Serum Cholecystokinin as a Predictive Biomarker for Peptic Ulcer Related to Depression: Clinical Application

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Abstract: Peptic ulcer disease (PUD) is characterized by mucosal damage of the stomach and duodenum. Depression is a chronic disorder characterized by a low mood and loss of interest. CCK is a hormone secreted by the small intestine that acts as a regulator for both the GIT and the CNS. Study aimed to estimate serum CCK levels and assess its potential as a predictive biomarker for PUD related to depression. A case-control study of 50 peptic ulcer patients and 50 healthy controls measured CCK and serotonin levels using ELISA; ROC curves were used to assess sensitivity and specificity. Results show there was a significant decrease in CCK and serotonin levels ($p < 0.001$) in patients compared to controls, with CCK AUC: 0.981, sensitivity: 100%, specificity: 92%; and serotonin AUC: 0.999, sensitivity: 100%, specificity: 100%. In conclusion: This study reports low serum CCK levels in patients with peptic ulcers. A difference in serotonin levels suggests a depressed mood, and CCK acts as an excellent predictor of PUD related to depression.

1 INTRODUCTION

Peptic ulcers are defined as ulcers that form in the gut mucosal layer when the mucosal barrier is disrupted and damaged by agents such as H. pylori or by an imbalance in stomach acidity, but the main cause is NSAID abuse, leading to local erosion that induces inflammation with symptoms including heartburn, vomiting, and epigastric pain. Delaying treatment leads to haemorrhage. If inflammation persists, these ulcers may develop into gastric cancer [1].

Depression is a common chronic mental disorder that can develop at any age due to various risk factors. This condition is marked by persistent fatigue, a loss of interest in normally enjoyable activities, a desire for solitude, a low mood, and abnormal thought patterns. People with depression often find it difficult to complete essential daily tasks [2].

Cholecystokinin (CCK) is a neuropeptide hormone secreted from the I-cells of the gastrointestinal tract, especially in the mucosa lining the small intestine, and from the central nervous system. From its sites of secretion, this hormone is regarded as a crucial regulator of both the gastrointestinal tract (GIT), overseeing the digestive process, and the central nervous system (CNS), modulating certain GIT-CNS functions, including intestinal motility and appetite [3]. CCK exhibits a variety of regulatory functions across the main organs of the gastrointestinal tract (GIT). In the stomach, it reduces acid production and gastric emptying by stimulating lower-stomach muscle contractions and increasing intestinal peristalsis. CCK's action on the accessory organs of the gut, especially the pancreas, involves stimulating the production of pancreatic juice and bicarbonate, as well as a small amount of insulin secretion, thereby regulating pancreatic exocrine and endocrine functions. The gallbladder is also influenced by this important hormone, as it regulates its contraction, relaxation, and refilling [4].

The ulcer healing efficacy of cholecystokinin (CCK) is attributed to mechanisms including the upregulation of CCK-A receptors, augmentation of somatostatin secretion, stimulation of sensory nerves, and the enhancement of blood flow (hyperemia) within the ulcer region, potentially mediated by nitric oxide (NO). Any diminished levels of CCK may impede this process or suggest an implication in the hormone's secretion [5].

Low CCK is responsible for reducing intestinal movement, degrading the mucosal layer of the gastrointestinal tract, and increasing gastric emptying time, all of which contribute to mucosal ulcer development [6]. Since CCK is a neural regulator peptide that plays a key role in controlling emotional and psychological responses, it significantly

influences depression by inhibiting the release of neurotransmitters like serotonin, which reduces neural activity. This makes CCK important in the development of depression, and any alteration in its levels can be a contributing factor in the condition [7], [8].

Serotonin, also known as 5-hydroxytryptamine, is a vital neurotransmitter hormone primarily produced in the gastrointestinal tract. It serves crucial local and peripheral functions, including regulating intestinal motility and influencing mood. This neurotransmitter is released by specialized cells called enterochromaffin cells when they convert the amino acid tryptophan into serotonin through a hydroxylation process triggered by specific stimulation [9]. This hormone is influenced by depression and peptic ulcers. A low level of serotonin contributes to depression symptoms, and studies show that patients with depression generally have low serotonin levels [10]. This statement essentially reiterates that certain 5-HT precursors are generated by gut microbiota through the metabolism of tryptophan, resulting in the production of indole. Depression affects the microbiota, leading to reduced 5-HT synthesis [11].

