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Adipokines Profile and Glucose Control of Saudi Patients with Nonalcoholic Fatty Liver Disease

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is a prevalent condition associated with obesity and insulin resistance (IR). Adipokines include fat-secreted proteins such as leptin or adiponectin and fat- or liver-derived cytokines such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) are considered to play an important role in the pathogenesis of the metabolic syndrome, including NAFLD.

Objective: The present study aimed to explore the role of adipokines in the pathogenesis of NAFLD and correlate them with glucose control.

Material and Methods: One hundred Saudi patients with NAFLD (45 males and 55 females) with NAFLD diagnosed by ultrasonographic findings, our group include one gender, age and body mass index (BMI) matched hundred healthy volunteers. Adiopkines and parameters of glucose control of all participants were detected.

Results: Serum glucose, insulin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT), serum levels of total cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C), serum TNF-α and L-6 levels were significantly higher in patients with NAFLD when compared to control group. However, serum high density lipoprotein cholesterol (HDL-C) and adiponectin levels were significantly lower in patients with NAFLD when compared to control group. Moreover, serum levels of adipokines showed an association with insulin resistance.

Conclusion: Within the limit of this study non-alcoholic fatty liver disease is associated with adipokines alteration that is correlated with abnormal glucose control and insulin resistance.

Keywords: Adipokines; Insulin resistance; Non-alcoholic fatty liver disease

Abbreviations: NAFLD: Non-Alcoholic Fatty Liver Disease; IR: Insulin Resistance; TNF- α: Tumor Necrosis Factor-α; IL-6: Interleukin 6; AST: Aspartate Aminotransferase; BMI: Body Mass Index; ALT: Alanine Aminotransferase; LDL-C: Low Density Lipoprotein Cholesterol; HDL-C: High Density Lipoprotein Cholesterol

Introduction

Nonalcoholic fatty liver disease (NAFLD) is currently a common chronic hepatic disorder, affecting about 30% of population in the Western nations [1]. NAFLD is common among obese subjects as the increasing prevalence of NAFLD parallels the raised risk of obesity [2]. However, insulin resistance (IR), obesity and metabolic syndrome are the principle risk factors for NAFLD [3]. IR appears plays the key role in the genesis of NAFLD, suggesting a possible interplay among IR, atherosclerosis and NAFLD [4].

Adiponectin is cytokine derived from adipose tissue and play a principle role in insulin sensitivity and glucose homeostasis [5]. Moreover, adiponectin has anti-atherosclerotic and anti-inflammatory properties in addition to improving insulin sensitivity [6]. Lower levels of adiponectin is an independent risk factor for insulin resistance among NAFLD patients [7].

Leptin was found to be increased among obese subjects that adversely affects homeostasis of glucose [8]. The degree of inflammation and hepatic steatosis usually correlated with the level of leptin among patients with NASH [9].

Macrophages and monocytes secret resistin [10]. There is debate in the link between pathogenesis of NAFLD and resistin as there is an association between obesity and NAFLD [11].

Moreover, it was proved the pro-inflammatory properties of the resistin as there is evidence that resistin enhances production of some inflammatory cytokines among patients with NAFLD [12].

The aim of the present study is to explore the role of adipokines in the pathogenesis of NAFLD and correlate them with glucose metabolism.

Subjects and Methods

Subjects

One hundred obese NAFLD patients (the mean of body mass index was 31.14±4.95Kg/m2 and the mean of age was 44.25±5.73 year) were selected from patients of the Liver Clinic in King Abdulaziz University Teaching Hospital. In addition, one hundred healthy subjects were enrolled as a control group who were matched with study group regarding the baseline criteria. Diagnosis of NAFLD diagnosis was based on ultrasonograhpic finding according to American Gastroenterology Association standard criteria [13,14]. Exclusion criteria included viral hepatitis infection and patients with liver cirrhosis, hypertension, diabetes, cancer, ischemic heart disease, thyroid disease and pregnancy in addition to corticosteroids, methotrexate, tamoxifen, oral contraceptives or alcohol intake. Detailed history, full clinical and anthropometric examinations were done for all participants [15]. Consent form was signed by all participants before sharing in the study and ethical approved was obtained by the Scientific Research Ethical Committee, Faculty of Applied Sciences, King Abdulaziz University.

