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Estimation of insulin-like growth factor-1 as a biomarker in nonalcoholic fatty liver disease in patients with metabolic syndrome

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Abstract

Background

Nonalcoholic fatty liver disease (NAFLD) is becoming the most common chronic liver pathology especially in developed countries, ranging from simple liver steatosis to nonalcoholic steatohepatitis. Patients with NAFLD having metabolic syndrome have abnormal liver enzymes that positively correlate with the number of metabolic syndrome components. Abdominal ultrasonography is frequently used in epidemiological studies to detect NAFLD. Insulin-like growth factor (IGF-1) is the critical hormone in the pathophysiology of metabolic syndrome and is associated with cardiovascular disease, diabetes mellitus, and abnormal lipid metabolism.

Participants and methods

A total of 70 patients, 50 patients having NAFLD by ultrasonography and 20 individuals as control, matched for age, sex, BMI, and waist circumference were clinically assessed. Abdominal ultrasonography was done, and laboratory investigations included estimation of IGF-1, homeostasis model assessment insulin resistance (HOMA IR), blood glucose, alanine aminotransferase (ALT), and lipid profile.

Results

IGF-1 is highly significantly lower in the patient group than in the control group ($P < 0.01$). Moreover, there was a highly significant correlation between the low concentration of IGF-1 and BMI, waist circumference, fasting blood glucose, homeostasis model assessment insulin resistance, ALT, and serum cholesterol in the patient group ($P < 0.01$) and insignificant correlation with serum triglyceride and serum insulin ($P > 0.05$).

Conclusion

IGF-1 is lower in patients with NAFLD, especially those with elevated ALT, and is associated with increased number of metabolic syndrome components. Improving lifestyle, by decreasing body weight and controlling blood sugar using insulin sensitizers like pioglitazone, GLP-1 inhibitors like liraglutide, and SGLT2 inhibitors, and improving lipid profile are associated with good prognosis of NAFLD.

Keywords: IGF-1, liver disease, metabolic syndrome

INTRODUCTION

Central obesity is associated with many cardiometabolic risk factors like nonalcoholic fatty liver disease (NAFLD), which is associated with type II diabetes mellitus, insulin resistance, and dyslipidemia. Hence, it is considered to be the hepatic manifestation of metabolic syndrome.

NAFLD is becoming the most common chronic liver pathology especially in developed countries in both adults and children and ranges from simple liver steatosis

to nonalcoholic steatohepatitis (NASH), which later progresses to advanced liver cirrhosis and end-stage liver disease [1].

However, most of the patients with NAFLD with metabolic syndrome have abnormal liver enzymes that positively correlate with the number of metabolic syndrome components,

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which suggests that the more the number of metabolic syndrome components, the higher the incidence of the elevated liver enzymes [2].

NAFLD is defined as the accumulation of fat in the liver exceeding 5% of its weight without significant alcohol intake; progression to steatohepatitis (NASH) occurs in up to 20% of patients with NAFLD, and until now why these percentages of patients develop NASH is not well understood [3].

Abdominal ultrasonography is frequently used in epidemiological studies to detect NAFLD. Detection of steatosis is only estimated when the hepatic fat content exceeds 33% on liver biopsy, so steatomarkers may be used like alanine aminotransferase (ALT) level and γ -glutamyl transferases [4].

Insulin-like growth factor (IGF-1) is considered the critical hormone in the pathophysiology of metabolic syndrome. The liver mainly produces it, and growth hormone stimulates its secretion, and its deficit is associated with cardiovascular disease, diabetes mellitus, and abnormal lipid metabolism [5].

IGF-1 decreases in NAFLD owing to hepatic insulin resistance modulate growth hormone-stimulated synthesis of hepatic (IGF-1) [6].

IGF-1 is responsible for increasing insulin resistance, impaired insulin metabolism, aggravating oxidative damage, and deregulating the neurohormonal axis, and there is an inverse relationship between IGF-1 levels and the metabolic syndrome-associated cardiovascular complications [7].

