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ORIGINAL ARTICLE

Cholecystokinin as a novel marker of gallstones risk factor

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Introduction

cholecystokinin plays a role role in both the regulation of digestion and appetite as well as its association with the development and management of gallstones.

Objective

The study aimed to investigate the relationship between the cholecystokinin hormone and the formation of gallstones.

Methods: The study collected a total of 97 samples of gallstones from both sexes, with an additional 83 samples used as a control group.

Results

There was a significant (p= 0.001) decrease in the cholecystokinin hormone levels in patients with gallstones. Furthermore, the study also observed a significant increase (p= 0.001) in various lipid markers such as cholesterol, low-density lipoprotein (LDL), triglycerides, lipoprotein, very low-density lipoprotein (VLDL), and atherosclerosis risk factor. The incidence of gallstones was found to be three times higher in females compared to males.

Conclusion

This study shed light on the role of the cholecystokinin hormone in the formation of gallstones. It revealed a significant decrease in cholecystokinin hormone levels in patients with gallstones, along with an increase in lipid markers associated with gallstone formation. Additionally, the study highlighted the gender disparity in the incidence of gallstones and provided reference ranges for the cholecystokinin hormone. These findings have the potential to contribute to the development of new diagnostic and treatment approaches for gallstone-related conditions.

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The biliary system is a series of ducts within the liver, gallbladder, and pancreas which function to empty their content into the small intestine. The gallbladder belongs to the biliary system which is also called the biliary tree or biliary tract. Through the cystic duct, it is connected to the rest of the biliary system outside the liver.[1] Despite its essential function of maintaining the balance of cholesterol, free fatty acids, and triglycerides in the entire organism, the gallbladder greatly influences the flow of bile into the intestine and thus the enterohepatic circulation of bile acids, when the gallbladder contracts, it forces bile into the common bile duct, which then transports it to the small intestine, where it performs its function in the digestion of fats.[2]

Gallstones are typically brought on by an unhealthy gallbladder. Bile sludge which is a viscous mixture of glycoproteins, calcium deposits, and cholesterol crystals in the gallbladder or bile ducts, is frequently present before the development of gallstones. It can also form in the biliary tree. Most of it is made of cholesterol that is absorbed from the system. food.[3] Cholecystokinin (commonly known as CCK or CCK-PZ) is a gastrointestinal neuropeptide hormone produced by discrete enteroendocrine cells (I cell) in the mucosa of the upper small intestine[4] and I cells (I cells) are granules. Medium-sized secretory cells in the discrete enteroendocrine cells that line the mucosa of the upper small intestine and are responsible for CCK synthesis.[5]

Through activation of CCK-1 receptors on vagus fibres that supply the intestines, cholecystokinin modulates gastrointestinal activities, including inhibition of gastric emptying and food intake. Additionally, CCK plays a crucial role in the secretion of pancreatic enzymes such as pancreatic amylase, chymotrypsinogen, and trypsinogen as well as the generation of stomach acid and pancreatic fluid. Alkaline phosphatase, Disaccharidase, and Enterokinase are a few other minor intestinal enzymes that are crucial for the digestion of carbs, lipids, and protein, respectively.[6] It lowers gastric emptying, makes digestion easier, and shrinks the gallbladder. Small peptides produced during the breakdown of proteins, long-chain fatty acids, amino acids, and saturated fats all encourage the release of CCK from the small intestine. Afferent nerve fibres in the jejunum and vagus are activated by both long-chain and short-chain fatty acids from meals but by different processes.[7]

MATERIAL AND METHODS

Collecting Samples: Blood samples were collected during the period (September 3, 2022, until June 25, 2023) from (Al-Salam Teaching Hospital and Al-Jumhuri Teaching Hospital) in Nineveh Governorate, after obtaining the original and ethical approvals according to the Declaration of Helsinki criteria and were authorized by our university

Gallstones Patients Group: Ninety-seven blood samples were collected for both men and women with stones in the gallbladder after the patients were diagnosed by specialized doctors their ages ranged between (16 and 70) years, and the clinical data for each case were included in a questionnaire. prepared for this purpose. Exclude patients with diabetes, hypertension and heart disease.

