]. In the liver, adiponectin acts through the activation of 5-AMP activated protein kinase and peroxisome proliferator-activated receptor-α pathways and inhibition of toll-like receptor-4 mediated signaling [10]. Adiponectin is more closely implicated in the pathogenesis of NAFLD/ NASH. Unlike other adipokines, serum levels of adiponectin are decreased in obesity and its associated medical complications. A negative association between serum levels of adiponectin and liver enzyme levels has been shown in healthy subjects .The decreased level of serum adiponectin represents an independent risk factor for NAFLD and liver dysfunctions in humans [11].

Several imaging techniques have been advocated as noninvasive diagnostic tests for NAFLD as they can detect liver steatosis. Ultrasonography (US) is a preferred method for screening asymptomatic patients with elevated liver enzymes and suspected NAFLD. Ultrasonographic findings of fatty liver include hepatomegaly, diffuse increase in echogenicity of the liver parenchyma, and vascular blunting [12].

2. MATERIALS AND METHODS

Fifty nondiabetic patients with NAFLD (22 males and 28 females) were enrolled in the current study. They were recruited from Gastroenterology Out-patients Clinic in Qena University Hospital. Inclusion criteria: Was based on ultrasonograhpic finding of bright liver, in patients with normal fasting and postprandial blood glucose, whatever their presenting complaint. Exclusion criteria: Patients with; hepatitis B, hepatitis C infection and autoimmune hepatitis. Other diseases: Diabetes, hypertension, malignancy, hypo-hyperthyroid disease, coronary artery disease and pregnancy. Also we excluded patients with history of alcohol consumption, cigarette smoking and use of amiodarone, corticosteroids, tamoxifen, methotrexate or oral contraceptives.

All participants gave informed consent, and the study was approved by Ethical Committee of Qena Faculty of Medicine, South Valley University.

All persons included in the study were subjected to detailed history taking, complete clinical examination, anthropometric evaluation (height, weight, and body mass index (BMI) and waist circumference were recorded. Overweight and obesity were defined as BMI between 25 and 30 kg/m² (<30) and ≥ 30 kg/m², respectively [13].

NAFLD diagnosis was based according to the standard criteria accepted by the American Gastroenterology Association [14]: The diagnosis was based on ultrasonograhpic finding of bright liver (the diagnosis of bright liver was based on abnormally intense, high level echoes arising from the hepatic parenchyma, with amplitude similar to that of echoes arising from the diaphragm). Ultrasonographic guided percutaneous needle liver biopsy was done to all patients to confirm the presence or absence of steatosis and determine its grade: Formalin fixed (10%), paraffin embedded liver sections stained with Hematoxylin and Eosin stain were examined using Olympus BH-2 light microscope. Steatosis was defined and graded according to Brunt scoring system [15].

Laboratory evaluation: Venous blood (5 ml) was collected after overnight fasting and allowed to clot for 30 min at room temperature and centrifuged at 3000 c/m for five min. The separated serum was stored into aliquots at-20°C until biochemical analyses.

Complete blood counts, serum glucose, cholesterol, triacylglycerol, albumin, alkaline phosphatase, bilirubin (total and direct), liver enzymes (ALT and AST) and prothrombin time and concentration measurements were done. Serum glucose, albumin, alkaline phosphatase (ALP), bilirubin (total & direct) and liver enzymes (ALT & AST) were estimated using [Cobas C311 (Roche diagnostics, Germany)]. Complete blood counts were measured using (Cell Dyn 1800-Abbott diagnostics, Germany). Prothrombin time and concentration were measured using (BFT-II analyzer, Germany). Total cholesterol, triglyceride and HDL cholesterol were analyzed enzymatically using kit obtained from Randox Laboratories Limited, Crumlin, UK.

Serum levels of adiponectin were determined using human ADP/Acrp30 (adiponectin) ELISA kit, Catalog No: E-EL-H0004 (Orgenium Laboratories, Finland).Serum LDL-cholesterol was determined from the values of total cholesterol and HDL-cholesterol using Friedewalds formula: LDL-cholesterol = TC – (TG/5) – HDL-cholesterol (mg/dl) [16].

