

Serum IGF-1, HOMA-IR and Estimated Glomerular Filtration Rate in Obese Patients with Different Stages of Hepatic Steatosis

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver injury in many countries around the world. The histological changes range over a wide spectrum, extending from simple steatosis, which is generally progressive, to non alcoholic steatohepatitis (NASH) which may progress to liver fibrosis, liver cirrhosis, liver cell failure, and sometimes even hepatocellular carcinoma. Liver biopsy is recommended as a gold standard method for the diagnosis and staging of steatosis and fibrosis in patients with NAFLD. low IGF-I level are a consequence of the presence of both NASH/advanced fibrosis in adult patients proved by liver biopsy which is a features of abdominal obesity and insulin resistance (HOMA-IR) and all contribute to the reduced eGFR.

Objectives: Assessing the link between HOMA-IR, IGF-I level and eGFR in obese patient with different grades of severity of hepatic steatosis proved by liver biopsy.

Methods: 54 overweight and obese patients preliminary diagnosed to have NAFLD by liver ultrasound ± elevated liver enzymes and documented by liver biopsy, and 20 age, and sex matched normal Body mass index (BMI), healthy participants as a control group, had been recruited in the current study. Diabetic patients and patients with elevated serum creatinine were excluded from the study. The patients subjected to full medical history, anthropometric measurement, biochemical studies (liver enzymes, HCV antibody, HBVs antigen, total lipid profile, serum creatinine, estimated glomerular filtration rate “eGFR”, fasting blood sugar, fasting insulin level to calculate Homeostatic model assessment of insulin resistance “HOMA-IR”, and IGF-I). Abdominal ultrasound (US), and liver biopsy for histological examination and NAS score to identify NASH patients, were conducted for each participant. According to NAS score, patients were divided into 3 subgroups; NASH, border-line NASH, and non-NASH (simple steatosis). Healthy control participants were not scheduled for liver biopsy for ethical consideration.

Results: According to the biopsy results; 7 patients had simple steatosis “not NASH”, 26 patients; border line NASH, and 21 patients had NASH. BMI, and waist circumference were significantly higher in patients than control participant” $p < 0.001$ ”, and the highest measurements were in NASH patients. ALT, GGT were significantly higher in NAFLD patients in general and in NASH patient subgroup. HOMA-IR reached 3.57 ± 1.57 compared to 1.87 ± 0.43 in control, and reached 3.94 ± 1.61 in NASH patients compared to 3.20 ± 1.22 in simple steatosis. IGF-I; was highly significantly lower in NAFLD patients compared to healthy control participants (58.15 ± 20.26 & 130.0 ± 19.44 ng/ml respectively), and was higher 66.81 ± 21.56 ng/ml in non-NASH compared to NASH patients 56.92 ± 19.80 ng/ml. eGFR was highly significantly lower in NAFLD patients 60.68 ± 10.17 ml/min compared to healthy control $95.81 \pm$

17.70 ml/min, with $p < 0.001$, to reach below 60ml/min in NASH subgroup 58.03 ± 9.01 ml/min resulting in p value of 0.004" when compared to patients with border line and non-NASH.

Conclusion: There was a definitive association between low IGF-1, high level of HOMA-IR, and reduced eGFR with the incidence of NAFLD with different grades of severity. In NAFLD patients' eGFR was lower than 90ml/min, and lower than 60ml/min in NASH and border line NASH patients

Keywords: NAFLD; NASH; IGF-I; HOMA-IR; eGFR

Abbreviations

BMI: Body Mass Index; CKD: Chronic Kidney Disease; eGFR: Estimated Glomerular Filtration Rate; ER: Endoplasmic Reticulum; HDL-c: High Density Lipoprotein Cholesterol; HGF: Hepatocyte Growth Factor; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; IGF-1: Insulin-Like Growth Factor 1; IL-6: Interleukin 6, LDL-c: Low Density Lipoprotein Cholesterol; MKFD: Mild Kidney Function Damage; NAFLD: Non Alcoholic Fatty Liver Disease; NAS: NAFLD Activity Score; NASH: Non Alcoholic Steatohepatitis; PNPLA3: Patatin-Like Phospholipase 3.