PARTICIPANTS AND METHODS

The study included seventy participants, comprising 50 patients diagnosed with NAFLD by abdominal ultrasonography and 20 healthy persons as a control group. They were selected from Internal Medicine Outpatient Clinic of Benha Teaching Hospital.

There were 15 male and 35 female patients, with age ranged from 30 to 60 years. The patients had at least one risk factor of metabolic syndrome (elevated blood pressure and dyslipidemia, dysglycemia, overweight, obesity, and family history of diabetes or cardiovascular disease); none of them were hepatitis C or B positive; none of them took drugs like corticosteroids, antidepressants, cordarone, or methotrexate; and none of the females were pregnant. The control group was composed of healthy persons, with 10 male and 10 female individuals. All participants were subjected to clinical examination, measurement of blood pressure, estimation of BMI, waist circumference, and abdominal ultrasonography.

Laboratory studies were also done, including serum blood glucose, lipid profile, ALT, estimation of IGF-1 and serum insulin, and calculation of homeostasis model assessment insulin resistance (HOMA IR).

Methods

Blood sampling

A volume of 5 ml of venous blood through venipuncture was obtained in a plain tube without anticoagulant from patients fasting for 12 h. Samples are allowed to clot for 30 min at 37°C before centrifugation for 20 min at 1000g. Separated serum was divided for measurement of total cholesterol, triglyceride, ALT, and 1 ml was aliquoted and stored at -20°C for measurement insulin and IGF-1.

- (1) Serum cholesterol was measured by enzymatic colorimetric cholesterol oxidase method using kits from Spinreact (SAU), Ctra. Sta. Coloma, 7 17176 St. Esteve de Bas GIRONA - Spain
- (2) Serum triglyceride was measured by enzymatic colorimetric lipoprotein lipase method using kits from Spinreact
- (3) Blood glucose level was measured by enzymatic colorimetric glucose oxidase method by using kits from Spinreact
- (4) ALT was measured by kinetic ultraviolet method by kits from Centronic GmbH (Germany) [8]
- (5) Enzyme-linked immunosorbent assay measured insulin using ELISA technique by commercial kit available from Immunospec Corporation (Canoga Park, California, USA) [9]
- (6) Serum IGF-1 measurements were done by ELISA technique using Mybiosource kits (MyBioSource, Inc., San Diego, CA 92195-3308, USA) [10].

The principle for the measurement of insulin and IGF-1.

The assay system utilizes anti-insulin or anti-IGF-1 antibody for solid phase immobilization and another anti-insulin or IGF-1 antibody in the antibody-enzyme (horseradish peroxidase) conjugate solution. If human insulin or IGF-1 is present in the specimen, it will combine with the antibody on the well and the enzyme conjugate, resulting in the insulin or IGF-1 molecules being sandwiched between the solid phase and enzyme-linked antibodies.

A solution of tetramethylbenzidine was added and incubated, resulting in development of a blue color. The concentration of insulin or IGF-1 is directly proportional to the color intensity of the test sample.

Homeostasis model assessment insulin resistance

Homeostatic model assessment/insulin resistance [11] is a method for assessing B-cell function (% B) and insulin sensitivity (%S) through a computer model (HOMA 2): fasting insulin \times fasting glucose/405.

It is used to assess the risk of developing diabetes and to assess response to treatment and is categorized as follows:

- (1) Normal insulin resistance HOMA score less than 3
- (2) Moderate insulin resistance between 3 and 5
- (3) Severe insulin resistance greater than 5.

Statistical analysis

The collected data were tabulated and analyzed using SPSS software version 14 (SPSS Inc., Chicago, Illinois, USA). Data were expressed as χ^2 , mean \pm SD, SD, analysis of variance, and Pearson's correlation studies.

RESULTS

Our study included 70 participants. There were 50 patients with NAFLD, diagnosed by abdominal ultrasonography and had at least one risk factor for metabolic syndrome [15 (30%) males and 35 (70%) females], and 20 healthy participants [10 (50%) males and 10 (50%) females]. Their age ranged from 30 to 60 years (Table 1).