Control group: Eighty-three persons of both sexes, aged 18 to 70 years participated in this study as a control group. During the early follicular phase, blood samples were obtained in the morning following 12 hours of fasting for cholecystokinin (CCK) and for both groups. A specific test kit (Bio Merieux, France) was used to assess cholecystokinin by ELISA, and kits for measurement of HDL, TG, TC (Bio Merieux, France) were used to measure lipid profile by UV/VIS Spectrophotometer as per manufacturer instructions. LDL, VLDL, and atherogenic index calculated as per standard formulas. Weight and height were measured and BMI was calculated.

Statistical analysis: Using SPSS software, the data was analyzed. T-test, Duncan test. Data expressed as mean±SD, a p-value less than 0.05 considered significant.

Ethical approval: The researcher's institutional review board gave its approval to the study, which was carried out by all applicable national laws, institutional policies, and the principles of the Helsinki Declaration (Approval letter 22221 on 05.07.2022).

RESULTS

The results shown in **Figure 1** provide valuable insights into the incidence of infection among females and males. The data reveals a significant disparity, with females experiencing a higher

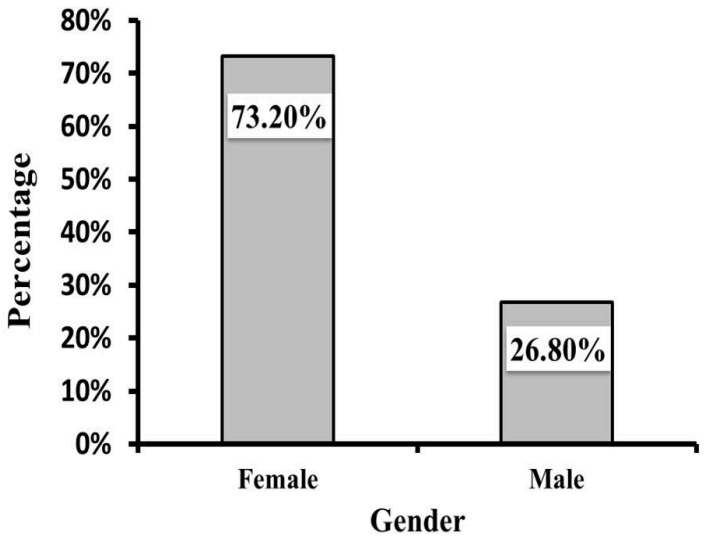

Figure 1 *Prevalence rate of gallstones in women and men*

incidence of infection by 73.2% compared to males, who had an incidence rate of 29.8% (**Table 1**).

The results presented in **Table 2** provide a comprehensive comparison of clinical variables between women with gallstones and healthy women. Notably, a significant decrease was observed in the concentration of the cholecystokinin hormone (P = 0.001) in women with gallstones compared to their healthy counterparts. The study showed a significant increase in the levels of various lipids, including cholesterol, triglycerides, LDL, VLDL, and atherogenic risk factors in women with gallstones (P=0.001, P=0.04, P=0.001, P=0.004, and P=0.001, respectively).

