CLINICAL EFFECT OF CHOLECYSTOKININ HORMONES ON GALLSTONES

Noor M. Al-Talib, Zena A.M. Al-Jawadi
University of Mosul, College of Science, Department of Chemistry, Iraq.
(Received in 12/9/2023 Accepted in 15/10/2023)

Abstract

The study focused on anthropometric measurements and their relationship with the hormone cholecystokinin (CCK) and its role in the incidence of gallstones for both sexes. The samples of the study included 97 ones which were collected from patients with gallstones and 83 samples as a control group. The results showed that the decrease in the hormone level compared to an increase in glucose, uric acid, bilirubin, creatinine, urea, and body mass index (BMI) for a group of people with gallstones compared with the control group, and that the infection rate in women is higher than in males. Also, Age is a major factor that affects hormone levels and reduces activity cholecystokinin hormone. Women of fertile age are usually more susceptible to gallstones due to increased obesity around the abdominal area and pregnancy. The incidence rate is almost equal with advancing age after the age of fifty due to menopause in women. Finally, this study discovered a relationship between the decrease of the cholecystokinin hormone and the increase of the risk factor of formation of gallstones, which have a strong role, especially in people who are obese with age.

Keywords: Cholecystokinin (CCK), Gallstones, BMI, Age, Sex, Gall Bladder.

التأثير السريري لهورمون الكوليسيستوكينين على حصى المرارة

نور مازن الطالب **زينة عبد المنعم الجوادي**

جامعة الموصل، كلية العلوم، قسم الكيمياء، العراق.

نبذة مختصرة:

ركزت الدراسة على القياسات الأنثرومبومترية وعلاقتها مع هورمون الكوليسيستوكينين (CCK) ودوره للإصابة بحصى المرارة لكلا الجنسين، حيث تم جمع ٩٧ عينة لمصابين بحصى المرارة و٨٣ عينة كمجموعة سيطرة. أظهرت النتائج أن انخفاض مستوى الهورمون مقابل زيادة كل من الكلوكوز وحامض اليوريك والبيليروبين والكرياتينين واليوريا ومؤشر كتلة الجسم (BMI) لمجموعة لمصابين بحصى المرارة مقارنة مع المجموعة الضابطة وان نسبة الاصابة لدى النساء اعلى مما لدى الذكور ، والعمر عامل رئيسي يؤثر على مستويات الهورمونات ويقلل من نشاط هورمون الكوليسيستوكينين وعادة ما يكونن النساء في سن الخصوبة أكثر عرضة للإصابة بحصى المرارة بسبب زيادة السمنة حول منطقة البطن والحمل وتتساوى تقريبا نسبة الاصابة مع تقدم العمر بعد سن الخمسين لانقطاع الدورة الشهرية لدى النساء.

اخيرا استنتجت هذه الدراسة وجود علاقة بين انخفاض هورمون الكوليسيستوكينين وزيادة عامل خطر تكوين حصوات المرارة، والتي لها دور قوي، خاصة عند الأشخاص الذين يعانون من السمنة المفرطة مع تقدم العمر.

الكلمات الدالة: هورمون الكوليسيستوكينين (CCK)، حصى المرارة ، مؤشر كتلة الجسم، العمر، الجنس، المرارة.

Introduction:

Gallstone disease (GSD) is the most common disorder affecting the biliary system and it is difficult to determine the true prevalence because it is often asymptomatic and gallstones affect more than 75% of patients without any noticeable symptoms in the initial stages (Sun *et al.*, 2022) . Gallstones are bile deposits that look like hard, round stones that can block the cystic duct They vary in size and shape They can range from as small as a grain of sand to as large as a golf ball They can develop into one large gallstone or hundreds of smaller gallstones, or a combination From small and large stones at the same time (Nithyakala *et al.*, 2022).

