Insulin Resistance and ß-Cell Function in Patients with Non-alcoholic Fatty Liver Disease

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Abstract

Background: Nonalcoholic fatty liver disease is a common hepatic disorder marked by the accumulation of lipids in the liver, frequently accompanied by metabolic disturbances, including insulin resistance (IR), a condition where cells become less responsive to insulin's glucose-lowering effects, important in the evolution and progression of NAFLD.
Objective: To evaluate the degree of IR and β-cell function among patients with NAFLD.
Methods: A case-control study was conducted on 75 patients diagnosed with NAFLD and 81 control subjects. Fasting blood glucose, glycated haemoglobin and insulin were determined in all participants. In addition, insulin resistance and pancreatic ß- cell function were estimated by HOMA-IR and HOMA-B equations respectively.
Results: HOMA-IR and HOMA-B were significantly higher among patients with NAFLD (3.59 ± 3.52, 277.57 ± 169.89) than controls (2.56±1.39, 153.46±106.17) respectively, with the comparative $P < 0.05$ and $P < 0.001$. In addition, FBG, HbA1c and insulin were significantly higher among patients with NAFLD than control subjects, $P < 0.01$.
Conclusion: The strong association between HOMA-IR and NAFLD imply the role of IR in the pathogenesis of NAFLD. The significant elevation of HOMA-B among patients with NAFLD reflects the degree of hyperinsulinaemia secondary to IR.

Keywords; NAFLD, insulin resistance, β-cell function

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Introduction

Nonalcoholic fatty liver disease(NAFLD) is identified by the buildup of lipids in the liver (hepatic steatosis) without other underlying causes. While a small amount of fat can naturally occur in a healthy adult liver, the condition is considered pathological when at least 5% of hepatocytes have fat deposition. [1,2] Fat accumulation in the liver can be attributed to multiple factors, including increased delivery of free fatty acids (FFAs), elevated hepatic synthesis of fatty acids (FAs), reduced oxidation of FFAs, or diminished synthesis or secretion of very-low-density lipoprotein (VLDL). Various factors may contribute to the development of NAFLD, such as infections like hepatitis C and HIV, medications like tamoxifen, amiodarone, and methotrexate, exposure to toxins, metabolic disorders such as glycogen storage disorders, Wilson's disease, and homocystinuria, as well as nutritional influences like overnutrition, and extreme dieting [3,4]

The prevalence of NAFLD varies significantly across different populations. Estimates demonstrated that it affects around 20% of the US people and ranges from 11.5% to 46% in the general population. In contrast, nonalcoholic steatohepatitis (NASH) is estimated to affect only 2% to 3% of individuals. While NAFLD is more common among white men compared to white women, there are no discernible differences in prevalence between Hispanic and African American individuals. [5] Insulin resistance (IR) refers to a reduced biological response to insulin in target tissues like the muscle, liver, and adipose tissue, leading to impaired glucose disposal and compensatory hyperinsulinemia. [6,7]. This condition often precedes type 2 diabetes (T2D) by 10 to 15 years. As IR develops, the body increases endogenous insulin production, which, being an anabolic hormone, promotes weight gain, exacerbating IR further.[8,9] This cycle persists until pancreatic ß-cell activity fails to meet the demand for insulin, resulting in hyperglycemia and eventually

T2D.[9] NAFLD can be categorized into two main types. The first type is closely linked to metabolic syndrome (MetS), with IR considered the primary underlying mechanism. The second type is associated with infectious factors, where conditions such as hepatitis C and HIV can contribute to liver steatosis. Additionally, medications, toxins, inherited or acquired metabolic disorders, intestinal bypass surgery, and other factors may also play a role in this type of NAFLD. [10,11] Obesity accompanied by IR results in an elevated influx of FFAs into the liver. These FFAs are either oxidized via β-oxidation or esterified with glycerol to produce triglycerides, contributing to hepatic fat buildup. Moreover, mounting evidence suggests that FFAs can induce toxicity by promoting oxidative stress and activating inflammatory pathways [12] NAFLD has become a serious public health concern because of its rising prevalence throughout the world, it encompasses a range of liver conditions, from simple fat buildup to nonalcoholic steatohepatitis, which is marked by liver damage and inflammation. While the exact causes are multifactorial, risk factors include obesity, T2D, and MetS. Early detection and lifestyle modifications, such as dietary adjustments and increased physical activity, are crucial for managing NAFLD and preventing its progression to more severe liver complications [13,14] In Barash, the consequence of IR, MetS, has been studied from various aspects. [15-17] The aim of the study was to assess the extent of IR and β-cell function among patients with NAFLD.