The comparison between patients group and control group showed the following.

Serum insulin was higher in the patient group in contrast to the control group (mean \pm SD: 24.0 \pm 3.4 vs. 15.1 \pm 3.2) and was highly significant ($P < 0.01$). HOMA IR was also higher in the patient group compared with the control group (mean \pm SD: 9.1 \pm 1.9 vs. 2.9 \pm 0.7) and the difference was highly significant ($P < 0.01$; Table 2).

IGF-1 was lower in the patient group in comparison with the control group (mean \pm SD: 286 \pm 14.3 vs. 340.5 \pm 12.6), and also the relationship was statistically significant ($P < 0.01$; Table 2, Fig. 1).

ALT showed higher concentration in the patient group in comparison with the control group (mean \pm SD: 73.2 \pm 21.9 vs. 16.6 \pm 4.7), and the difference was highly significant ($P < 0.01$; Table 2).

There was also a highly significant correlation between fasting blood glucose (FBG), BMI, waist circumference, serum cholesterol, and serum triglycerides between the patient group and the control group ($P < 0.01$; Table 2).

The correlation between IGF-1 and different variables showed the following: there was a significant correlation between the lower concentration of IGF-1 and BMI and waist circumference in the patient group ($P < 0.05$), and this correlation was insignificant in the control group ($P > 0.05$; Table 3, Fig. 2).

Moreover, the correlation between IGF-1 and FBG, HOMA IR, ALT, and serum cholesterol was highly significant in the patient group ($P < 0.01$) whereas insignificant in the control group ($P > 0.05$). However, the correlation between IGF-1 and serum triglyceride and serum insulin was negligible in both patient and control groups ($P > 0.05$; Table 3, Figs. 3 and 4).

DISCUSSION

NAFLD is the most common liver condition in the world. The prevalence is up to 30% in developed countries and ~10% in the developing countries. It is caused by accumulation of triglyceride in the hepatocytes. Patients with NAFLD are also liable to increased risk of cardiovascular diseases, diabetes, hepatocellular injury, inflammation, and cirrhosis [12,13].

NAFLD is the hepatic manifestation of metabolic syndrome and is associated with obesity, insulin resistance, and independent predictor of type II diabetes mellitus [14]. IGF-1 is a protein encoded by IGF-1 gene. It is similar in molecular structure to

Table 1: Sex difference in the studied groups

Sex	Patients group [n (%)]	Control group [n (%)]	χ^2	P
Male	15 (30)	5 (20)	0.175	>0.05
Female	35 (70)	15 (80)		

Table 2: Comparison between the studied groups

	Patient group (mean \pm SD)	Control group (mean \pm SD)	F	P
FBG (mg/dl)	149.8 \pm 25.9	79.9 \pm 9.5	136.6	<0.01**
Insulin	24 \pm 3.8	15.1 \pm 3.2	85.2	<0.01**
HOMA	9.1 \pm 1.9	2.9 \pm 0.7	196.8	<0.01**
IGF (pg/ml)	286 \pm 14.3	340.5 \pm 12.6	218	<0.01**
ALT	73.2 \pm 21.9	16.6 \pm 4.7	129.9	<0.01**
BMI	33.7 \pm 6.4	23.3 \pm 1.8	50.0	<0.01**
Waist	107.5 \pm 18.9	79.3 \pm 7.7	41.1	<0.01**
Cholesterol (mg/dl)	222.4 \pm 74.6	113 \pm 25.4	40.6	<0.01**
TG (mg/dl)	185.7 \pm 112	89.9 \pm 14.6	14.4	<0.01**

ALT, alanine aminotransferase; FBG, fasting blood glucose; HOMA, homeostasis model assessment insulin resistance; IGF, insulin-like growth factor; TG, triglycerides. * $P < 0.05$, significant. ** $P < 0.01$, highly significant.