The findings presented in **Table 3** shed light on the clinical variables when comparing males with gallstones to healthy males. One notable result is the significant decrease in the concentration of cholecystokinin hormone (P = 0.001) in males with gallstones. This decrease could potentially be attributed to a decline in plasma cholesterol levels. On the contrary, there seems to be an increase in biliary cholesterol or a decrease in phospholipid levels among male patients. Additionally, the results in Table 3 indicate a significant increase in the concentration of various fats, including cholesterol,

Table 1 *The normal level of cholecystokinin in healthy people.*

Normal Concentration of Cholecystokinin (CCK)		
Male Normal Range (pg/ml)	56.79 - 58.49	Normal Range 56.82 - 58.68 (pg/ml)
Female Normal Range (pg/ml)	56.85 - 58.87	

Table 2 *Comparison of clinical variables of women with gallstones with healthy women (control group).*

Clinical Parameters	Gallstones Patients	Control Group	p value
Female	69 (72%)	50 (59%)	
CCK (pg/ml)	55.32±0.86	57.86 ± 1.01	*0.001***
Cholesterol(mg/dl)	161.04 ±17.79	133.32 ±9.88	*0.001***
Triglyceride (mg/dl)	124.49 ± 19.55	101.90 ±5.44	*0.04**
LDL (mg/dl)	92.41 ± 11.19	64.83 ±13.41	*0.001***
HDL (mg/dl)	43.73 ±8.22	48.10 ±10.59	*0.001***
VLDL(mg/dl)	24.89 ± 9.91	20.37 ±5.08	*0.004***
Atherogenic Risk factor (mg/dl)	4.21 ±1.92	2.86 ±0.84	*0.001***
BMI (Kg/m^2)	28.56 ±3.94	27.34 ±3.74	*0.05**

**Significant differences at P≤0.05*
***Significant differences at P≤0.01*
data represented as Mean±SD

Table 3 *Comparison of clinical variables of males with gallstones with healthy males (control group).*

Clinical Parameters	Gallstones Patients	Control Group	p value
Male	28 (29%)	33 (39%)	
CCK (pg/ml)	55.38 ±1.04	57.77 ±1.27	*0.001***
Cholesterol(mg/dl)	169.11 ±13.51	135 ±12.52	*0.005***
Triglyceride (mg/dl)	129.17 ±6.08	103.82 ±8.66	*0.037**
LDL (mg/dl)	106.02 ±13.03	72.22 ±6.53	*0.005***
HDL (mg/dl)	37.24 ±5.75	42.01 ±6.21	*0.05**
VLDL(mg/dl)	25.83 ±4.21	20.76 ±5.73	*0.037**
Atherogenic Risk factor (mg/dl)	4.97 ±1.08	3.27 ±0.92	*0.001***
BMI (Kg/m^2)	28.20 ±3.86	25.59 ±3.25	*0.001***

**Significant differences at P≤0.05*
***Significant differences at P≤0.01*
data represented as Mean±SD

triglycerides, LDL, VLDL, and atherogenic risk factor (P = 0.005, P = 0.037, P = 0.005, P = 0.037, and P = 0.001, respectively).

The results presented in Table 4 provide compelling evidence of a noteworthy finding: a significant decrease in the concentration of the hormone cholecystokinin in patients afflicted with gallstones, as compared to healthy individuals. The statistical analysis conducted revealed a P-value of 0.001, further solidifying the significance of this observation. The data reveals a substantial rise in the concentration levels of various components, such as cholesterol, triglycerides, LDL, VLDL, and atherosclerotic factor, in patients diagnosed with gallstones. The statistical analysis conducted for this study demonstrated a highly significant increase in the aforementioned parameters among the gallstone patients, as compared to the healthy subjects. The p-values associated with these findings were found to be extremely low (P = 0.001), indicating a high level of statistical significance.

DISCUSSION

The present study confirmed a higher incidence of infection among females compared to males, perhaps the reason for this is due to sex hormones such as estrogen, as exogenous estrogen affects the physiological signs that facilitate the formation of gallstones. In addition, estrogens play a role in increasing cholesterol secretion and decreasing bile salt secretion.[8] These female sex hormones negatively affect hepatic bile secretion and gallbladder function. Oral hormone replacement therapy can increase the risk of developing gallstones.[9]

Table 4 *Comparison of clinical variables of patients with gallstones with healthy persons (control group).*