Methods:

This case-control study was conducted from December 2022 throughout April 2023 and involved 156 participants aged 18 to 75 years. Among them, 75 patients diagnosed with NAFLD by ultrasound at the Gastroenterology and Hepatology Hospital in Basrah, Southern Iraq, were included (34 males and 41 females). In addition, 81 control subjects were included. They were 46 males and 35 females, who were apparently healthy individuals and confirmed to be in good health, by careful clinical examination and biochemical tests. Informed written agreement was obtained from all participants. The study was approved by the Ethical Committee, College of Medicine, University of Basrah. Exclusion criteria comprise alcoholic liver disease, chronic liver disease, viral hepatitis, renal failure, and thyroid disease. A comprehensive questionnaire was used to gather information on a variety of sociodemographic factors, such as age, sex, marital status, level of education, history of systemic disorders in the family and self, smoking and alcohol intake. All participants underwent measurements of weight, height, and waist circumference while wearing light clothing and without shoes. Body mass index (BMI) was calculated by the formula (kg/m²). systolic blood pressure (SBP) & diastolic blood pressure (DBP) were measured twice with a mercury sphygmomanometer, with at least a 10-minute interval between measurements. Determination of Fasting blood glucose [18] measured by automated enzymatic reference method using Hexokinase kit provided by Roche Diagnostic Germany by using COBAS INTEGRA system, glycated haemoglobin (HbA_{1c}) [19] by ion exchange high-performance liquid chromatography (HPLC) using Bio-Rad USA's VARIANT TURBO HbA1c Kit and insulin measured by using fully automated COBAS e411 system Immunoassay [20]. β-cell function and insulin resistance (IR) were assessed using the following equations: [21-23]

HOMA-B = 360 × fasting insulin (µIU/ml) / FBG (mg/dL) – 63 Where, B: % of ß-cell function, FBG is fasting blood glucose. Normal value of HOMA-B: 100%. HOMA-IR = FBG (mg/dL) × fasting insulin (µIU/ml) / 405 Where IR represents insulin resistance and FBG represents fasting blood glucose. The normal value of HOMA-IR is ≤ 2.5. Statistical analysis was performed by Statistical Package for the Social Sciences (SPSS) version 23. The Results were presented as mean ± standard deviation and percentages. A p-value < 0.05 was considered statistically significant.

Results:

Table 1 displays the socio-demographic and anthropometric features of the study groups. Patients with NAFLD exhibited significantly higher BMI and WC compared to the control group (p < 0.001 and

p < 0.05, respectively). However, there were no significant differences in age, sex, SBP, and DBP between patients and controls (p > 0.05).

Table 1: Sociodemographic and anthropometric characteristics among study groups

Characteristic		Patients (n=75)	Control group (n=81)
Sex	Male	34 (45.3%)	46 (56.8%)
	Female	41 (54.7%)	35 (43.2%)
Age (year)		40.53 ±13.79	37.62± 9.43
BMI (kg/m^2)		33.82 ± 4.87#	28.02 ± 2.28
WC (cm)		109.12±13.63*	104.36±10.14
SBP (mmHg)		119.84 ± 9.83	118.32 ± 8.64
DBP (mmHg)		81.76 ± 7.84	81.32 ± 6.95

Data are expressed as mean ± SD

***:** P < 0.05 (patients vs controls)

#: P < 0.001 (patients vs controls)

As presented in Table 2, FBG, HbA_{1c} and insulin were significantly higher in patients with NAFLD than control subjects, P < 0.01.