Gallstones are usually caused by a malfunctioning gallbladder. The formation of gallstones is often preceded by the presence of bile sludge, which is a viscous mixture of glycoproteins, calcium deposits, and cholesterol crystals in the gallbladder or bile ducts. It can also form in the biliary tree. Most of it is made of cholesterol that is absorbed from the system. food (Hjaltadottir *et al.*, 2020)

An excess of bilirubin may also lead to the formation of gallstones (Chung & Duke, 2018). Loss of movement of the muscular wall of the gallbladder and excessive contraction of the sphincter may also lead to bile stagnation and imbalances in the components of bile sludge, which may lead to precipitation. Insoluble stones (Bayram *et al.*, 2013). It is possible that gallstones usually develop as a result of the slow emptying of bile into the gallbladder, as the bile stored in the gallbladder hardens into a stone-like substance and may occur as a result of obstruction of the bile ducts through various causes such as narrowing of the bile ducts or tumors (Rebholz *et al.*, 2018). The gallbladder experiences increased pressure, enlargement, wall thickness, decreased blood flow, and potential exudate formation as more water is withdrawn (Singh *et al.*, 2020).

In the case of obesity, it weakens the effect of CCK, which means the insensitivity of the vagal afferent neurons to CCK and that this decreased expression of CCK explains the reduced effect on satiety and the fact that most obese people always complain of feeling hungry. Consumption of high-fat diets with impaired expression of the CCK-1 receptor increases plasma crelin levels (Breit *et al.*, 2018). L-type calcium channels also play a central role in the release of CCK from the gastrointestinal mucosa, the increase in intracellular calcium concentrations is regulated by receptor-dependent activation of calcium channels on the extracellular membrane and intracellular calcium stores (Alheyali & Al-Jawadi, 2022; Egberts *et al.*, 2020).

Materials and methods:

Gallstones Patients Group: 97 gallstones patients were included in this study; they were diagnosed by experts in AL-Salaam Hospital and Al-Jumhuri Teaching Hospital / Al-Mosul, Iraq from September 3, 2022, until June 25, 2023. Their ages range from 18 to 70 years, and clinical data for each patient was collected using a specially designed questionnaire.

Control group: Consisted of 83 Young fertile women ranging in age from 18 to 70 years old.

During the early follicular phase, blood samples were obtained in the morning following 12 hours of fasting for cholecystokinin (CCK) and for both group. Cholecystokinin was measured by ELISA using a specific test kit, and glucose, uric acid, bilirubin, creatinin, and urea were measured using a specific kit (Bio Merieux Kits) by UV/VIS Spectrophotometer.While Body Mass Index (BMI) was calculated using the following formula:

$$BMI(Kg/m^2) = weight(Kg) / length(m^2)$$

Finally, SPSS software was used to analyze the data.

Results:

Comparison of anthropometric variables between patients with gallstones and healthy subjects (control group) based on cholecystokinin (CCK):

The results shown in Table-1 anthropometric variables for those with gallstones compared with healthy people showed a significant decrease in the concentration of the hormone cholecystokinin at a probability level ($P = 0.001$, $P = 0.001$) depending on age and sex, and this reason may be due to a defect and a decrease in the sensitivity of the gallbladder muscle to stimulation by CCK With advancing age, this imbalance may lead to weakness and stagnation of biliary motility in patients with elevated blood triglyceride levels (Lee *et al.*, 2017).

There was also a significant decrease in the concentration of the hormone cholecystokinin at the level of probability ($P = 0.001$) for patients with gallstones compared to healthy people, depending on the body mass index, where obesity leads to an increase in the probability of forming gallstones because it may change the balance of cholesterol versus lecithin versus bile acids in the gallbladder, in addition to the activity of the rate-limiting cholesterol synthesis enzyme, can cause hypersaturation of cholesterol and it is secreted into the bile duct, which contributes to the formation of gallstones (Al-Ttaie & Aljawadi, 2021; Liu *et al.*, 2018).