Introduction

Non-alcoholic fatty liver disease (NAFLD) represent a spectrum of liver disease with key stages consisting of hepatic steatosis (NAFL), steatohepatitis (NASH), fibrosis, and eventual cirrhosis, NAFLD affects more than 20 % of population worldwide [1]. Imaging studies and laboratory tests do not reliably differentiate patients with NAFLD from those with NASH, or predict the severity of liver disease [2]. Only a liver biopsy can establish a definite diagnosis and determine the severity of the condition as well as being the most sensitive and specific means of providing important prognostic information [3]. IGF-I levels have been associated with liver steatosis, progressively decreasing with liver fat accumulation [4].

The liver is the source of most (75 percent) of plasma IGF-I, as proven by organ specific gene targeting studies. Variables that regulate synthesis and release by the liver, primarily GH, also regulate its plasma concentrations. It has been reported that IGF-I stimulates both DNA synthesis and the production of hepatocyte growth factor (HGF) in hepatic stellate cells *in vitro* [5]. IGF-1 has been reported to predict the occurrence of liver steatosis in obese patients and as a marker of both fibrosis and steatosis in patients with NAFLD [6]. More recently, IGF-I has been shown to prevent the development of NASH in a genetically modified animal model prone to the disease [7].

NAFLD is now believed to be an integral part of the metabolic syndrome, with insulin resistance as a central pathogenic factor [8]. CKD is associated with severity of liver histopathology in adult biopsy-proven NAFLD [9]. Insulin resistance has been shown to be extensively linked to an increase in incidence of chronic kidney disease [10]. Studies have shown positive association between serum IGF concentrations and risk of chronic kidney disease [11].

Aim of work

The aim of the current study is to evaluate the link between insulin resistance (HOMA-IR), IGF-I level and kidney function assessed by glomerular filtration rate in obese patient with different grades of severity of hepatic steatosis proved by liver biopsy.

Patients and Methods

The present study includes 60 overweight and obese female patients, they were selected from the hepatology outpatient clinic of Kasr Al Ainy Hospital, Cairo University, from (January - May 2016); they were preliminary diagnosed to have NAFLD by abdominal ultrasound +/- elevated liver enzymes, and confirmed by liver biopsy. In addition to twenty age-matched normal BMI, healthy participants were recruited as a control group.

The selection of participants in this study was based on the following inclusion criteria: Patients at age 18 - 65 years old, over weight and obese participants with BMI > 25 kg/m², and normal serum creatinine. Diabetes mellitus, liver cirrhosis, elevated serum creatinine, viral hepatitis, autoimmune hepatitis, history of intake of hepato-toxic medications in last 3months, and alcohol abuse were an exclusion criteria.

All the 60 NAFLD cases were subjected to full history, clinical examination, anthropometric measures, liver function tests, total lipid profile, fasting blood sugar (FBS), anti HCV antibody, HBsAg and abdominal ultrasound.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki; a written informed consent was obtained from all patients participating in the study, after a full explanation of the procedures, and Ethical Committee approval of internal medicine department of faculty of medicine Cairo University in December 2015.

Twenty healthy age matched non-obese participants (BMI >5kg/m²) with no manifestations of NAFLD by abdominal ultrasound were chosen as a control. They were also subjected to the same investigations as patients, but they did not undergo liver biopsy for ethical reasons.

Methods

- All participants were interviewed for their medical history.
- The weight and height of each participant were measured while the participant was clothed only in a light gown, and the BMI was calculated as body weight in kg divided on height square in meters (Kg/ m²).
- The waist circumference was measured midway between last rib margin and the iliac crest in a standing position by the same examiner.
- Blood pressure was measured.
- Blood samples were obtained from each participant after a fasting period of at least 8 hours.
- The blood glucose level was measured using the glucose oxidase method.
- Serum total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride levels were measured on an autoanalyser using enzymatic calorimetry.
- Serum levels of ALT, AST and GGT.
- ELISA for IGF-I and insulin level.
- Calculation of HOMA to determine insulin resistance :
- International Formula: fasting Glucose (mmol/L) x fasting Insulin (mU/L) / 22.5. American Formula: fasting Glucose (mg/dl) x fasting Insulin (μU/mL) / 405 [12].
- Serum creatinine was measured on an autoanalyser using enzymatic calorimetry.
- Calculation of estimated glomerular filtration rate (eGFR): it was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.
- Human IGF-I was measured by Elisa kit supplied by (Quantikine Immunoassay, USA).

