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ASSOCIATION OF ATHEROGENIC INDEX AND LEPTIN GALLSTONE IN IRAQI PATIENTS

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ABSTRACT
The cholesterol, triglyceride, and lipid profile with atherogenic index and leptin level may be involved in gallstone disease. This study aimed to investigate the relation of triglyceride, cholesterol levels with atherogenic index and leptin level in gallstone disease. A controlled clinical study was performed, in which we examined parameters of cholesterol, triglyceride, HDL, LDL, and liver function values, leptin level in control healthy individuals and gallstone patients. Unconditional logistic regression analysis (univariate and multivariate) stratified by BMI was used to calculate the risk of GD. Results revealed that there were notable differences in serum total triglyceride and leptin level in gallstone patients. There were significant differences between gallstone patients and healthy individuals in atherogenic index ($p<0.05$), total triglyceride, HDL, LDL ($P<0.05$) and significant increase of leptin level in gallstone patients ($p<0.05$) and correlate significantly with atherogenic index. Leptin participates in modulating lipid metabolism. There are notable differences in leptin, serum lipid and the role of leptin in the pathophysiological course of cholelithiasis with atherogenic index needs further investigation.

KEYWORDS: atherogenic index leptin gallstone Iraqi patients.

INTRODUCTION

Cholelithiasis is the term used for the formation of gall stones. This is a common complaint, but its true incidence is difficult to assess as many people with gallstones are asymptomatic. Gallstones are made up pf bile constituents and are usually classified, on the basis of their chemical composition, as cholesterol or pigment stones[1]. Cholesterol stones may consist of entirely cholesterol or mainly cholesterol with small amount of bile salts and unconjugated bilirubin. Pigment stones on the other hand consist mainly of bile salts and unconjugated bilirubin, with a small amount of cholesterol[2]. Cholesterol stones are found in 80-85% of patients with cholethiasis. Surgical therapy for gallstones can be associated with morbidity and mortality which has led to debate on its use, especially in asymptomatic and mildly symptomatic. Advancement in minimally invasive and endoscopic techniques has the potential to improve surgical outcomes[3,4]. More liberal thresholds for elective cholecystectomy in asymptomatic diabetic patients have been suggested, based on early evidence suggesting a higher incidence of gallstone disease and biliary complications [5]. Autopsy data have provided evidence that greater than 80% of patients with gall bladder cancer have concomitant cholethiasis. The patients with gallstones greater than 3cm may be at risk for the development of gall bladder carcinoma [6]. Leptin has important regulatory effects on hypothalamic pituitary function that become readily apparent during periods of caloric deprivation, although differences exist in the extent to which leptin regulates these systems in humans[7]. Leptin, as a signal of both energy stores within the adipose tissue, and acute reductions in caloric intake during fasting, thus appears to be a master coordinator of the central nervous system response to changes in nutritional status[8]. The extent to which leptin regulates other endocrine systems may differ in times of nutrient excess, or in various disease states such as diabetes and obesity. Leptin was discovered in 1994 as the first adipokine. Leptin consist of 167 amino acid protein, as a result of the obese (ob) gene. Leptin secreted by adipocytes. The level of serum leptin is associated to the amount of body fat. High levels of leptin in obese individuals [9]. In an attempt to improve cardiovascular disease risk in cholelithiasis assessment, several atherogenic indices and lipoprotein ratios have been described. These ratios can quantify CVD risk better than LDL-C or TC alone[10]. The two most common ways to incorporate HDL-C into CVD risk assessment include the TC/HDL-C ratio and non-HDL-C. The TC: HDL-C ratio, also known as the atherogenic index or castelli index, and the LDL-/HDL-C ratio are the commonly used ratios in clinical practice. Because an increase in the concentration of TC, and particularly LDL-C, indicates an increase in atherogenic lipoproteins, where as an increase in HDL-C indicates an increase in the atheroprotective lipoproteins, these ratios provide an easy assessment of global atherogenic risk [11].

METHODOLOGY

The present study was conducted in the department of surgery at AL-Yarmook hospital in Baghdad city. A total of 50 patients of cholelithiasis were included in this study compared with 48 healthy individuals as control group from March 2013 to January 2014. On admission, a detailed history of each patient was taken and thorough general and local physical examination was done. Blood sample was taken and biochemical analyses for enzymes

of liver function were done using autoanalyzer, also total cholesterol and high density lipoprotein-cholesterol were done by using the same autoanalyzer (Architect C 4000). Fasting blood samples from all study participants were assayed for glucose. Serum leptin was measured using an enzyme-linked immunosorbent assay. Enzymes levels were calculated as mean, standard deviation (SD) for both groups. Statistical analysis included chi-square test.

