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Risk Factors Associated with Coronary Artery Disease in Iraqi Patients with Non-Alcoholic Fatty Liver

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Abstract: The prevalence of Non-alcoholic fatty liver disease (NAFLD) is increasing every day. In addition to hepatic morbidity and mortality, also it is linked with an increased cardiovascular risk. NAFLD and Coronary artery disease (CAD) have a number of common risk factors. This study aimed to evaluate glycemic parameter, liver enzymes and lipid profile serum levels and its abilities to indicate the prognosis of CAD in patients with NAFLD. Serum from 180 Individuals were collected from both genders, and divided into three groups, blood samples were collected from participants and sent for biochemical tests in the laboratory. Data from the current study showed a significant increase in glycemic parameter and aspartate aminotransferase (AST). Also, the lipids profile included Total Cholesterol (TC), Triglyceride (TG), Low-density lipoproteins (LDL), Very Low-density lipoproteins (VLDL), shows a significant increase in serum level with the exception of High-density lipoproteins (HDL) in CAD group compared to NALD and control groups. Obesity and metabolic syndrome patients that suffers from NAFLD along with CAD have a higher serum level of fasting blood glucose (FBS), (TC, TG, LDL, VLDL) and AST when compared to NAFLD patients and healthy individuals, Therefore obesity and metabolic syndrome is considered a risk factor for CAD.

Keywords: Coronary Artery Disease, NAFLD, lipids profile, metabolic syndrome.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) has been increased in the last few decades in parallel with the incidence of dyslipidemia, obesity, heart disease, and other factors of metabolic syndrome (1, 2). It is anticipated to be the dominant indication for liver transplantation (3). However, NAFLD is defined by macrovesicular steatosis ≥5% in hepatocytes, with the absence of secondary cause, such as drugs or alcohol consumption. Non-alcoholic fatty liver (NAFL) includes a spectrum of diseases from non-alcoholic fatty liver diseases (NAFLD) that can progress to non-alcoholic steatohepatitis (NASH) to fibrosis, then cirrhosis. (4,5). Currently, there is no effective therapy available for NAFLD (6).

Currently, Coronary artery disease (CAD) is by far the most predominant disease that may affect the heart, and because of its severe clinical symptoms and acute complications, it is ranked the world's leading cause of death.(7). However, Coronary artery is the main blood artery that provides oxygen-rich blood to the heart (8, 9), while, CAD is an injury or disease in the cardiovascular of the main heart's blood arteries, due to the typical reason, which

is the buildup of plaque. And plaques are often forming due to fat accumulation, cholesterol, and other substances, that will leads the coronary arteries vessels to narrow (8).

On the other hand, obesity is considered a common health concern in many areas around the globes, also it is known as a body mass index (BMI) ≥ 30 kg/m^2 (10-12). Furthermore, there is significant indication that environmental factors along with genetic are essential in the development of obesity. However, genetic factors remaining poorly understood, on the other hand, Obesity is considered the risk factor for the development of insulin resistance (IR) and a significant element in etiology of metabolic syndrome and T2DM. The main reason for obesity development is a positive chronic energy balance characterized by energy expenditure is being less that caloric intake. Moreover, IR indorses development of the disease in NAFLD patients to a more aggressive form, e.g. NASH (13,14). Nevertheless, Insulin is a polypeptide hormone produced by β-cells that stimulates glucose transport and storage from the blood circulation into muscle, fat, and liver at higher concentrations (15). However, IR is a physiological disorder that reduces the effectiveness of the insulin to control blood sugar levels. Additionally, all obese patients do not have NAFLD, and on the contrary, all NAFLD patients are not obese (16). However, NAFLD can be diagnosed in lean individuals (non-obese) who are metabolically different compared to non-obese individuals without NAFLD. This is why many of the patients fail to seek medical attention (17).

Material and method

This study was carried out at Baghdad Hospital in Medical City, in Baghdad during the period (Dec. 2021 to March of 2022). One hundred and eighty participants were participate in the study and categorized into three groups. The first group involved (60) patients with NAFLD, The second group involved (60) patients with NAFLD along with CAD. The third group which represented the healthy control group, involved (60) subjects. The NAFLD patients were diagnosed by Ultrasound abdomen examination method. While, The CAD patients were diagnosed by coronary angiogram and electrocardiogram, as well as their medical history and clinical reports for heart diseases. The calculation of BMI was done by dividing weight by height squared (18, 19). Biochemical measurements were studied with HumaLyzer 3500 semi-auto analyzer. For determination AST & ALT activity, the kinetic method was utilized by using (Human Gesell schaft) kits, While FBG is estimated by enzymatic oxidation of glucose using glucose oxidase, however insulin was calculated by using (Insulin-Check-1 Disks) and measured by (vedalab easy reader),on other hand HOMA-IR was calculated by Matthews equation.