Table-1: Comparison of anthropometric variables between patients with gallstones and healthy subjects (control group) based on cholecystokinin (CCK)

Anthropometric Measurements		Patients with Gallstones Mean ± SD	Control Group Mean ± SD	p-value
Age		55.34 ±0.91	57.77 ±0.95	0.001 **
BMI (Kg/m^2)		55.34 ±0.91	57.77 ±0.95	0.001**
Sex	Male	55.38 ±1.04 b	57.64 ±0.85 a	0.001**
	Female	55.32 ±0.86 b	57.86 ±1.01 a	0.001**

**Significant differences at P≤0.01, a, b denote Duncan-test

Comparison of clinical parameters between gallstones patients and healthy individuals (control group):

The results listed in Table-2 show that A significant decrease in the concentration of the cholecystokinin hormone in patients with gallstones at a probability level (P = 0.001) compared to healthy subjects, possibly due to the association of cholecystokinin stimulation activity at the CCK1R receptor. Binding to Cholecystokinin, with decreased contraction of the gallbladder in response to this hormone, these patients are also known to have bile that is highly saturated with cholesterol, with the potential for translocation of these lipids to neighboring cell membranes (Miller *et al.*, 2021; Al-Omari *et al.*, 2021). The results also showed in the same table a significant increase in glucose concentration in patients with gallstones at a probability level (P = 0.001) compared to healthy people. A rise in glucose may occur due to insulin resistance or a relative decrease in insulin secretion, as this resistance increases cholesterol secretion. They reduce bile acid synthesis and decrease the cholecystokinin response, which slows the motility of the gallbladder and causes cholesterol to remain in the gallbladder, which increases the risk of gallstone formation (a Zhang *et al*., 2022). And a significant increase in uric acid concentration in patients with gallstones at a probability level (P = 0.001) compared to healthy people, where gallbladder injury can lead to damage to liver cells and bile acid secretion, and hemolysis and chronic bacterial infections lead to the production of pigment stones in the gallbladder (Kim *et al.*, 2019). The reason may be due to an increase in serum uric acid concentrations in patients with gallstones, and this increase may be due to a parallel increase in the activity of xanthine oxidoreductases, which is observed in patients with gallstones, which reflects the fact that the catabolic pathway is increased (Zainulabbdeen & Naser, 2016). The results in the same table also showed a significant increase in the concentration of bilirubin in patients with gallstones at a probability level (P = 0.01) compared to healthy people. Bitterness and a deficiency in liver cells (Khurshid & Mohammed, 2021).and showed a significant increase in creatinine concentration in patients with gallstones at a probability level (P = 0.01) compared to healthy people. It may

be due to pancreatic necrosis, protein degradation metabolism and renal function. In the case of pancreatic necrosis, a large amount of toxic substances are released as dimethylbenzo[a]anthracene, ethionine, 4-hydroxyaminoquinoline-1-oxide, beta-oxidized derivatives of dipropylnitrosamine, oleic acid, and streptozotocin. and inflammatory factors and directly attack the kidneys, exacerbating renal injury (Zhao *et al.*, 2020). The results also showed a significant increase in the concentration of urea in patients with gallstones at a probability level (P = 0.001) compared to healthy people. bacteria and that this enzyme hydrolyzes urea into ammonia and bicarbonate and the ammonia causes the pH to increase, resulting in the production and precipitation of an insoluble form of calcium (Jahantab *et al.*, 2021).

The results also showed a significant increase in the concentration of body mass index in patients with gallstones at a probability level (P = 0.002) compared to healthy people. Obesity can increase leptin secretion, and it can regulate bile fat metabolism to promote the disposal of excess cholesterol stored in tissues. Therefore, an increase in serum leptin can lead to increased excretion of cholesterol in the bile, leading to hypersaturation of bile with cholesterol and an increased risk of developing gallstones (Zhang *et al*., 2023; Al-Jawadi, 2020).

Table-2: Comparison of clinical parameters between gallstones patients and healthy individuals (control group).

Clinical Parameters	**Patients With Gallstones Mean ± SD No.= 97**	**Control Group Mean ± SD No.= 83**	**p-value**
CCK (pg/ml)	55.34±0.91	57.77 ±0.95	0.001**
Glucose (mg/dl)	106.52 ±9.07	86.68 ±10.06	0.001**
Uric Acid (mg/dl)	4.46 ±1.09	3.85 ±1.07	0.001**
Bilirubin (mg/dl)	0.97 ±0.79	0.79 ±0.23	0.01*
Creatinin (mg/dl)	0.93 ±0.19	0.87 ±0.11	0.01*
Urea (mg/dl)	35.12 ±10.22	22.62 ±6.11	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

The relationship between age and sex for patients with gallstones:

The results shown in Figure-1 when comparing sex with the incidence of gallstones in different age groups showed that the infection rate was higher in females than in males. It was also found that both sexes are susceptible to gallstones at all ages. It was found that the prevalence of gallstones increases with age. In both men and women, the reason is that bile saturation with cholesterol increases with age as a result of increased liver secretion of cholesterol and decreased bile acid synthesis, and a gradual change in the ratio between bile acid synthesis and cholesterol saturation leads to cholesterol hypersaturation (Aljawadi, 2020; Kwon *et al.*, 2018).