Table 3: Correlation between insulin-like growth factor-1 and other variables in patient and control groups

IGF (pg/ml)	Patient group		Control group	
	r	P	r	P
FBG (mg/dl)	-0.437	<0.01	-0.272	>0.05
Insulin	-0.07	>0.05	0.252	>0.05
HOMA	-0.529	<0.01	0.09	>0.05
ALT	-0.682	<0.01	0.29	>0.05
BMI	-0.333	<0.05	-0.19	>0.05
Waist	-0.326	<0.05	-0.33	>0.05
Cholesterol (mg/dl)	-0.714	<0.01	-0.06	0.05
TG (mg/dl)	0.163	>0.05	-0.22	0.05

ALT, alanine aminotransferase; FBG, fasting blood glucose; HOMA, homeostasis model assessment insulin resistance; IGF, insulin-like growth factor; TG, triglycerides.

insulin and plays a vital role in childhood growth and has an anabolic effect in adults. IGF-1 consists of seventy amino acids in a single chain with three intramolecular disulfide bridges [15].

The liver produces IGF-1 as an endocrine hormone stimulated by growth hormone; it is created throughout life, but the highest rates of IGF-1 production occur during the pubertal growth and the lowest levels in infancy and old age [16].

NAFLD has been described in adults with growth hormone-deficiency syndrome, and chronic liver disease can be associated with significant changes of levels of IGF-1, IGF-binding proteins and insulin growth factor-binding proteins and acid labile subunits [17,18].

In epidemiological studies, ultrasonography has been extensively used to detect NAFLD and detect steatosis

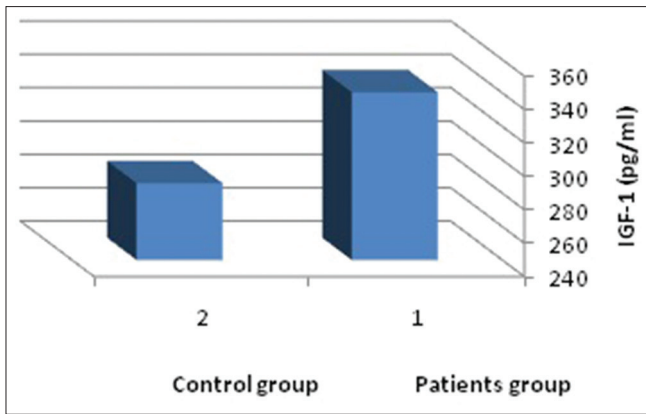


Figure 1: Insulin-like growth factor-1 mean in the patient and the control groups.

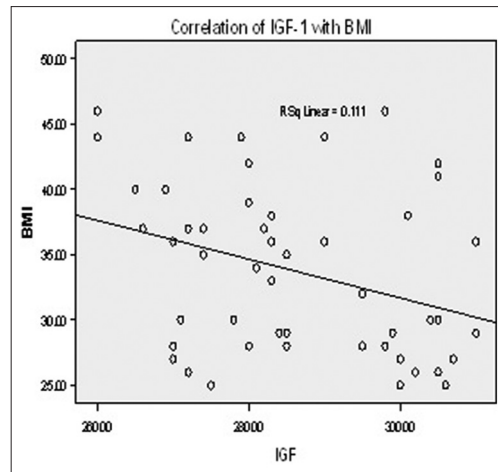


Figure 2: Correlation of insulin-like growth factor-1 and BMI.

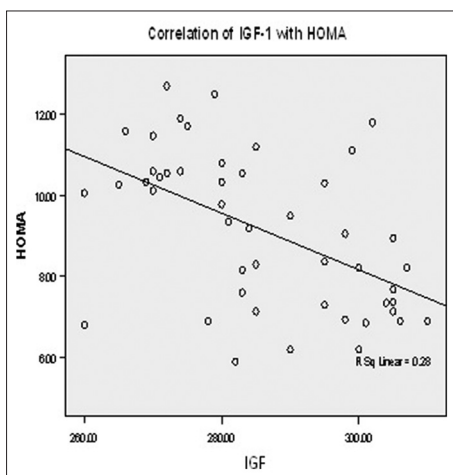


Figure 3: Relationship of insulin-like growth factor-1 and homeostasis model assessment insulin resistance.