The research aims to estimate serum CCK levels in peptic ulcer disease with depression and assess its potential as a biomarker for peptic ulcer disease.

2 METHODOLOGY

2.1 Subjects

In a case-control design comprising 100 male subjects (50 healthy controls versus 50 cases), to reduce biological diversity since the female's estrogen hormone acts as an ulcer protective factor [12], cases were strictly limited to adult males with an endoscopically confirmed peptic ulcer diagnosis, diagnosed by Olympus endoscopy performed by a gastroenterologist at the Kerbala center for gastrointestinal and liver disease in Kerbala, Iraq. The selection protocol mandated the removal of any female candidates, minors under the age of 18, or records lacking complete data. To ensure clinical isolation of the ulcer condition, the study further excluded individuals with a history of upper gastrointestinal surgery in the prior three months; patients with Crohn's disease, ulcerative colitis, or celiac disease; patients with a malignant tumor; and any cases with a surgical history in the last three months. Healthy controls were confirmed to be free of gastrointestinal symptoms and peptic ulcer history through clinical interview and physical examination; endoscopic confirmation was not performed in this asymptomatic group, since routine endoscopy is not ethically justified in the absence of a clinical indication.

2.2 Data Collection

Participants underwent a comprehensive assessment encompassing biological, behavioral, and psychological health determinants. In addition to standard metrics such as age, BMI, and smoking status, the researchers documented lifestyle behaviors, including physical activity and employment status. H. pylori infection was identified via a biopsy culturing technique for patients, while control was achieved via stool Ag detection. Moreover, a psychologist administered the Patient Health Questionnaire-9 (PHQ-9) to evaluate the extent and severity of depression.

2.3 Samples

From October to December 2025, 5 mL of venous blood was collected from each participant via venipuncture using a sterile syringe and aseptic technique. Each specimen was immediately assigned a unique identifier in the laboratory information system and transferred into a gel tube to facilitate clot formation. After centrifugation at 4,000 RPM for 15 minutes. The samples were labeled and stored at -20°C until the end of the collection phase, at which point CCK and serotonin levels were measured.

2.4 Ethical Statement

The study protocol was approved by the Medical Ethics Committee of the College of Applied Medical Sciences at Karbala University (Ref. No.: CLAMSKU/19). All procedures were conducted in strict adherence to the ethical standards set forth by this committee and to relevant national and international guidelines for human participant research; these ethical principles are outlined in the Declaration of Helsinki.

2.5 Biomarkers Measurement

At the end of the collection phase, all frozen serum samples were thawed to room temperature prior to biomarker analysis. Cholecystokinin (CCK) concentrations were measured using an ELISA Kit (ELK Biotechnology, USA) following a competitive inhibition protocol. All frozen samples and reagents

were equilibrated to ambient temperature prior to assessment. The colorimetric output was measured, with optical density inversely related to the target analyte concentration due to competitive binding by conjugated secondary antibodies. Higher colorimetric signals corresponded to lower CCK levels. To evaluate depression biomarkers [10], serotonin concentrations were measured concurrently using an ELISA Kit (ELK Biotechnology) and quantified via a standard sandwich assay. Body Mass Index (BMI) was calculated by dividing each participant's weight in kilograms by the square of their height in meters [13].

2.6 Statistical Analysis

All statistical analyses were performed using SPSS 26.0 (SPSS Inc., Chicago, IL, United States). Serum CCK and serotonin levels were compared between patients and controls using the Student t-test, given the normal distribution as confirmed by the Shapiro-Wilk test ($p > 0.05$ for CCK and serotonin levels in both groups). Multiple comparisons were evaluated using ANOVA, followed by Tukey's post hoc test to identify intergroup differences. Demographic variables were assessed using the Chi-square test and Fisher's Exact Test. The predictive value of CCK for peptic ulcer disease was analyzed using ROC curve analysis. A P-value of less than 0.05 (two-tailed) was considered statistically significant for all analyses.