2.1 Ethical Approval

Ethical approval of the research was obtained from the Faculty Ethical Committee before the start. A confidential interview is conducted and written consent was obtained from each subject.

2.2 Statistical Analysis

Analysis of data was done by IBM computer using SPSS (statistical program for social science version 16). Independent sample -t- test was used for comparison between the two groups. One way ANOVA test was used for comparison between different grades of steatosis. The chi-square test was used for categorical variables. Correlations between different variables and hepatic steatosis were analyzed using Sperman correlation test.

3. RESULTS

3.1 Characteristic Data for All Patients

The study included 50 patients, 22 males and 28 females with their main age 40±12 years old. Overweight was found in 20 (40%) patients and obesity in 20 (40%) patients. The mean serum adiponectin level was 10.95 µ/ml. Steatosis was found in 40(80%) patients. This is illustrated in Table 1. In the current study BMI and WC were

significantly higher in patients with steatosis than those without (*P* value = 0.000). This is illustrated in Table 2.

3.2 Laboratory Data for Both Groups Showed That

- Liver enzymes (ALT and AST): Were significantly higher in patients with steatosis than in those without steatosis (*P* value = 0.000).
- Fasting lipogram showed that: Serum levels of cholesterol, triglycerides and LDL-C were significantly higher in patients with steatosis than those without (*P* value = 0.00), while HDL-C was significantly lower in patients with steatosis (*P* value = 0.00).
- Serum adiponectin level showed that: It was significantly lower in patients with steatosis than those without (*P* value = 0.00).

3.3 Ultrasonographic Examination Showed That

The size of both the liver and the spleen were significantly higher in patients with steatosis (*P* value = 0.000). This is illustrated in Table 3.

3.4 In Patients with Advanced Grade of Steatosis

BMI and WC were significantly higher in patients with grade 3 than those with grade 1 or 2 (*P* value = 0.003 and 0.001 respectively). Serum cholesterol, LDL-C and triglycerides were also significantly higher in patients with advanced grade of steatosis (*P* value= 0.02), while HDL-C showed significantly lower value in those patients (*P* value = 0.00). Serum adiponectin level was significantly lower in those with advanced steatosis than in patients with mild or moderate grade (*P* value = 0.01).This is illustrated in Table 4.

3.5 Correlations with the Grade of Steatosis

Age, BMI, WC, cholesterol, LDL-C and triglycerides showed positive correlations, on the other hand HDL-C and serum adiponectin showed negative correlations with the grade of steatosis. This is illustrated in Table 5 and Fig. 1.

4. DISCUSSION

NAFLD comprises a wide spectrum of histologic categories which range from steatosis to nonalcoholic steatohepatitis (NASH), which is a term first used in 1980 [17] to describe a clinicopathologic syndrome that occurred in obese, diabetic females who denied alcohol use, but in whom the hepatic histology was consistent with alcoholic hepatitis. NASH is considered the major cause of cryptogenic cirrhosis [18].

Table 1. Characteristic data for all patients

Variable	Value
Number	50
Age (yrs)	40±12
Sex	
Male	22(44%)
Female	28(56%)
BMI (average)	29±8.6
<25	10(20%)
25-30	20(40%)
>30	20(40%)
WC	
Female	93±17
Male	112±14
Adiponectin (µ/ml)	10.95±3.1
Steatosis (US)	
No	10(20%)
Yes	40(80%)

Data are expressed as number % and mean± SD

Table 2. Demographic characteristic data for patients with and without steatosis

Parameter	No steatosis (n= 10)	Steatosis (n= 40)	*P* value
Age (yrs)	39±10	45±7	NS
Sex			
Female	6(60%)	22(55%)	
Male	4(40%)	18(45%)	NS
BMI (value)			
Female	21±3.6	33±6.6	
Male	20±4.2	32±5.9	0.000
Average WC			
Female	73±11	100±10	
Male	80±23	118±9	0.000