Clinical Parameters	Gallstones Patients	Control Group	p value
n	97	83	
CCK (pg/ml)	55.34±0.91	57.77 ±0.95	*0.001***
Cholesterol(mg/dl)	163.37 ±12.78	133.99 ±13.77	*0.001***
Triglyceride (mg/dl)	125.84 ±11.27	102.66 ±6.61	*0.001***
LDL (mg/dl)	96.33 ±12.53	67.76 ±2.68	*0.001***
HDL (mg/dl)	41.86 ±6.81	46.68 ±9.54	*0.05**
VLDL(mg/dl)	25.16 ±0.25	20.53 ±5.32	*0.001***
Atherogenic Risk factor (mg/dl)	4.43 ±1.9	3.02 ±0.89	*0.001***
BMI (Kg/m^2)	28.45 ±3.91	26.64 ±1.07	*0.002***

*Significant differences at P≤0.05
**Significant differences at P≤0.01
data represented as Mean±SD

The result has shown a significant decrease in the concentration of the cholecystokinin hormone (P = 0.001) in women with gallstones compared to healthy women, which might be due to a decrease in the concentration of intestinal CCK and delayed intestinal transit due to impaired biliary emptying.[10] Because reduced CCK production in the intestine considerably increases susceptibility to gallstones through a process involving impaired gallbladder and small intestinal motility, celiac disease is a significant risk factor for gallstone formation.[11]

In addition, the progesterone hormone suppresses the activity of the neuron killers cells in the central nervous system and stimulates the activity of the generative neurons, which leads to an increase in energy consumption, unlike the estrogen hormone, and thus the hormones estrogen and progesterone lead to slower emptying of the gallbladder.[12] The hormone progesterone, which is involved in the menstrual cycle and can slow down the process of emptying the gallbladder, increases the amount of cholesterol in the bile, which is a major component in the formation of gallstones. If there is more cholesterol in the bile juice, there is a high likelihood that it will clump together and form a stone. If the gallbladder cannot release bile at the normal rate, gallstones can get stuck in the bile duct instead of being passed. This supports the hypothesis that female reproductive hormones divert bile toward the lithogenic composition.[13]

The results also showed a significant increase in the concentration of lipids in women with gallstones compared with healthy women. The rise in estrogen levels led to an increase in triglycerides and low-density lipoprotein cholesterol and thus leads to an increase in the secretion of cholesterol in the bile, which indicates that sex hormones have a relationship in the associations between blood fats

and the formation of gallstones, in addition to that it has been proven that high fats Triglycerides and cholesterol in hepatocytes trigger inflammatory responses that lead to leakage of liver enzymes into the bloodstream, which lead to cholecystitis and induce gallstone formations.[14] The results showed a significant decrease (P = 0.001) in the concentration of HDL in women with gallstones compared with healthy women, where the decrease in levels of good cholesterol (HDL), which participates in the transfer of cholesterol to bile, is significantly associated with the risk of gallstone formation. In women, especially before menopause, hepatic bile acid synthesis will be decreased, causing biliary hypercholesterolemia. In addition, decreased The increased hepatic insulin resistance linked to HDL cholesterol raises biliary cholesterol production and gallstone risk. formation.[15]

There was also a significant increase in the concentration of body mass index (P = 0.05) in women with gallstones compared with healthy women, where the increase in body mass index is associated with an increase in the activity of (cholesterol synthase), which promotes hyper saturation of bile cholesterol and leads to this increase in the index body mass index slows the metabolism of endogenous fats and hormones, which reduces motility of the gallbladder and increases the risk of developing gallstones.[16]