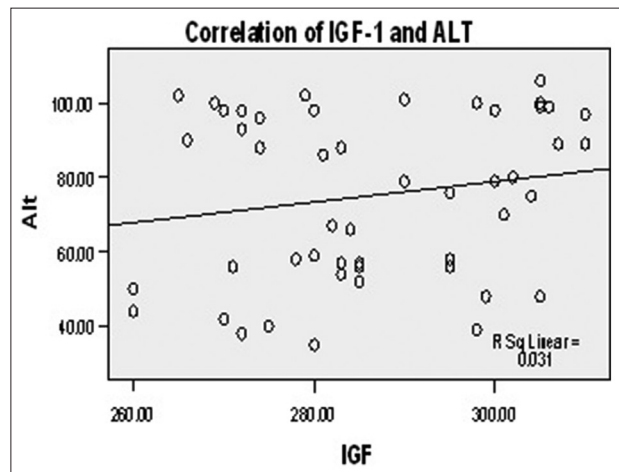


Figure 4: Correlation of insulin-like growth factor-1 and alanine aminotransferase.

when fat content of hepatocytes exceed 33% on liver biopsy. Moreover, steatemarkers are used such as ALT and γ -glutamyl transferase [4].

Exploring the relation between metabolic risk factors related to type II diabetes mellitus and development of NAFLD, a study was done on 185 patient with type II diabetes and NAFLD versus 204 cases of type II diabetes alone. The study reported that postprandial blood glucose and insulin as well as BMI and HOMA IR were higher in patients with type II diabetes with NAFLD [19]. Moreover, Savastano *et al.* [20] demonstrated that HOMA IR, ALT, and CRP were significantly higher in patients with severe hepatic steatosis than in those with mild hepatic steatosis. This is concomitant with a study on 115 obese patients with BMI greater than 30 kg/m² (65 patients with liver steatosis and 50 controls), where HOMA IR, serum insulin, and blood glucose were significantly higher in patients than in control [17]. These results came in agreement with our study, which shows a highly significant correlation between FBG, serum insulin, and HOMA IR in the patient group with metabolic syndrome and NAFLD in comparison with the control group ($P < 0.01$).

Waist circumference is a risk factor for metabolic syndrome and is related to insulin resistance and elevated ALT in patients with NAFLD, which was significantly associated with an increase in waist circumference [21].

In a Brazilian study, both BMI and waist circumference were associated with increased steatohepatitis with liver fibrosis on liver biopsy [22]. However, Graffigna *et al.* [23], demonstrate also a high prevalence of NAFLD in patients who were overweight or obese, and hepatic steatosis detected by abdominal ultrasonography was positively correlated with waist circumference and serum triglyceride. This was in agreement with our study, which shows a highly significant correlation of BMI, waist circumference, serum triglycerides, and serum cholesterol in the patient group in comparison with the control group ($P < 0.01$).

Most patients with NAFLD have abnormal liver enzymes and higher in patients with metabolic syndrome. Liver enzyme levels significantly increase with the number of metabolic syndrome components [2].

Leite *et al.* [24], demonstrated that low adiponectin and low transforming growth factor (IGF-B1) are associated with severe NAFLD stages in type II diabetes, and a combination of HOMA and adiponectin to hepatic leptin ratio and ALT ratio may be a useful noninvasive technique to determine the severity of liver damage [24,25]. Cruz *et al.* [26], also found that ALT and HOMA IR are correlated with the degrees of hepatic steatosis on ultrasonography and can help in the selection of patients for liver histological evaluation.

In a study was done on 235 patients with biopsy-proven NAFLD, patients with NAFLD and diabetes mellitus were significantly older, predominantly females, had significantly higher AST/ALT ratio and FIB-4 index, and have higher fibrosis score compared with nondiabetic ones [27].