Data are expressed as number % and mean±SD

Table 3. Laboratory and sonographic data for patients with and without steatosis

Parameter	No steatosis (n= 10)	Steatosis (n= 40)	*P* value
ALT (IU/L)	22.8±11.2	56±16.3	0.000
AST (IU/L)	28.1±10.3	52.5±12.8	0.000
ALP (IU/L)	92.2±23.3	92.8±22.4	NS
PLT count (x1000/ml)	277±81	222±76	0.03
Cholesterol (mg/dl)	171.9±25.4	205.8±33.8	0.00
LDL-C (mg/dl)	85.6±24.1	109.8±28.6	0.00
HDL-C(mg/dl)	62.2±5.6	41.7±8.2	0.00
triglycerides (mg/dl)	156.9±45.2	350.9±70.6	0.00
Adiponectin (µ/ml)	12.21±3.9	9.3±1.27	0.00
US			
Liver size	12.6±2.1	16.6±1.8	0.000
Splenic size	9±2.8	14.2±1.6	0.000

Data are expressed as mean ± SD. Independent sample t test was used. P value =0.05= significant

Table 4. BMI, WC, adiponectin and lipid profile in patients with different grades of steatosis

Variable	Grade 1 (n=18)	Grade 2 (n=14)	Grade 3 (n=10)	*P* value
BMI	27±2.8	32±2.3	36±1.6	0.003
WC	85±5	90±9	98±11	0.001
Cholesterol (mg/dl)	184±19	201±11	220±18	0.02
LDL-C (mg/dl)	78±12	100±18	130±16	0.02
HDL-C(mg/dl)	50±2.1	43±1.3	36±3.3	0.00
Triglycerides(mg/dl)	300±50	348±23	370±48	0.02
Adiponectin (µ/ml)	10.2±1.3	9.2± 1.0	7.7± 0.9	0.01

All data are expressed as mean±SD. One-way ANOVA test was used. P value=0.05= significant

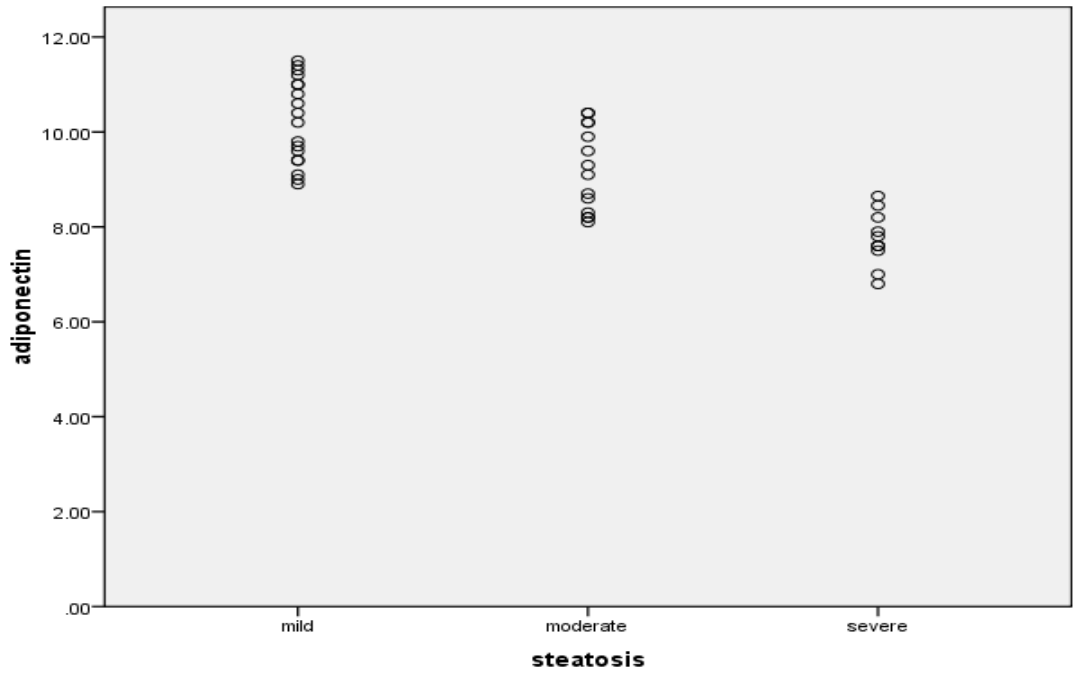

Fig. 1. Correlation between serum adiponectin level and steatosis grade
(rho= - 0.76 and P value=0.000)