The results of comparing the clinical variables of males with gallstones with healthy males showed a significant decrease in the concentration of the hormone cholecystokinin (P = 0.001) in males with gallstones and the reason may be due to a decrease in the level of cholesterol in the plasma. Conversely, there is an increase in biliary cholesterol or there is a decrease in the level of phospholipids in male patients.[17,18] The results also showed a significant increase in the concentration of fats for each of the cholesterol, triglycerides, LDL, VLDL, and atherogenic risk factors. Perhaps the reason is that low levels of testosterone are negatively associated with triglycerides and that a high level of triglycerides in the blood is positively associated with an increase in the cholesterol saturation index and the rapid nucleation of cholesterol crystals.[14] The results also showed a significant decrease in the concentration of beneficial fats (HDL) in males with gallstones compared to the control group (P = 0.05). This may be due to the tendency of patients with low testosterone to lower levels of HDL and Apo A1 and higher levels of total cholesterol, triglycerides, and LDL.[19] In addition, a significant increase was found in the body mass index in males with gallstones. Previous studies have shown that the level of total and free testosterone is lower compared to non-obese men. There are high levels of circulating estrogens in obese men, which results from the conversion of androgens to estrogens by aromatase.[20,21]

The concentration of the hormone cholecystokinin was reduced in patients with gallstones compared to healthy people. This was distinguished by a reduced gallbladder contraction in response to cholecystokinin and an increased affinity for binding to this hormone. Additionally, it is well known that the bile of these patients contains a lot of cholesterol, with the potential for translocation of this lipid to neighbouring cell membranes.[22]

The results for the same table above showed a significant increase in the concentration of each of cholesterol, triglycerides, LDL, VLDL, and atherosclerotic factor in patients with gallstones compared to healthy subjects, perhaps this is due to the weak natural metabolism of fats in the liver, and the low ability of the liver to synthesize phospholipids, which leads to a relatively high ratio of cholesterol to phospholipids, and high cholesterol stimulates the expression of inflammatory factors that may cause inflammation of the gallbladder and stimulate the formation of gallstones, which leads to an increase in Its size, and the impairment of the synthetic secretory function of hepatocytes, will lead to a decrease in bile acid secretion and other factors that support gallbladder motility, which slows bile flow.[23,24] The results showed a significant decrease in the concentration of HDL in patients with gallstones (P = 0.05) compared to healthy people, which may be a result of the association between low HDL and insulin resistance, and this may cause a higher rate of HDL catabolism, which increases the rate of biliary cholesterol excretion.[25,26]

The results also showed a significant increase in the concentration of the body mass index in patients with gallstones compared to healthy people. Obesity can boost leptin production and control bile fat

metabolism to encourage the excretion of extra cholesterol that has been accumulated in tissues. The excretion of cholesterol in the bile can therefore rise in response to an increase in serum leptin, leading to hypersaturation of bile with cholesterol and an increased risk of developing gallstones.[27-29]

Limitations of the present study include a small sample size and unicentric study, moreover, hyperlipidemia, in particular, is an additional predisposing factor for modulation of lipid concentration in biliary tree resulting in gallstone formations.[30,31] It is highly recommended to use weight and lipid-reducing agents including metformin,[32] herbal products,[33] and statins [34] in highly susceptible people.

CONCLUSION

In conclusion, the findings from this study provide significant insights into the hormonal and metabolic changes associated with gallstones in overweight patients. The observed decrease in the cholecystokinin hormone, coupled with the significant increases in cholesterol, low-density lipoprotein, triglycerides, lipoprotein, very low-density lipoprotein, and atherosclerosis risk factor, highlight the multifaceted nature of gallstone formation and its association with metabolic dysregulation. Moreover, the striking gender disparity in the incidence of gallstones, with females having three times higher rates than males, underscores the potential influence of hormonal and physiological factors in gallstone pathogenesis. Additionally, this study contributes to the existing body of knowledge by establishing the normal range of the cholecystokinin hormone for both females (56.85-58.87 pg/ml) and males (56.79-58.49 pg/ml). These findings collectively emphasize the importance of further research and clinical interventions targeting metabolic imbalances and gender-specific factors to effectively manage and prevent gallstone formation in the overweight population.

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