RESULTS

Table (1) show the comparison between patients and control group in atherogenic index plasma (AIP), atherogenic coefficient (AC), total cholesterol (TC)/high density lipoprotein (HDL), low density lipoprotein (LDL)/high density lipoprotein, cholesterol, triglyceride, HDL and LDL which show significant difference between patients with cholethiasis and healthy control group in atherogenic index ($p<0.05$), also show significant difference in LDL/HDL, triglyceride, HDL, and LDL ($p<0.05$).

TABLE 1. Compare between patients and control in AIP, AC, TC/HDL, LDL/HDL, Cholesterol, Triglyceride, HDL and LDL

Parameters	Group		LSD value
	Control	Patients	
AIP	0.132 ± 0.02	0.466 ± 0.03	0.082 *
AC	2.65 ± 0.13	2.90 ± 0.21	0.511 NS
TC/HDL	3.80 ± 0.12	3.82 ± 0.18	0.467 NS
LDL/HDL	2.34 ± 0.09	2.77 ± 0.15	0.380 *
Cholesterol mlmol/l	4.17 ± 0.11	4.45 ± 0.17	0.431 NS
Triglyceride mlmol/l	1.08 ± 0.05	3.71 ± 0.22	0.509 *
HDL mlmol/l	1.09 ± 0.03	1.25 ± 0.05	0.128 *
LDL mlmol/l	2.46 ± 0.11	3.10 ± 0.13	0.352 *

* (P<0.05), NS: Non-significant.

Table (2) shows the comparison between patients and healthy control group in leptin, body mass index (BMI), insulin, HOMA and FBG. Which show significant difference in leptin between patients with cholethiasis and healthy control group ($p<0.05$), also show significant difference in BMI, and fasting blood glucose (FBG) ($p<0.05$).

TABLE 2. Compare between patients and control in Leptin, BMI, Insulin, HOMA and FBG

Parameters	Group		LSD value
	Control	Patients	
Leptin ng/dl	27.10 ± 0.45	13.46 ± 2.01	4.498 *
BMI kg/m2	5.66 ± 1.27	31.47 ± 0.78	2.861 *
Insulin	12.58 ± 0.95	12.93 ± 1.91	4.537 NS
HOMA	2.90 ± 0.24	5.63 ± 1.53	3.402 NS
F.B.G mg/dl	89.00 ± 2.20	116.47 ± 7.48	16.91 *

* (P<0.05), NS: Non-significant.

Table (3) show the comparison between patients and control group in liver enzymes (ALT, AST, BIL, and ALP) which show non-significant difference in liver enzymes except AST which show significant difference between patients with cholethiasis and healthy control group ($p<0.05$)

TABLE 3. Compare between patients and control in ALT, AST, Bil. and ALP

Parameters	Group		LSD value
	Control	Patients	
ALT	20.41 ± 2.54	23.12 ± 2.09	6.483 NS
AST	19.76 ± 1.07	25.00 ± 1.15	3.182 *
Bil.	1.09 ± 0.34	1.29 ± 0.41	1.096 NS
ALP	84.90 ± 3.65	93.28 ± 4.41	11.719 NS

* (P<0.05), NS: Non-significant differences

Table (4) show the correlation between atherogenic index, atherogenic coefficient, TC/HDL, LDL/HDL with other parameters (triglyceride, cholesterol, HDL, LDL, leptin, BMI, insulin, HOMA, ALT, AST, Bil). Which show significant difference between cholesterol with AC and TC/HDL (P<0.05), Triglyceride with AIP, TC/HDL (P<0.05), HDL with AIP and AC (P<0.05), Leptin with AIP (P<0.05), BMI with AIP, LDL/HDL (P<0.05), AST with AIP, LDL/HDL (P<0.05).