Table 2. FBG, HbA_{1c} & insulin values among study groups

Parameter	Patients (n=75)	Control group (n=81)
FBG (mg/dl)	105.58 ± 30.96**	92.18 ± 8.85
HbA1c (%)	5.90 ± 1.24**	5.03 ± 0.47
Insulin (µIU/ml)	15.77 ± 12.73**	11.19 ± 5.78

expressed as mean ± SD

****:** P < 0.01 (patients vs controls)

Table 3 displays the HOMA-IR and HOMA-B values for both the patients and the control group. Patients of NAFLD exhibited significantly higher levels of both HOMA-IR and HOMA-B compared to control subjects, P<0.05 and P<0.001 respectively.

Table 3. HOMA-IR and HOMA-B among study groups

Parameter	Patient group (n=75)	Control group (n=81)
HOMA-IR	3.59 ± 3.52*	2.56 ± 1.39
HOMA-B	277.57 ± 169.89#	153.46 ± 106.17

Data expressed as mean ± SD

***:** P<0.05 (patients vs controls)

#: P<0.001 (patients vs controls)

Discussion

The present study revealed no significant change among patients with NAFLD and the control group concerning sex and age. Age and sex factors with

NAFLD were evaluated in various studies with controversial results. Uppalapti and Harish [24] reported findings in patients with diabetic consistent with the present study. Similarly, Pardhe et al [25] found no significant relationship between age and NAFLD. Furthermore, Chalasani et al [14] also noted that age and sex were not significant predictors of advanced fibrosis in NAFLD patients. Furthermore, a meta-analysis by Younossi et al [13] showed no significant difference in NAFLD prevalence between males and females. However, other studies have reported a significant association between age and NAFLD. [26,27]

The current study showed there is a significant increase in FBG, HbA1c and insulin levels in NAFLD patients compared to control subjects. This finding agrees with other studies. [25,26,28,29] Several factors contribute to the increase in FBG, HbA1c, and insulin levels. IR and lipid accumulation in the liver lead to disruption of insulin signaling pathways, The combined effects of IR, inflammation, lipid accumulation, and pancreatic dysfunction in NAFLD collectively lead to the rise in FBG, HbA1c, and insulin levels observed in affected individuals.

HOMA-IR is a mathematical model that estimates IR based on FBG and insulin levels. It provides valuable insights into the impaired response of peripheral tissues, such as the liver and muscle, to insulin signaling, a hallmark of metabolic dysfunction in NAFLD. [30] The present study showed a significant increment in HOMA-IR among patients with NAFLD. This observation is similar to the results of others. [31-35] IR is the principal pathogenic mechanism of NAFLD. It affects the liver as well as extrahepatic tissues such as skeletal muscle and adipose tissue. Together, these tissues and the liver cause systemic inflammation and the production of proatherogenic and nephrotoxic substances. [36] This dysregulated metabolic state leads to the increased influx of FFAs to ectopic tissues, driven by heightened lipolysis in dysfunctional adipose tissue. Consequently, liver, and skeletal muscle develop IR and apoptosis, fostering a "lipotoxic state" in NASH characterized by hepatocyte inflammation and necrosis. [37] The intricate interplay between IR and NAFLD carries significant clinical implications. Elevated HOMA-IR not only serves as a marker of metabolic dysfunction but also correlates with the severity of liver conditions within the NAFLD spectrum. It is associated with an increased risk of progression from simple steatosis to NASH, fibrosis, and cirrhosis, underscoring its utility as a prognostic indicator. Moreover, IR in NAFLD heightens the risk of cardiovascular comorbidities, including atherosclerosis and hypertension, underscoring the systemic ramifications of this condition. [30]

In large-scale investigations, HOMA-B is frequently utilized to estimate ß-cell function by calculating the pancreatic ß-cell function as a percentage of normal reference populations. However, it is important to note that the β-cell function is compensatory and can be enhanced by IR in the environment. [38] This study demonstrated a significant increase in HOMA-B among patients with NAFLD, Table 3. This finding aligns with one study [39] but differs from others, [40] suggesting potential factors such as genetic variations, racial differences, and sample sizes may contribute to this apparent controversy.