3 RESULTS

Table 1 shows a significant difference between the patient and control groups in work status ($p < 0.05$) and difficulty at work ($p < 0.001$), with the patient group reporting higher rates of difficulties (24%) than the controls (2%). There were significant differences between patients and controls in NSAID use ($p < 0.01$); Patients tended to use this drug more than controls, which puts them at risk of ulcer formation. Only 12% from patients had positive H. pylori infection. No statistically significant differences were found in smoking status or physical activity. Classification of the study individuals based on the severity of depression, which results from the PHQ-9 application, since all patients had a degree of depression compared to the control group ($p<0.001$ for both). Notably, none of the patients fell into the "no depression" category, whereas 14% of controls did; depression severity was assessed as an outcome measure following recruitment rather than as a selection criterion, suggesting that at least mild depressive symptoms were common among the peptic ulcer patients examined in this study.

Table 2 shows highly significant differences in CCK and serotonin levels between patients with peptic ulcer disease and controls ($p<0.001$), as CCK levels decreased in the patient group (53.21 ± 9.91) compared to the control group (108.73 ± 30.83), and serotonin levels were lower in patients (504.11 ± 177.63) compared to controls (1005.36 ± 141).

Table 3 presents a comparison of the study biomarkers (CCK and serotonin) across BMI and age classes, indicating that there were significant differences between patients and controls ($p<0.001$) only in terms of disorder, with no significant differences between groups based on age and BMI, except in the patients group; there were significant differences ($p<0.05$) in CCK levels between patients age–18-29 years ($57.36\ b \pm 10.19$) compared to patient above 30 years old ($53.49\ c \pm 9.08$ and $51.95\ c \pm 10.21$).

Table 4 and Figure 1 reflect the results of the ROC curve: a decrease in CCK can diagnose peptic ulcer disease with a standard error of 0.0012 ($p < 0.001$), a cutoff point of 65.244, an AUC of 0.981, a sensitivity of 100%, a specificity of 92%, and an accuracy of 96%. For serotonin, low serotonin levels were used. Error: < 0.001, $p < 0.001$, Cutoff Point: 791.911, Area Under Curve (AUC): 0.999, sensitivity: 100%, specificity: 100%, and accuracy: 100%.

4 DISCUSSION

Based on the findings, there exist highly significant disparities in cholecystokinin (CCK) hormone levels between the patient and control groups. These differences are associated with the pathogenesis of peptic ulcer disease and suggest one of the following underlying mechanisms: This hormone acts on D-cells to stimulate somatostatin secretion, which inhibits gastrin-17 secretion and thereby reduces acid production. Low stomach acidity, elevated somatostatin levels, or increased pancreatic secretion inhibit CCK secretion through a negative feedback mechanism, which agrees with [14].

Since peptic ulcer disease is known to damage the inner mucosal layer, which contains enteroendocrine cells such as I-cells that secrete CCK, this disease will result in the destruction of some of these cells, leading to low production of CCK [15], which agrees with the ablation procedure to part of the duodenum [16]. Depression, a common mental disorder, causes low secretory function, resulting in retardation of all neuropeptides, such as CCK [7]. On the other hand,

the vagus nerve that regulates the GI tract shows a decrease in function in depressive patients; therefore, a decrease in neuropeptides that are secreted in the GI tract, like CCK [17]. CCK levels are not affected by BMI, consistent with a study by [18], which previously showed that intestinal CCK is not affected by sex or obesity status [19]. Another study shows ambiguities regarding the role of increasing BMI and obesity in CCK hormone levels, as levels may remain unchanged, decrease, or increase with obesity [20]. A study by [21] shows the reduction in CCK levels with age, attributable to reduced CCK mRNA expression in I-cells as they atrophy with age, which in turn leads to reduced CCK secretion. This age-related decline is consistent with the significantly higher CCK levels observed among our patients aged 18–29 years compared with those aged ≥45 years (Table 3), suggesting that I-cell secretory capacity may decline further with advancing age even within the patient group.