Abdominal ultrasound: was performed by the same operator using a Toshiba Apilo XV scanner equipped with a broad band 3.5 MHz curved array probe to assess the presence of liver steatosis (bright liver).

Liver biopsy

It was taken for all patients who were suspected NAFLD guided by abdominal US (according to guidelines of liver biopsy for patients with NAFLD in 2012 by the American Association for the Study of Liver Disease). Liver biopsy was fixed in ten percent neutral buffered formalin then embedded in paraffin blocks. Five micrometer thick sections were cut and stained with hematoxylin and eosin and examined under light microscope for histopathological diagnosis and scoring using NAS scoring system according to Histological Scoring System for Nonalcoholic Fatty Liver Disease. This scoring system addresses the full spectrum of lesions of NAFLD and allows a diagnostic categorization into NASH, borderline NASH or not NASH. Fibrosis staging was evaluated (separately from NASH) from 0 to 4 scales [13].

Statistical Methods

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 21. Data was summarized using mean, standard deviation, median minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between patients and control groups were done using unpaired t test. Comparisons between liver biopsy subgroups were done using analysis of variance (ANOVA) with multiple comparisons post hoc test in normally distributed quantitative variables while non-parametrical kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed variables [14]. Correlation was done to test for linear relations between quantitative variables by Pearson correlation coefficient [15]. P-values less than 0.05 were considered as statistically significant.

Results

The present study was conducted on 60 overweight and obese patients, who have variable degree of severity of NAFLD preliminary diagnosed by abdominal ultrasound, confirmed by liver biopsy. Six of them were excluded because the biopsy specimen was not enough for complete assessment of NAS score and fibrosis with refusal of the patients to repeat the biopsy, so we ended by enrollment of 54 patients. And 20 healthy participants, their age was 42.65 ± 7.11 year, with a BMI of 22.01 ± 3.76 kg/m².

In spite that, none of our NAFLD patients were diabetic, fasting blood sugar, fasting insulin were significantly elevated compared to the healthy control participants. And IGF-1 was significantly lowered in NAFLD patients as shown in table 1.

Parameter	Patients (n.54)	Control (n.20)	P value
FBS(mg/dl)	105.48 ± 9.68	97.25 ± 6.66	< 0.001**
Fasting Insulin (µIU/mL)	12.75 ± 5.19	7.79 ± 1.68	< 0.001**
HOMA-IR	3.57 ± 1.57	1.87 ± 0.43	< 0.001**
IGF-1 (ng/ml)	58.15 ± 20.26	130.00 ± 19.44	< 0.001**

Table 1: Comparison between FBS, insulin level, HOMA-IR, and IGF-1 in the studied case and control participant.

*IGF-1: insulin like growth factor; p < 0.001**, highly significant*

Serum creatinine and eGFR were significantly higher in healthy participants.

According to the results of liver biopsy, patients were divided by NAS score [13], into 3 subgroups: Group A includes patients who have NASH; they were 21 patients with age 42.81 ± 6.39 years, Group B includes patients who have borderline NASH; they were 26 patients with age 42.96 ± 8.28 years, and Group C includes patients who don't have NASH (simple steatosis), they were 7 patients 45.29 ± 6.63 years. Their BMI were (43.61 ± 3.71 , 35.27 ± 4.12 , and 33.44 ± 2.33 kg/m² respectively), and their waist circumference were (107.74 ± 15.94 , 107.48 ± 14.96 , and 98.10 ± 10.82 cm respectively).