Laboratory investigation

Venous overnight fasting blood samples were drawn to determine levels of the biochemical parameters aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, glucose, cholesterol, low-density lipoprotein, high-density lipoprotein (HDL), triglycerides, insulin, leptin, adiponectin, TNF-α and IL-6. Serum blood glucose was measured using reagent from Boehringer Mannheim on the Hitachi 912 Chemistry. Serum level of leptin was measured using ELISA via DRG instruments GmbH, Germany. Serum level of adiponectin was determined using AviBion human adiponectin using Orgenium Laboratories, Finland. Serum level of resistin was measured via ELISA using commercially available kits. Serum insulin was measured by insulin kit using a cobas immunoassay analyzer (Roche Diagnostics).Insulin resistance was assessed by homeostasis model assessment (HOMA-IR), it was computed with the formula:

Fasting plasma glucose (mmol/l) times fasting serum insulin (mU/l) divided by 22.5 [16]. However, insulin sensitivity was assessed by The quantitative insulin-sensitivity check index (QUICKI) using the formula: QUICKI=1/[log(insulin)+log(glucose)] [17].

Statistical analysis

Independent t-test was used to compare mean differences between both groups. Statistical analysis of data was performed using SPSS (Chicago, IL, USA) version 17. The degree of correlation between adiopkines and parameters of glucose control in NAFLD patients was detected by Pearson's product moment correlation coefficients (r). All data were expressed as the Mean±SD. $P<0.05$ indicated statistical significance.

Results

One hundred NAFLD Saudi subjects were enrolled including 55 women and 45 men, had age ranged from 30 to 57 years and one hundred healthy subjects had age ranged from 31 to 58 years, there was no significant differences in baseline characteristics between both groups (Table 1).

Table 1: Demographic and anthropometric characteristics of NAFLD patients and control subjects.

	NAFLD (no=100)	Healthy Control (no=100)	P- Value
Age (year)	43.83 ± 6.12	45.16±5.97	0.54
Gender(F/M)	55/45	57/43	0.62
BMI (kg/m2)	31.5±5.16	30.94±4.87	0.31
Hip circumference (cm)	121.31±13.94	119.21±13.52	0.17
Waist circumference (cm)	106.46±11.27	104.83±10.78	0.28
waist hip ratio	0.933±0.036	0.915±0.029	0.54

BMI: Body Mass Index

NAFLD patients were more insulin resistant as indicated by significantly higher values of fasting glucose, insulin and HOMA-IR and lower values of QUICKI, with no significant differences in leptin concentration between patients and controls. Also, NAFLD patients showed significantly higher resistin level, aspartate aminotransferase (AST), alanine aminotransferase (ALT), aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT), serum levels of total cholesterol, triglycerides, serum high density lipoprotein cholesterol (HDL-C) and adiponectin levels in comparison to controls (Table 2).

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Table 2: Mean value and significance of biochemical parameters of NAFLD and control subjects.

	NAFLD	Healthy Control	P- Value
Fasting glucose(mg/dl)	145.43±26.14*	97.61±18.56	0.015
Insulin(mU/l)	16.52±4.17*	8.31±2.98	0.001
QUICKI	0.121±0.01	0.185±0.024	0.025
HOMA-IR	5.28±1.95*	2.73±1.13	0.003
AST (IU)	68.22±11.26*	34.75±7.25	0.007
ALT (IU)	57.17±9.53*	38.11±5.42	0.024
AST/ALT	1.19±0.98*	0.92±0.67	0.018
Total cholesterol (mg/dl)	193.35±42.22*	116.24±31.46	0.006
HDL-C (mg/dl)	34.23±8.41*	53.28±10.17	0.015
LDL-C (mg/dl)	127.15±26.18*	92.91±18.43	0.023
Triglycerides (mg/dl)	161.27±31.15*	95.16±20.31	0.017
Leptin (ng/ml)	22.16±3.93	15.82±3.16	0.084
Adiponectin (µg/ml)	4.18±1.79*	8.12±2.53	0.005
Leptin/adiponectin ratio	5.21±1.98*	1.93±1.21	0.012
Resistin (ng/mL)	16.83±4.52*	13.17±4.11	0.025
TNF-α (pg/mL)	6.12±1.91*	3.64±1.17	0.016
IL-6 (pg/mL)	3.46±1.52*	1.81±1.14	0.004