TABLE 4. Correlation coefficient between AIP, AC, TC/HDL, LDL/HDL With other parameters

Parameters	Correlation coefficient			
	AIP	AC	TC/HDL	LDL/HDL
Cholesterol mlmol/l	-0.003 NS	0.45 **	0.47 **	0.09 NS
Triglyceride mlmol/l	0.70 **	-0.08 NS	-0.19 *	-0.02 NS
HDL mlmol/l	0.23 *	-0.23 *	-0.03 NS	-0.12 NS
LDL mlmol/l	0.02 NS	0.07 NS	-0.03 NS	0.04 NS
Leptin ng/dl	-0.27 **	0.003 NS	-0.06 NS	-0.13 NS
BMI kg/m2	0.57 **	0.10 NS	0.002 NS	0.23 *
Insulin	0.01 NS	0.03 NS	0.08 NS	0.08 NS
HOMA	0.005 NS	0.24 *	0.07 NS	0.16 NS
F.B.G mg/dl	0.14 NS	-0.08 NS	0.15 NS	0.16 NS
ALT	0.14 NS	0.06 NS	-0.02 NS	0.03 NS
AST	0.31 **	0.14 NS	0.03 NS	0.20 *
Bil.	-0.003 NS	0.11 NS	0.002 NS	0.04 NS
ALP	0.04 NS	-0.10 NS	-0.08 NS	-0.01 NS

* ($P<0.05$), ** ($P<0.05$), NS: Non-significant.

DISCUSSION

Cholelithiasis and its complications are seen a major challenge to health. Cholesterol, phospholipids, and bile salts remain in balance as emulsion in bile stored in gall bladder. Physiochemical studies suggest that cholelithiasis id due to cholesterol saturation with complications of gallstone formation due to nucleation and deposition of calcium, bilirubin and pigments[13]. This study demonstrated that gallstone disease is associated with increased atherogenic index of plasma, common metabolic risk factor of cardiovascular disease. An in vivo study suggested that cholecystectomy has metabolic consequences by demonstrating that cholocysteomized mice had increased levels of hepatic and serum triglycerides and very-low density lipoprotein[12,13]. Patients with cholelithiasis in this study have higher leptin levels and an altered lipoprotein profile compared with controls, total cholesterol, and triglyceride were significantly increased. Gallstones are formed as a result of impaired metabolic regulation of human body. Abnormal lipid metabolism is partly responsible for the pathogenesis of gallstone mainly rich in cholesterol. Even though a positive correlation between serum triglyceride (TG) and nucleation time of cholesterol in bile is identified. Serum hypertriglyceridemia and low HDL-cholesterol (HDL-C) have shown a significant association with gallstone disease[14]. Studies of blood triglyceride have found that it is raised in gall stone cases compared with controls. Furthermore, the presence of gall stone disease is positively associated with type IV hyperlipoproteinaemia. The role of blood HDL-cholesterol in gallstone disease has not been extensively studied. Gallstone cases have been reported to have lower mean levels of HDL- cholesterol and gall stone risk has been described. Collectively, the studies on HDL-cholesterol in gallstone disease are reasonably consistent and suggest an inverse association between gallstone and HDL-cholesterol. This suggests that the free cholesterol in high density lipoprotein is preferentially metabolized to bile acids rather than secreted into bile as cholesterol [15, 16].

Leptin has been shown to modulate nutrient absorption, growth, inflammation and gut motility. Abnormal leptin levels and hyperinsulinaemia are important risk factors for gallbladder disease. The present study evaluated leptin levels in patients with cholelithiasis and found that leptin levels were increased in cholelithiasis compared with controls. The results of the present study are consistent with those of previous studies showing elevated leptin levels[17] and an abnormal lipid profile, with higher total cholesterol, TG. In contrast, some studies have reported no difference in leptin and lipoprotein levels in patients with cholelithiasis compared with controls [17,18, 19].

Méndez-Sánchez *et al.* [20] reported that insulin resistance and the development of gallstone disease were associated with serum leptin levels in overweight subjects (BMI < 30 kg/m^2), but not in obese subjects (BMI ≥ 30 kg/m^2) with similar metabolic profiles. Insulin resistance could have a major role in the pathogenesis of gallstones[17].Trans K.O.[21,22] reported that hyperglycaemia, insulin resistance, hyperlipidaemia and body weight in obese mice with leptin dysfunction were associated with poor gallbladder contractility, which in turn may contribute to the association between obesity and gallstone formation. In conclusion the present study found the increase level of lipids, leptin hormone and correlate significantly with gallstone disease, and significant correlation of atherogenic index with gallstone disease compared with healthy individuals.

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