ALT, GGT, and serum creatinin level; were significantly elevated in patients with NASH, and border line NASH compared to simple steatosis. While eGFR, was significantly reduced in NASH patients compared to non-NASH, as shown in table 2.

	NASH (n.21)	Borderline NASH (n. 26)	NOT NASH (n.7)	P value
ALT (IU/L)	41.95 ± 23.56	30.08 ± 13.37	18.86 ± 7.99	0.008*
AST (IU/L)	42.00 ± 28.32	28.15 ± 9.75	24.14 ± 6.12	0.094
GGT (IU/L)	53.33 ± 31.31	50.31 ± 40.21	20.00 ± 9.52	0.006*
T-CHOL (mg/dl)	197.90 ± 26.98	209.04 ± 35.32	220.14 ± 39.33	0.257
LDL-c (mg/dl)	106.10 ± 17.48	104.12 ± 26.00	98.71 ± 10.55	0.736
HDL-c (mg/dl)	44.71 ± 9.14	49.00 ± 18.33	54.43 ± 17.96	0.276
TGs (mg/dl)	169.48 ± 51.70	176.62 ± 36.27	159.00 ± 47.60	0.625
Creat. mg/dl	1.18 ± 0.14	1.115 ± 0.14	0.96 ± 0.08	0.002*
eGFR ml/min	58.03 ± 9.01	59.74 ± 9.77	72.07 ± 8.06	0.004*

Table 2: Laboratory data of the NAFLD subgroups.

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: G-Glutamyl Transpeptidase; NASH: Nonalcoholic Steatohepatitis; Tgs: Triglycerides; Total-C: Total Cholesterol; *P < 0.05: significant.

Fasting blood sugar, insulin, estimated insulin resistance by HOMA-IR, and IGF-1 levels in different NAFLD subgroups according to NAS score in liver biopsy shown in table 3.

	NASH (n.21)	Borderline NASH (n. 26)	NOT NASH (n.7)	P value
FBS (mg/dl)	106.43 ± 20.29	107.62 ± 17.51	100.71 ± 15.86	0.066
INSULIN (µIU/mL)	11.97 ± 5.59	13.68 ± 5.01	11.63 ± 4.64	0.447
HOMA-IR	3.72 ± 1.50	3.94 ± 1.61	3.20 ± 1.22	0.093
IGF-1 ng/ml	56.92 ± 19.80	56.80 ± 20.52	66.81 ± 21.56	0.397

Table 3: Comparison between FBS, insulin level, HOMA-IR, and IGF-1 in the NAFLD subgroups.

Correlation was assessed between IGF-1, HOMA-IR; eGFR in NAFLD patients' subgroup, There was no statistical significant correlation between IGF-1 and the rest of the parameters, as shown in table 4.

		Insulin	HOMA-IR	IGF-1	GFR	Creat.
Insulin	R	1	0.850	-0.238-	0.097	-0.137-
	P value		< 0.001*	0.084	0.484	0.324
	N	54	54	54	54	54
HOMA-IR	R	0.850	1	-0.268-	0.045	-0.083-
	P value	< 0.001*		0.050	0.747	0.549
	N	54	54	54	54	54
IGF-1	R	-0.238-	-0.268-	1	0.190	-0.211-
	P value	0.084	0.050		0.169	0.125
	N	54	54	54	54	54

eGFR	R	0.097	0.045	0.190	1	-0.942-
	P value	0.484	0.747	0.169		< 0.001*
	N	54	54	54	54	54
Creat.	R	-0.137-	-0.083-	-0.211-	-0.942-	1
	P value	0.324	0.549	0.125	< 0.001*	
	N	54	54	54	54	54

Table 4: Correlation between insulin, HOMA-IR, IGF-1, creatinine and GFR in NAFLD patients.

Discussion

NAFLD represents a spectrum of disorders characterized by predominantly macro-vesicular hepatic steatosis that occur in individuals in the absence of consumption of alcohol in amounts considered harmful to the liver. NAFLD is a leading cause of chronic liver disease and its incidence is rising worldwide [16].