HDL-c: High Density Lipoprotein Cholesterol; LDL-c: Low Density Lipoprotein Cholesterol; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; AST/ALT: Aspartate Aminotransferase/Alanine Aminotransferase Ratio; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance Index; QUICKI: Quantitative Insulin-Sensitivity Check Index; TNF- α: Tumor Necrosis Factor-Alpha; IL-6: Interleukin-6, (*) indicates a significant difference between the two groups, P<0.05.

Table 3: Correlation coefficient (r) of adiopkines and parameters of glucose control in NAFLD patients.

	Insulin(mU/l)	QUICKI (%)	HOMA-IR (%)
Leptin (ng/ml)	0.611*	-0.725**	0.512*
Adiponectin (µg/ml)	0.742**-	0.661**	0.843**-
Resistin (ng/mL)	0.526*	0.672*-	0.721**
TNF-α (pg/mL)	0.728**	-0.593*	0.621*
IL-6 (pg/mL)	0.531*	-0.684**	0.513*

Spearman's correlation was used*: P<0.05**: P<0.01

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Table 3 summarizes the relationship between adipokines and parameters of glucose control in NAFLD patients. Serum levels of leptin, resistin, TNF-α and IL-6 showed an inverse relationship with QUICKI and a direct relationship with serum insulin, HOM-IR. However, levels of adiponectin showed a direct relationship with QUICKI and an inverse relationship with serum insulin, HOM-IR (Table 3).

Discussion

Insulin resistance is related to development of NAFLD and adipose tissue [18]. Our study underscores that NAFLD is associated with IR and adipokines alterations. Though NAFLD patients had raised ALT suggestive of some hepatocellular injury. In our study, NAFLD patients showed significantly higher serum glucose, insulin, HOMA-IR, resistin level, AST, ALT, AST/ALT ratio, lipid profile, serum TNF-α levels, serum IL-6 levels and significantly lower values of QUICKI, serum HDL-Cand adiponectin level in relation to control subjects.

A recent study conducted by Sanches and colleagues proved that patients with IR have 65% greater risk of developing NAFLD. Because they found that obese patients with NAFLD presented greater baseline HOMA-IR values and insulin concentration than their peers without NAFLD [19]. Willner et al. [20] reported a strong relation between IR and NAFLD and IR.

Concerning the results regarding to the serum adiponectin, NAFLD patients had a significantly lower level of adiponectin in comparison to the control subjects. Also, our study showed that adiponectin levels were also associated with increased IR in NAFLD patients. Several previous researches reported reduction in the level of adiponectin among obese and NAFLD subjects [21,22]. Also, in the study by Hu et al. [23] reported reduced level of adiponectin expression among obese subjects and mice.

Our study confirmed a previous study found that leptin higher in NAFLD children [24] and an earlier clinical trial reported significantly higher serum leptin levels in patients with NASH as compared to controls [25]. The increases in leptin levels in NASH is not explained by obesity alone but is also due to peripheral leptin resistance. In NASH leptin receptors become resistant to its effect leading to hyperleptinemia which alters insulin signaling and promotes accumulation of intracellular fatty acids in hepatocytes thereby increasing hepatic steatosis and steatohepatitis [26].

Our results revealed higher levels of resistin among the NAFLD patient than control, which approved by previous study reported that higher resistin level among obese subjects than lean individuals [27]. Shen et al. [28] stated that NASH patients had increased level of resistin.

Conclusion

Within the limit of this study non-alcoholic fatty liver disease is associated with adipokines alteration that is correlated with abnormal glucose control and insulin resistance.

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