Table 5. Correlation between age, BMI, WC, lipogram and adiponectin and the grade of steatosis

Variable	rho	*P* value
Age	+0.68	0.00
BMI	+0.74	0.00
WC	+0.82	0.00
Cholesterol	+0.63	0.02
HDL-C	-0.81	0.000
LDL-C	+0.71	0.00
Triglycerides	+0.67	0.02
Adiponectin (µ/ml)	- 0.76	0.000

Sperman test was used (rho)

NASH-associated cirrhosis can decompensate into subacute liver failure [19], progress to hepatocellular carcinoma [20] and re-occur post-transplantation [21]. In contrast, steatosis alone is reported to have a more benign clinical course, although progression of fibrosis and cirrhosis has occurred in 3% of these patients with steatosis alone [22].

The current study was conducted to assess if there is association between the grade of steatosis and anthropometric measures, fasting lipid profile and serum adiponectin in nondiabetic patients, as most of the previous studies concerned in diabetic patients.

In the present study, BMI and WC were significantly higher in patients with steatosis compared to those without steatosis. Also, a positive correlation was found between steatosis grade and BMI. The same result obtained by Goland et al. [23] who proved that patients with NAFLD had a significantly higher BMI. Also Lee et al. [24] showed higher anthropometrics values among NAFLD patients than among controls. Insulin resistance and visceral obesity lead to a hepatic influx of free fatty acids, resulting in increased triglyceride synthesis and decreased triglyceride export. This leads to hepatic steatosis. At this stage, patients have the relatively benign condition of NAFLD [25]. Leptin plays an important role in the regulation and metabolism of body fat and may induce insulin resistance, increase fatty acid concentrations in the liver, and enhance lipid peroxidation. Leptin may act as an immunomodulator, inducing the release of cytokines, such as tumor necrosis factor (TNF)-α, interferon (INF)-γ, interleukin (IL)-18, and tumor growth factor (TGF)-β1, thus promoting liver steatosis and fibrosis [26].

In our study, cholesterol, triglycerides and LDL-C levels were significantly higher in patients with steatosis than those without steatosis. This is in accordance with the results obtained by de Alvis et al. [27]. Lorando et al. [28] reported that, hyperlipidemia was an independent predictor of the development of NAFLD. Also Nimer et al. [29] documented that approximately one half of hyperlipidemic patients will have evidence of fatty infiltration of the liver on abdominal ultrasound. In over 55% of these patients the fatty infiltration would be considered moderate or severe.

In the current study serum value of adiponectin was significantly lower in patients with hepatic steatosis and its level showed more reduction with more progression of steatosis. Also we found a statistically significant negative correlation between serum adiponectin and the grade of steatosis. This agrees with Wafaa et al. [30] who found that serum adiponectin level was negatively correlated with steatosis. Berg et al. [31] supported our results and stated that serum adiponectin as well as hepatic gene expression of adiponectin and its receptors are decreased and inversely related to the degree of liver injury and they explained role of adiponectin in NAFLD as adiponectin directly counteracts the effects of TNF-α on insulin signaling and lipid metabolism. Unlike most adipocytokines, adiponectin is decreased in the setting of obesity. Adiponectin is an antidiabetic hormone that correlates with insulin sensitivity [32].

As regard liver enzymes, in the present study we reported that ALT level was significantly higher in the steatosis group. This is consistent with results obtained by Mona et al. [33] who declared that ALT level was higher in patients with liver steatosis when compared with participants with normal liver. Elevated serum ALT and AST levels are the primary abnormality seen in patients with NAFLD and tend to be higher in patients with NASH as compared with NAFL [34].

In the current study, steatosis grade was found to be increased with the advancement of age and a significant correlation was present between the age of patients and hepatic steatosis. This agrees with results of Frith et al. [35] who reported that the prevalence of NAFLD increases with age and the likelihood of disease progression to advanced fibrosis or mortality increases in older patients with NAFLD.

5. CONCLUSION

Evaluations of anthropometric measures, fasting lipogram and serum adiponectin are valuable in nondiabetic patients with hepatic steatosis. So

detection and management of their abnormalities are beneficial.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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