Statistical analysis

The software was used for detecting the effect of difference factors in study parameters is Statistical Analysis System- (SAS) 2018. Least significant difference LSD test (Analysis of Variation-ANOVA) was used to significant compare between means. Chi-square test was used to

significant compare between percentage (0.05 and 0.01 probability in this study

Results

This study included 120 patients divided into two groups, sixty NAFLD patients as group one with a mean age of 44.83 ±1.32 (years), and sixty NAFLD along with CAD as group two with a mean age of 51.45 ±1.17 (years), with 60 healthy individuals as a control group with a mean age of 41.50 ±1.20 (years). The participants in this study included both genders. However, BMI value was significantly higher in group one compared to CAD and control group with *P-Value ($P \leq 0.01$),* as shown in Table (1).

Table (1): The mean ± SE of parameters in the NAFLD patient without CAD, NAFLD patient with CAD, and control groups

Group	Group one (G1)	Group two (G2)	Group three (G3)	LSD value	*P-value*
	Mean ± SE				
Age (year)	44.83 ±1.32 b	51.45 ±1.17 a	41.50 ±1.20 b	3.451 **	0.0001
BMI (kg/m^2)	34.74 ±0.87a	32.71 ±0.57 b	24.52 ±0.31 c	1.749 **	0.0001
FBG (mg/dl)	111.17 ±2.16 b	137.39 ±5.10 a	81.72 ±0.52 c	8.965 **	0.0001
Insulin (µUI/ml)	11.83 ±1.69	12.73 ±1.12	12.28 ±0.36	3.316 NS	0.867
HOMA-IR	3.38 ±0.51 ab	4.40 ±0.43 a	2.47 ±0.07 b	1.087 **	0.0026

Means having with the different letters in same column differed significantly. ** (P≤0.01).

G1: NAFLD patient without CAD G2: NAFLD patient with CAD G3: Control

Table (1) show a significant increase in serum level of fasting blood glucose (FBS), and homeostasis model assessment-estimated insulin resistance (HOMA-IR in CAD group compared to NAFLD and control groups with *P-Value ($P \leq 0.01$).* However, there is no difference in insulin serum levels between the three studied groups with *P-Value ($P > 0.01$).*

Table (2): Liver enzymes and lipid profile in the NAFLD patient without CAD, NAFLD patient with CAD, and control groups

Group	Group one (G1)	Group two (G2)	Group three (G3)	LSD value	*P-value*
	Mean ± SE				
ALT (IU/I)	26.93 ±1.12 a	20.38 ±1.02 b	21.97 ±0.44 b	2.539 **	0.0001
AST (IU/I)	27.84 ±1.10 b	64.63 ±2.28 a	18.41 ±0.33 c	4.119 **	0.0001
Total Cholesterol	179.36 ±4.65 b	243.06 ±4.82 a	166.78 ±3.05 c	11.87 **	0.0001
Triglyceride	192.77 ±13.10 b	347.89 ±8.39 a	107.44 ±1.56 c	25.21 **	0.0001
HDL	62.25 ±2.66 b	39.74 ±0.45 c	68.81 ±2.22 a	5.643 **	0.0001
LDL	78.56 ±4.45 b	133.74 ±4.30 a	76.49 ±3.88 b	11.78 **	0.0001
VLDL	38.55 ±2.62 b	69.57 ±1.67 a	21.48 ±0.31 c	5.041 **	0.0001

Means having with the different letters in same column differed significantly. ** (P≤0.01).

G1: NAFLD patient without CAD G2: NAFLD patient with CAD G3: Control

Table (2) show a significant increase in alanine amino-transferase (ALT) serum level in NAFLD group when compared to CAD and control groups with *P-Value ($P \leq 0.01$).* While, aspartate amino-transferase (AST) shows a significant increase in serum level of CAD Group when compared to

NAFLD and control groups with *P-Value ($P \leq 0.01$).* Although lipid profile included s total cholesterol (TC), Triglycerides (TG), low-density lipoprotein (LDL), and Very-low-density lipoprotein (VLDL) show a significant increase in serum level in CAD group compared to NAFLD and control groups with *P-Value ($P \leq 0.01$),* with the exception of high-density lipoprotein (HDL), that shows a significant decrease in CAD group compared to NAFLD and control groups, with *P-Value ($P \leq 0.01$).*

Discussion

NAFLD is a disease that effects the liver which presently has great clinical, laboratory, and imaging relevance. Furthermore, NAFLD may be associated with other disorders such e.g. CAD, but it can also proceed to liver cirrhosis on its own. The result of the current study is in agreement with *Nielson C.* (20) which demonstrates FBG elevation is associated with a greater incidence of CAD in the absence of diabetes despite of other recognized risk factors, including age, weight, hyperlipidemia, and hypertension. And this result is in agreement with *Nielson C.* (20). However, the risk of higher FBG in the absence of diabetes is unclear, higher glucose levels were related with a higher incidence of myocardial infarction (21).