The relationship between NAFLD and pancreatic β-cell function is influenced by two factors. Initially, the pathophysiology of glucose metabolism dysregulation and hyperinsulinemia involves pancreatic β-cell failure, which may also contribute to the advancement of NAFLD and hepatic lipid metabolism problems. [41] Secondly, NAFLD is a multiple-system disease, [42] that could affect pancreatic ß-cell function. The liver secretes various metabolites, proteins, and extracellular vesicles involved in metabolic processes not only within the liver but also in other tissues. [43]

One study revealed that hepatocytes overloaded with lipids could induce Atherogenesis and endothelial inflammation via extracellular vesicles. [44] In Addition, hepato-kines, such as fibroblast growth factor 21 (FGF21), which are secreted from the liver, can significantly affect pancreatic β-cell function. [45,46]

It is noteworthy that there is still limited understanding of the precise mechanism behind the link between β-cell malfunction and NAFLD.

In conclusion, strong association exists between IR and NAFLD. This finding may imply the role of IR in the pathogenesis of NAFLD. There was a

significant elevation of HOMA-B among patients with NAFLD which reflects the degree of hyperinsulinaemia secondary to IR.

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انتشار مقاومة الانسولين بين مرضى الكبد الدهني غير الكحول

الخلاصة:

خلفية الدراسة: مرض الكبد الدهني غير الكحولي (NAFLD) يُعد اضطراب كبدي شائع يتصف بتراكم الدهون في الكبد , و يترافق مع اضطرابات ايضية لاسيما مقاومة الانسولين (IR) وهي حالة تضعف فيها استجابة خلايا الجسم للأنسولين. تعد مقاومة الأنسولين مهمة لنشوء وتطور مرض الكبد الدهني غير الكحولي.

الهدف: تقييم درجة مقاومة الانسولين ووظيفة خلايا بيتا في البنكرياس بين مرضى الكبد الدهني غير الكحولي

طرق العمل: شملت الدراسة ٧٥ من المرضى الذين تم تشخيصهم بمرض الكبد الدهني غير الكحولي و ٨١ من الاصحاء كمجموعة ضابطة. تم قياس مستويات سكر الصائم (FBG) و الانسولين (Insulin) وخضاب الدم السكري (HbA1c) وحساب مقاومة الانسولين بواسطة مؤشر (HOMA-IR)و وظيفة خلايا بيتا بواسطة مؤشر (HOMA-B) لكل من المرضى والاصحاء.

النتائج: كانت قيم HOMA-IR و HOMA-B أعلى وبشكل معنوي عند مرضى الكبد الدهني غير الكحولي (٣,٥٢±٣,٥٩ , ١٦٩,٨٩ ±٢٧٧,٥٧) على التوالي بالمقارنةً مع الأصحاء (١,٣٩ ± ٢,٥٦ , ١٠٦,١٧±١٥٣,٤٦) , وكانت قيم (P<0.05) و (P < 0.001) على التوالي. بالإضافة الى ذلك، أظهر المرضى مستويات عالية وبشكل معنوي لسكر الصائم،الانسولين وخضاب الدم السكري مقارنة مع الاصحاء (P<0.01).

الاستنتاجات: العلاقة القوية بين مرضى الكبد الدهني غير الكحولي و HOMA-IR تشير الى دور لمقاومة الانسولين في التسبب في مرض الكبد الدهني غير الكحولي , كان هناك ارتفاع كبير في HOMA-B بين مرضى الكبد الدهني غير الكحولي مما يعكس درجة فرط أنسولين الدم الثانوي لـمقاومة الانسولين.

مفاتيح الكلمات: مرض الكبد الدهني غير الكحولي، مقاومة الانسولين , وظيفة خلايا بيتا