SHORT COMMUNICATION

Single Gallstone Associated with High Fasting Insulin Level

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ABSTRACT

Gallstone (GS) formation is a multifactorial process and one of the associated factors is hyperinsulinemia. The aim of this cross-sectional study was to determine the association between size and count of gallstones, and insulin levels and resistance. The study group composed of 84 patients who have ultrasonographically confirmed gallstone(s). Insulin level of all participants were measured and insulin resistance was calculated with the homeostasis model assessment of insulin resistance (HOMA-IR) index. All p-values < 0.05 were considered statistically significant. There were 28 patients with single stone and 56 with multiple stones. Mean insulin level was 12.54 ±11.66 ml/U (median 9.91 ml/U, IQR 6.33) and 56.3% of patients had insulin resistance. Mean stone size was 7.82 ±7.52 mm (median 6 mm and IQR 11.75). There was a non-significant association and correlation between insulin level and size of GS (p=0.129; r =0.16). There was significant difference between single stone group and multiple stones group, according to the insulin level.

Key Words: *Gallstone. Insulin resistance. Gallstone size. Number.*

Gallstone (GS) disease is still an important public health problem due to its increasing prevalence and burden on healthcare. Its prevalence is estimated to be 10 - 25% in western populations.[1] GS formation is multifactorial. The well known risk factors are age, female gender, ethnicity, diet, obesity, rapid weight loss, medicines and lack of physical activity.[1] Diabetes is one of the GS formation associated diseases, mainly cholesterol GS. It is thought that diabetes, obesity and gallstones are associated with metabolic syndrome,[2] one component is hyper-insulinemia.

Insulin causes gallstone formation by two ways. Firstly, it increases the cholesterol saturation of bile acid. Experimental studies on rats showed that insulin can promote GS formation by increasing activity of hyroxyl-3-methylglutaryl-coenzyme A reductase.[3] This enzyme is the rate limiting enzyme in hepatic synthesis of new cholesterol and activate low density lipoprotein receptors which results in hepatic uptake of low density lipoprotein cholesterol.[4] Secondly, insulin decreases basal gallbladder motility and cholecystokinin stimulated motility.[4,5]

Epidemiological and experimental data show the relation between insulin and gallstone formation. The authors hereby hypothesized that gallstone size and count are related with insulin levels and insulin resistance. Therefore, this relationship of gallstone size and fasting serum insulin levels was examined in this study.

The study was carried out at Dr Lutfi Kırdar Kartal Education and Training Hospital, Istanbul in 2009. The study group composed of 84 patients who had ultrasonographically confirmed gallstone(s). The ultrasonographic examinations were performed by the same radiologist using the same device at a single center. Cases with gallbladder sludges, and cases diagnosed as diffuse low amplitude echoes forming fluid-fluid levels were excluded. Patients with chronic diseases like diabetes, hypertension, hyperlipidemia etc., and patients with haematological diseases associated with hemolysis were also excluded because of the risk of pigment stone formation.

The study data included the subjects' medical history, physical and laboratory examinations, and anthropometric measurements. All patients gave informed consent. Anthropometric measurements included body mass index (BMI) and waist circumference. BMI was calculated as the weight (kg) divided by the height (m) squared. Waist circumference was determined as measurements taken at the midpoint between lowest rib and iliac crest after a normal inspiration and expiration. Blood pressure was measured on the right arm with subjects in a sitting position after a 5 minutes rest. Hypertension is defined as levels exceed systolic 140 mm/Hg and diastolic 90 mm/Hg.

Blood samples were obtained from the antecubital vein and collected in evacuated plastic tubes after overnight fasting. Fasting plasma glucose was measured by the

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Received: January 31, 2014; Accepted: November 26, 2015.

glucose oxidase method and fasting insulin was determined by radioimmunoassay. The HOMA-IR index was calculated using the following formula :

HOMA-IR = [fasting serum insulin (μU/mL) x fasting plasma glucose (mmol/L)/22.5].

Statistical analyses were performed using SPSS version 12.0. All descriptive statistics are reported as mean ±SD, median with interquartile ranges (IQR) and frequencies with percentages. Independent t-test or Mann-Whitney U test was used to compare two independent groups. Spearman's correlation coefficient was used to find out correlation between variables. X^2 tests were employed to analyze categorical data. All p-values were two-tailed and p-values < 0.05 were considered statistically significant.The study was approved by local ethical committee of Dr Lutfi Kırdar Kartal Education and Training Hospital, Turkey.