ROC curve result compared to a study that shows the AUC of serum CCK level was 0.762, with a sensitivity of 0.590 and a specificity of 0.844 [6]. Our results (Table 4), with a CCK AUC of 0.981, indicate a stronger diagnostic tool for peptic ulcer disease compared to this earlier study.

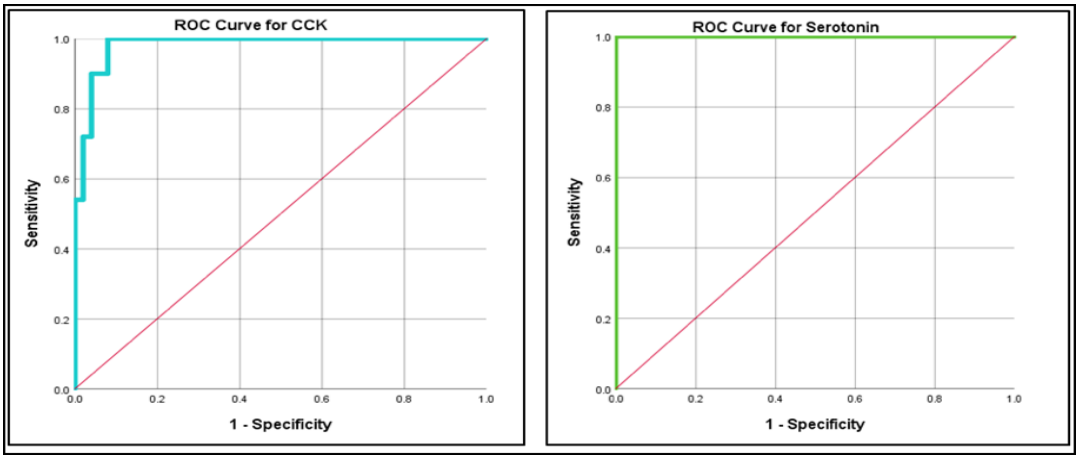

Figure 1: Receiver operating characteristic (roc) curve for cholecystokinin and serotonin.

Table 1: Classification and distribution of the subjects based on demographic results.

Parameter		Patients	Control	P-value
Smoking status	Never	36.0%	58.0%	0.083
	Former	18.0%	10.0%	
	Current	46.0%	32.0%	
NSAIDs usage	Yes	64.0%	10.0%	< 0.01
	No	36.0%	90.0%	
H. pylori	Positive	12.0%	0.0%	<0.05
	Negative	88.0%	100%	
Work status	Employment	42.0%	62.0%	<0.05
	Unemployment	58.0%	38.0%	
Difficult at work	Yes	24.0%	2.0%	< 0.001
	No	76.0%	98.0%	
Physical activity	Non activity	74.0%	88.0%	0.341
	Once per week	8.0%	4.0%	
	Twice per week	6.0%	2.0%	
	Three times per week	12.0%	6.0%	
Depression classes	No depression	0.0%	14.0%	<0.001
	Minimal depression	12.0%	38.0%	
	Mild depression	16.0%	30.0%	
	Moderate depression	38.0%	18.0%	
	Moderate-severe depression	30.0%	0.0%	
	Severe depression	4.0%	0.0%	

Table 2: Study biomarkers comparison between cases and controls.

Biomarker	Group	Mean ± S. D	P-value
CCK (pg/mL)	Patient	53.21 ± 9.91	< 0.001
	Control	108.73 ± 30.83	
Serotonin (pg/mL)	Patient	504.11 ± 177.63	< 0.001
	Control	1005.36 ± 141	

Table 3: Research biomarkers comparison between study groups based on BMI and age.