The pathogenesis of nonalcoholic fatty liver disease has not been fully elucidated. The most widely supported theory implicates insulin resistance as the key mechanism leading to hepatic steatosis, and perhaps also to steatohepatitis. “Multiple hits hypothesis” in NAFLD and NASH; Genome-wide association studies have confirmed the importance of the patatin-like phospholipase 3 (PNPLA3) gene polymorphism in NAFLD. This genetic polymorphism is able to differentiate simple steatosis with or without minimal inflammation and fibrosis progressing to NASH [17]. Obesity and diabetes induce insulin resistance, adipocyte proliferation and changes in intestinal flora [18]. Macrophages play an important role in the induction of inflammation and insulin resistance; also Ingestion of free fatty acids and free cholesterol induce ER stress and oxidative stress, resulting in hepatic inflammation and fibro genesis that induces progression to NASH and insulin resistance. In some instances, inflammation could precede steatosis, and antitumor necrosis factor (TNF)- α antibody improves steatosis in ob/ob mice. CD4 (+) T cells are found after NASH development. Adipokines such as Adiponectin, IL-6 and TNF- α produced by adipocytes affect hepatocyte fat content, the liver inflammatory environment and are considered to be the major inflammatory mediators found in NAFLD and insulin resistance [19].

IGF1 has been reported to predict the occurrence of liver steatosis in obese patients and as a marker of both fibrosis and steatosis in patients with NAFLD [6]. Proinflammatory cytokines stimulate the development of NASH and inhibit IGF-I secretion from hepatocytes either by decreasing growth hormone levels or inducing growth hormone resistance. NAFLD and hepatic insulin resistance could contribute to modulate circulating IGF-I levels as chronic hyperinsulinemia decreases the expression of GH receptor in liver [20].

NAFLD and CKD share common risk factors and therefore both liver and kidney injury may be driven by obesity-associated mechanisms of disease, including lipotoxicity, oxidative stress, enhanced pro-inflammatory cytokine, and renin-angiotensin-aldosterone system (RAAS) axis activation. It also has been suggested that insulin resistance is a susceptibility factor of CKD, making insulin resistance a possible mechanistic link between NAFLD and CKD [21]. A pprevious study showing that: Plasma IGF-1 concentrations is a determinant of eGFR, and suggest that lower amounts of circulating IGF-1 associated with NAFLD could contribute to the reduced eGFR observed in individuals with high or intermediate probability of advanced liver fibrosis [22].

Knowledge of whether a patient has simple steatosis or NASH is very important prognostically. Subjects with simple steatosis have a good long-term prognosis with low rates of liver-related morbidity and mortality, and therefore do not require specific liver-related treatment. However, patients with NASH can progress to cirrhosis, and therefore should be more actively managed trying to prevent disease progression [23].

In the present study, there is no significance for age as a precipitating factor for NAFLD also there is no significant age difference between NASH patient’s subgroups. This agrees with Cao and colleagues who stated that: there is no significance regarding age as precipi-

tating factors for NAFLD [24]. It was previously suspected that; progression to NASH need a long time meaning that patients will develop NASH and fibrosis in their late fifties [25], but we didn't found any difference in the present study groups with all patient aged from late twenty to early fifty and this predict early progression to NASH.

BMI was lower in patients with simple steatosis (33.44 ± 2.33 kg/m²), compared to (35.27 ± 4.12 kg/m²) in patients with borderline NASH, and reached the highest (43.61 ± 3.71 kg/m²) in patients with NASH, but the difference didn't reach significant level with (P value 0.515). This agrees with the study done by Clark and Diehl, they found that: two thirds of patients with a BMI above 30, and more than 90 % of patients with a BMI greater than 39 have steatosis [26]. Also Harnois and colleagues found that BMI was the only predictive factor for NASH [27].