Moreover, in a study done on 141 people with diabetes with fatty liver detected by abdominal ultrasonography showing increased hepatic echogenicity and vascular blunting, where liver stiffness measurement greater than or equal to 7 kPa represented hepatic fibrosis, it was found that 16% of diabetic with NAFLD have significant hepatic fibrosis and significant elevated ALT [28].

Another study on 52 patients of nondiabetic NAFLD with hyperechogenicity of the liver by ultrasonography found HOMA insulin resistance was significantly related to hepatomegaly and ALT increase, which was present in 36% of patients [29].

Those studies were concomitant with our research, as there was a highly significant correlation of ALT and HOMA IR in the patient group with NAFLD than in the control group ($P < 0.01$).

Insulin growth factor deficiency is associated with deregulated lipid metabolism, cardiovascular disease, diabetics, and altered metabolic profile in diabetics, and also it is responsible for stimulation of protein synthesis in the muscle, lowering glucose level in type I and II diabetes mellitus by enhancing insulin sensitivity [5,30].

The liver mainly produces serum IGF-1 and its deficiency is a determinant of metabolic syndrome like insulin resistance, abnormal lipid profile, type II diabetes mellitus, and increased waist-hip ratio, and growing risk of fatal coronary events [31].

In a study by Colak *et al.* [32], IGF-1 level was significantly decreased in patients with moderate to severe fibrosis and proved that IGF-1 might be useful to differentiate advanced fibrosis in patients with NAFLD.

In another Japanese study on 199 patients with biopsy-proven NAFLD, serum IGF-1 was significantly lower in patients with NASH compared to NAFLD with increasing lobular inflammation [33].

These studies are in agreement with our study, as IGF-1 was considerably lower in the patient group compared with the control group.

Moreover, ALT and IGF-1 level were significantly associated with differences in fibrosis [34]. Graffigha *et al.* [23], also found that the ultrasonographic features of steatosis were correlated positively with waist circumference, serum triglyceride, serum insulin, and HOMA IR and negatively correlated with IGF-1.

In our study, lower level of IGF-1 is significantly associated with BMI and waist circumference ($P < 0.05$) and highly significant correlation with FBG, HOMA IR, ALT, and serum cholesterol ($P < 0.01$) but insignificantly correlated with serum triglyceride and serum insulin ($P > 0.05$).

Lifestyle usually improves insulin sensitivity and hepatic steatosis, and weight loss by about 10% can significantly reverse hepatocyte injury, enhancing bariatric surgery can also achieve NASH [35].

The use of insulin sensitizers like pioglitazone, especially with type II diabetes mellitus or impaired glucose tolerance, can decrease hepatic steatosis and reduce necroinflammation and hepatic fibrosis [36].

However, a recent meta-analysis of clinical trials of liraglutide in type II diabetes mellitus has suggested that glucagon-like peptide-1 receptor agonist could improve NASH; in contrast, studies with dipeptidyl peptidase (DPP4-inhibitors) have reported mixed results. Sodium-glucose co-transporter 2(SGLT2 inhibitors) have antifibrotic properties on animal models with NASH and in patients treated with SGLT2, and ALT decreases during treatment [37].

CONCLUSION

Estimation of IGF-1 is a critical noninvasive biomarker in patients with NASH with metabolic syndrome; its decrease is associated with cardiovascular disease, diabetes mellitus, and abnormal lipid metabolism. The lower the serum IGF-1, the more the liability to metabolic and cardiovascular complications and hepatic complications like steatohepatitis and hepatic fibrosis.

Improving patients' lifestyle, decreasing body weight, and controlling lipid profile and blood sugar in people with diabetes using insulin sensitizers like pioglitazone, GLP-1 inhibitors like liraglutide, and SGLT2 inhibitors have prognostic value in improving patients with NASH.

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Conflicts of interest

There are no conflicts of interest.

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