Nevertheless, the result of the current study is in agreement with the study Mossmann *M.* (22) regarding HOMA-IR that concludes the patients whom suffers of CAD with the absence o diabetes, HOMA-IR determination was above 4.21, which indicates increased risk for clinically severe form of coronary disease. However, IR is a critical factor in several clinical situations, such as metabolic syndrome and CVD (23). Likewise, IR is related with endothelial dysfunction, a pro-inflammatory state, and CAD that considered a dominant factor which indorsing the development of atherosclerosis (24). Results of the current study are in agreement with the study, in which HOMA-IR was related with CAD (25). Another study was concluded that elevated HOMA-IR can be used as an indicator that we might able to predict the severity of CAD (26).

The results of the current study regarding the ALT show a low elevation in ALT serum level, and this result is not in agreement with (27) that reported a normal ALT value in individuals the different histologic spectrum of NAFLD, Also another study report that ALT level is in the normal range or might be increased in patients with NAFLD (28). Thus, it comes to no surprise tha, normal or elevated level of ALT is a association with NAFLD risk mostly due to underlying liver disease (29). While the result of AST serum level of the current study is in agreement with *Liu, X. and Liu, P.* (30). That show and elevation in AST serum level in CAD patients. However, the relationship between CAD and high AST level can be clarified by four mechanisms. First, disease that related to the liver is the greatest prevalent that elevate AST levels in the blood. NAFLD is the most significant liver disease in terms of the connection with CVD (31).

Second, a high AST level is linked to CVD risk factors, including insulin resistance, metabolic syndrome, abdominal obesity, and diabetes (32). Third, a high AST level may indicate persistent alcoholism. A comprehensive examination of alcohol's cardiovascular effects is beyond the scope of this study

(33), (34). Fourth, a high AST level may serve as an indicator of CVD. AST is released from the myocardial in situations of heightened stress (such as stress forced by CVD risk factors) or acute coronary artery syndromes, or damage in the muscles of the heart that may also account for the increased CVD risk associated with elevated AST levels.in the end a high level of AST that is not related with inflammatory liver disease may indicate a higher CVD risk associated with NAFLD, drinking, or structural heart disease (35).

Lipid abnormality plays a significant influence in the development of vascular disease in individuals with CAD. Elevated lipids and lipoproteins may impair vascular endothelium function and hyperlipidemia, may disrupt vascular endothelial function and impede anti-thrombotic regulatory and fibrinolytic functions, that may lead to the development of atherosclerosis (12), (36). In the present study, highly significant levels of (TC, TG, LDL, and VLDL) with the expectation of HDL, that shows significantly low levels in the CAD patients' group when compared to NFLAD and control groups. Dyslipidemia is the primary risk factor for CAD, and might potentially be a requirement for CAD, that taking place before additional significant risk factors become relevant before additional significant risk factors become relevant (37).

Studies have reported low HDL, and high TG serum level concentration have been identified as factors of predictors of CVD (38) and the combination of these two conditions is called atherogenic dyslipidemia (39). In dyslipidemia, most lipoprotein in the blood is LDL. Also, some studies indicate that elevated LDL is the single largest cholesterol risk factor for CAD, due to the oxidized LDL is taken up by macrophages, which will lead to the development of atherosclerotic plaques. (40). Numerous prospective population-based studies have been undertaken to examine the effect of dyslipidemia on CVD. In individuals with angiographically confirmed CAD, only a small number of studies have evaluated the differential association between different dyslipidemias and CVD risk factors (41). In a study that conducted in Asian (below 40 years) CAD patients, reported a high prevalence of raised TG and low HDL serum levels results, which is similar to current study results (42). In the current study in patients with CAD, hypocholesterolemia HDL is considered the most common lipid abnormality, along with elevated triglycerides and elevated LDL cholesterol, and high levels of total cholesterol. Therefore, Lipid abnormality plays a major role in the development of vascular complications in CAD patients.

Conclusion

Patients with obesity and metabolic syndrome that suffering from NAFLD along with CAD have a higher serum level of FBS , TC , TG , LDL ,VDL and AST when compared to NAFLD patients and healthy individuals, Therefore obesity and metabolic syndrome is considered a risk factor for coronary artery disease.

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