In the present study, eGFR was significantly lower in NAFLD patients (60.68 ± 10.17 ml/min) compared to normal control participants (95.81 ± 17.70 ml/min) with (P value < 0.001). eGFR was higher in patients with simple steatosis (72.07 ± 8.06 ml/min), compared to (59.74 ± 9.77 ml/min) in patients with borderline NASH, and (58.03 ± 9.01 ml/min) in patients with NASH with (P value 0.004). So it was found that eGFR < 90 in NAFLD patients. And in between NASH subgroups it was > 60ml/min in simple steatosis patients and eGFR < 60 in borderline NASH and NASH patients.

The present study results have agreement with Armstrong and colleagues who found that; the presence and severity of NAFLD are associated with an increased risk and severity of CKD [28].

According to the National Kidney Foundation Practice Guidelines, mild kidney function damage (MKFD) occurs early before CKD appearance. Therefore, to explore the relationship between NAFLD and kidney function, it was applied the cut-off point of eGFR < 90 mL/min/1.73 m² for MKFD [29]. So the results of our current study had showed a graded positive relationship between the histological severity of NAFLD and kidney disease, and it can suggest that GFR > 90 almost exclude NASH subgroups and < 60 include NASH and border line NASH.

HOMA-IR was significantly higher in NAFLD patients (3.57 ± 1.57) than in normal healthy control participants (1.87 ± 0.43) with (P value < 0.001). In the current study the inter subgroups HOMA-IR value difference between NAFLD patients was higher in patients with borderline NASH (3.94 ± 1.61), and NASH (3.72 ± 1.50) compared to (3.20 ± 1.22) in patients with simple steatosis with (p value 0.093). Also HOMA-IR had showed almost close values between borderline NASH and NASH. Angelico and colleagues in 2005 had reported that, Subjects with a more pronounced insulin resistance had a higher prevalence of severe steatosis [30].

IGF-1 was significantly lower in NAFLD patients (58.15 ± 20.26 ng /ml) compared to normal healthy participant (130.00 ± 19.44 ng /ml) with (P value < 0.001). IGF-1 was higher in patients with simple steatosis (66.81 ± 21.56 ng /ml), compared to (56.80 ± 20.52 ng/ml) in patients with borderline NASH, and (56.92 ± 19.80 ng/ml) in patients with NASH but it didn't reach significant level with (P value 0.397). The results of the present study agree with Mallea-Gil and colleagues who reported that IGF-I level had been associated with NAFLD, progressively decreasing with liver fat accumulation [4]. Also Colak and his colleagues found that the highest values for IGF-I were observed in individuals classified as at low risk of NASH and fibrosis, and the lowest values were in those at high risk of NASH and fibrosis [31].

The result of the current study are in agreement with Petta and his colleagues who reported that, plasma IGF-1 concentration is a determinant of eGFR [32]. Also Arturi and his colleagues suggest that lower amounts of circulating IGF-1 associated with NAFLD/NASH could contribute to the reduced eGFR observed in individuals with high or intermediate probability of advanced liver steatosis and fibrosis [33]. But in the current study we didn't reach statistical significant level with P value 0.169.

In korean patient, NASH was significantly associated with lower eGFR, even after adjusting for the clinical traits of the metabolic syndrome, HOMA-estimated insulin resistance it is also possible to speculate that NASH is not only associated with CKD as a consequence

of the shared risk factors but that NASH itself might at least in part contribute to the development of CKD independently of shared risk factors [34].

That in agree with the above previous study HOMA-IR was higher value in NAFLD compared to normal healthy participant with eGFR < 90 ml/min , and in patient with borderline NASH and NASH eGFR had lower value < 60ml/min, also HOMA-IR was higher in borderline NASH and NASH compared to simple steatosis patients.

Conclusion

There is a definitive association between NAFLD, IGF-I, HOMA-IR, and eGFR. IGF1 and eGFR were lower in NAFLD patients than normal healthy control participant, also HOMA -IR was higher in non diabetic NAFLD patients compared to normal healthy control participant.

In NASH patients subgroups eGFR was lower than 90 ml/min in patients with simple steatosis and less than 60ml/min in patients with borderline NASH and NASH , also low level of IGF-1 in patients with borderline NASH and NASH compared to simple steatosis patients and HOMA-IR was higher in borderline NASH and NASH patients compared to simple steatosis patients.

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