Biomarkers	Indicators	Groups	Controls	Patients	P-value
			Mean ± S. D	Mean ± S. D	
CCK (pg/mL)	BMI	Normal weight	106.71 a ± 30.79	51.74 b ± 11.86	< 0.001
		Over weight	110.13 a ± 32.21	55.20 b ± 8.77	< 0.001
		Obese	108.23 a ± 30.94	52.18 b ± 9.76	< 0.001
		p-value	0.885	0.537	
Serotonin (pg/mL)		Normal weight	1011.00 a ± 124.22	429.01 b ± 198.29	< 0.001
		Over weight	984.29 a ± 153.76	500.68 b ± 156.10	< 0.001
		Obese	1025.68 a ± 138.46	494.61 b ± 171.31	< 0.001
		p-value	0.540	0.750	
CCK (pg/mL)	Age	18 - 29	114.05 a ± 32.12	57.36 b ± 10.19	< 0.001
		30 – 44	104.93 a ± 30.96	53.49 c ± 9.08	< 0.001
		≥ 45	99.05 a ± 25.92	51.95 c ± 10.21	< 0.001
		p-value	0.577	< 0.05	
Serotonin (pg/mL)		18 - 29	1024.00 a ± 159.07	462.20 b ± 252.81	< 0.001
		30 – 44	977.93 a ± 135.45	487.17 b ± 159.10	< 0.001
		≥ 45	999.65 a ± 80.33	509.70 b ± 151.57	< 0.001
		p-value	0.605	0.744	

Table 4: Results of the receiver operating characteristic (roc) curve for cholecystokinin and serotonin.

Metrics		CCK	Serotonin
Std. Error		0.012	< 0.001
Asymptotic Sig.		< 0.001	< 0.001
Asymptotic 95% Confidence Interval	Lower Bound	0.985	0.958
	Upper Bound	1.000	1.000
Cutoff Point		65.244 pg/mL	791.911 pg/mL
Area Under Curve (AUC)		0.981	0.999
Sensitivity		100%	100 %
Specificity		92%	100%
Accuracy		96%	100%
Positive Predictive Value		92.6%	100%
Negative Predictive Value		100%	100%

Low serotonin levels are linked to the fact that some 5-HT precursors originate from gut microbiota via tryptophan metabolism, which produces indole. Depression can disrupt the microbiota, leading to reduced 5-HT synthesis [11]. In ROC curve comparisons for serotonin, platelet serotonin exhibited high diagnostic accuracy in detecting depression among untreated patients, with an AUC of 0.996 and an overall accuracy of 96%. The test achieved a sensitivity of 100% and a specificity of 96.67% [22].

Although H. pylori infection is considered, together with NSAID use, one of the principal causes of peptic ulcer disease, only 12% of patients in this cohort tested positive for H. pylori. This relatively low prevalence suggests that NSAID-induced mucosal injury, rather than H. pylori infection, was the predominant etiological factor in this study population, consistent with the markedly higher NSAID usage rate observed among patients (64%) compared to controls (10%). Patients use NSAIDs compared to controls, which puts them at risk of ulcer formation since NSAIDs induce peptic ulcers through direct irritation to the mucosal layer, then inhibit protective prostaglandins, resulting in open pores in the mucosal layer and damaging inner layers with gastric acid. Some NSAIDs act through COX_2 and cause direct inflammation [23].

5 CONCLUSIONS

In conclusion, serum CCK levels were significantly decreased in patients with peptic ulcer disease compared with healthy controls. The observed difference in serotonin levels suggests an association between altered serotonin status and depressive symptoms in male patients with peptic ulcer disease. Low serum CCK demonstrated potential diagnostic value for distinguishing patients with peptic ulcer disease from healthy individuals, while reduced serotonin levels may serve as a potential marker of coexisting depressive symptoms.

These findings suggest that the assessment of CCK and serotonin levels may provide additional information during the clinical evaluation of male patients with peptic ulcer disease, particularly for identifying patients at risk of depressive manifestations. However, further validation studies are required before these biomarkers can be incorporated into routine clinical practice.

6 LIMITATION

This study has several limitations. First, the sample size was relatively limited and the study population included only male participants from a single center, which may restrict the generalizability of the findings. Second, different diagnostic methods were used for *H. pylori* detection between patients and controls (biopsy-based culture in patients and stool antigen testing in controls), which may have introduced methodological variability and affected direct comparison of infection status. Future studies involving larger, multicenter cohorts, including both sexes and using standardized diagnostic methods for *H. pylori* detection, are recommended to confirm these findings.

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