Eighty-four patients were enrolled in the study. Out of which 32.1% of patients (n=27) were male. The mean age was 52.6 ±13.07 years. Mean BMI was 29.61 ±5.81 kg/m^2 and mean waist circumference of the group was 98.25 ±19.70 cm. Mean insulin level was 12.54 ±11.66 ml/U (median 9.91 ml/U, IQR 6.33). Insulin resistance was calculated according to HOMA-IR formula and was found 3.61 ±5.03 (median 2.30, IQR 1.88). Here 56.3% of patients had insulin resistance. The parameters are shown in Table I.

There were 28 patients with single stone and 56 with multiple stones. Mean stone size was 7.82 ±7.52 mm (median 6, IQR 11.75). Only 6 patients (1 male and 5 females) had stones above 20 mm. There was a positive but non-significant correlation between insulin level and size of GS (p=0.129; r=0.16). There was significant difference between single stone group and multiple stones group, according to the insulin level. The data related with gallstone/s and insulin parameters are shown in Table II.

Table I: Baseline characteristics of patients.

	Female (n=57)	Male (n=27)	p-value
Age (year)*			
Mean ±SD	52.91±13.76	51.96±11.76	0.758
BMI (kg/m2)**			
Median	29.41	27.83	0.172
IQR	8.90	4.40	
Waist circumference (cm)**			
Median	101.0	89	0.270
IQR	42.50	18	
Insulin level (ml/U)**			
Median	11.41	9.60	0.135
IQR	7.51	6.86	
HOMA-IR**			
Median	2.6	2.3	0.370
IQR	2.20	1.90	
Stone size (mm)**			
Median	5	6	0.924
IQR	11	14	
Patients with IR (%)***	70.1 (n=40)	55.5 (n=15)	0.188
Patients with single stone (%)***	29.9 (n=17)	40.7 (n=11)	0.322

** Student's t-test was performed; ** Mann-Whitney U test was performed; *** X^2 test was performed*

Table II: Relationship between gallstone/s and insulin parameters.

	Single stone (n=28)	Multiple stones (n=56)	p-value
Insulin levels (ml/U)*			
Median	12.11	9.47	0.043
IQR	8.15	6.09	
HOMA-IR level*			
Median	2.90	2.30	0.027
IQR	4.50	1.88	
BMI (kg/m^2) **			
Mean ±SD	30.64 ±4.83	29.09 ±6.21	0.252
Waist circumference (cm) **			
Mean ±SD	104.28 ±20.19	95.23 ±18.92	0.047
Age (year)**			
Mean ±SD	52.71 ±12.14	52.65 ±13.62	0.958
Presence of insulin resistance (%) ***	75.0 (n=21)	60.7 (n=34)	0.194

** Student's t test was performed; ** Mann-Whitney U test was performed; *** X^2 test was performed*

The relationship between hyperinsulinemia and gallstones is known for a long time. Gallstones are related with high levels of fasting insulin levels independent from patients' serum triglyceride levels.[6] A community-based study with abdominal ultrasound showed that patients with high serum insulin levels have two-fold greater risk compared with the patients with low insulin levels.[7] Some of the studies revealed that the relationship between hyperinsulinemia and gallstone formation was valid in females only.[4] In this study, females had higher insulin levels than men, but this was statistically non-significant. This condition may be a result of the difference between BMI and waist circumference of the two groups; both of them were higher in women than men.

Cholesterol gallstones are the result of cholesterol precipitation, which is due to increased secretion of cholesterol supersaturated bile from liver. Increased biliary cholesterol output, decreased bile acid pool and biliary secretion rate are common abnormalities induced supersaturated bile secretion.[8] Solitary gallstones are developed after a precursor phase of over 2 years, but formation of multiple gallstones occur without a precursor phase. After formation of the core, solitary stones begin to grow with aggregation and form a compact spheroid-shape stone. On the other hand, in multiple stones very thin cholesterol crystals abruptly aggregate to form spheres. These spheres are coalesced to form mulberry stones within 3 months and turns to faceted or barrel stones over a period of 3 years.[9]

Insulin has effects on cholesterol metabolism. It inhibits expression of the enzyme that controls the rate limiting

step of bile acid synthesis (Cyp7a1);[10] not only that, but also insulin inhibits normal motility of gallbladder.[9] Therefore, high insulin levels can cause single and large gallstones due to the decrease of gallbladder motility and hypersaturation of cholesterol in bile. This hypersaturated cholesterol is deposited in gallbladder. Moreover, high level of insulin causes inflammatory process in gallbladder and increases the level of mucus secretion and the core gets bigger.

There are two important limitations of this study. First is the small size of study population, so it is not suitable to generalise the results of the study for whole population. Second, the gallstone size measurements were done by ultrasonography not after surgery.

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