However, the prevalence of gallstones was higher in women than in males, especially in the age of fertility and childbearing, between the ages of 20-40 years, but its symptoms do not appear until later stages of life, when the risk is higher by 2-3 times. Hormones play such Estrogen and progesterone play an important role in high-risk diseases of women, where estrogen causes cholesterol hypersaturation by increasing cholesterol excretion (while reducing bile acid synthesis) while progesterone prevents contraction of the gallbladder and causes cholestasis (Zhang *et al*., 2022). But the difference between the sexes becomes less significant after the age of 50, perhaps because after the age of 50, when women enter perimenopause, estrogen levels drop, and the risk of developing gallstones becomes similar to that of men (Zhang *et al*., 2023).

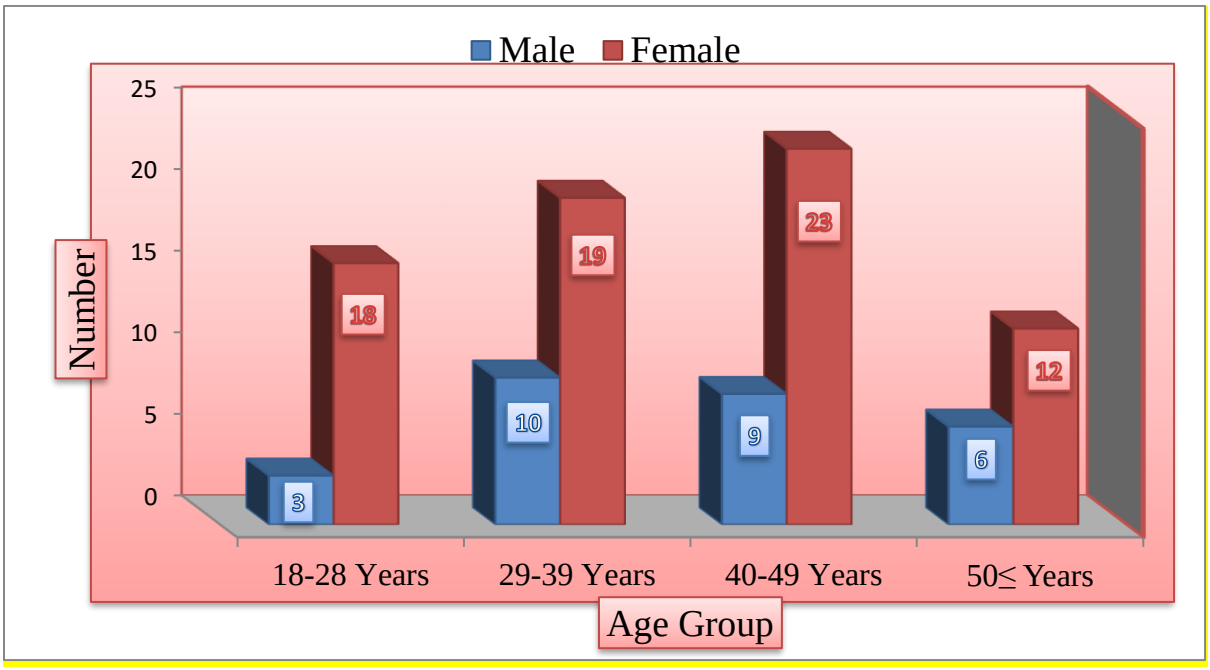

Figure-1: The relationship between age and sex for patients with gallstones.

Conclusion:

This study discovered a relationship between low CCK and an increased risk factor for gallstone formation, which has a strong role, especially in people who are obese and with age.

Acknowledgments:

The researchers are grateful the Mosul University, the management, and the medical staff of Hospitals for their helping.

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