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Study The Effect of Serotonin and Cholecystokinin in Men with Irritable Bowel Syndrome

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Abstract: Irritable Bowel Syndrome (IBS) is a complex gastrointestinal disorder with an unclear etiology. Recent research highlights the gut-brain axis, particularly the roles of serotonin and cholecystokinin (CCK), as key factors in IBS pathophysiology. Altered serotonin signaling and CCK levels may contribute to IBS symptoms by influencing gastrointestinal motility and visceral sensitivity. A deeper understanding of these relationships could lead to improved diagnostic tools and more effective treatment strategies for IBS patients.

IBS is more frequently studied in women, while its presentation in men remains underexplored. This study investigated IBS-related biomarker levels in 90 adult male patients diagnosed at Falluja General Hospital between October 2023 and July 2024. Serum levels of serotonin, cholecystokinin, and selenium were measured and compared with those of 40 healthy controls. Statistical analysis used IBM SPSS v27.0, with independent samples t-tests ($p < 0.05$).

The results revealed significant alterations in CCK, serotonin, and selenium levels between IBS patients and controls, suggesting their potential role in IBS pathophysiology. Strong correlations among these biomarkers indicate a complex interplay of physiological processes.

Notably, all three parameters demonstrated high diagnostic performance, with CCK and serotonin exhibiting near-perfect discrimination. These findings highlight their potential as valuable biomarkers for IBS diagnosis and screening. However, the exceptionally high diagnostic accuracy, particularly of CCK, necessitates further validation in larger, more diverse populations. The slightly superior diagnostic performance of CCK and serotonin compared to selenium suggests their prioritization in clinical applications. These findings support their potential as IBS biomarkers, warranting further research to confirm their clinical utility.

Key Words: Irritable Bowel Syndrome (IBS), Gut-brain axis, Serotonin, Cholecystokinin (CCK), Selenium, Biomarker

INTRODUCTION:

Irritable Bowel Syndrome (IBS) is a common gastrointestinal disorder that affects millions of individuals globally. It is characterized by abdominal pain, changes in bowel habits, including constipation, diarrhea, or both and bloating [1]. Despite its prevalence, the exact cause of IBS remains unknown. It is classified as a functional gastrointestinal disorder, meaning there are no identifiable structural or biochemical abnormalities. Recent research has focused on the interactions between the gut and the brain, known as the gut-brain axis. This connection is believed to play a significant role in IBS development and progression. Serotonin, a neurotransmitter commonly associated with mood regulation, also plays a vital role in gastrointestinal function. Approximately 90% of the body's serotonin is found in the gut, where it regulates intestinal motility, secretion, and sensitivity [2, 3]

Serotonin is produced by enterochromaffin cells in the gut lining and controls peristalsis, the wave-like contractions that move food through the digestive tract. It also influences fluid secretion and gut sensitivity to stimuli. In IBS patients, serotonin regulation is often disrupted, leading to characteristic symptoms [4, 5]. A number of studies found that serotonin plays a vital role in the development of irritable bowel syndrome [6, 7, 8]. The best techniques used to study this relationship were Gene knockout and Gene transformation. Researchers found that a reduction in the production of intestinal serotonin causes the intestinal lining to weaken. This leads to clogging or constipation and an increase in serotonin levels in the gut.

A hypothesis is that enterocytes of IBS individuals are deficient in the Serotonin Transporter—SERT. A second hypothesis focuses on fewer enterochromaffin cells in the GI tract of people with IBS. However, altered serotonin signaling is a key finding in IBS research. Studies show that patients with IBS may have increased or decreased serotonin levels depending on their predominant symptoms [9].

IBS is divided into four types based on the predominance of symptoms presentation such as stool frequency and consistency, IBS with constipation (IBS-C), IBS mixed (IBS-M), IBS with diarrhea (IBS-D), and IBS unclassified [10]. Diagnosis of IBS is made based on symptom presentation; there is no single diagnostic test for IBS,

People with diarrhea-predominant IBS (IBS-D) have high serotonin levels. This leads to increased gut motility and secretion. On the contrary, constipation-predominant IBS (IBS-C) is characterized by low serotonin levels and slow intestinal transit. However, the presence of different serotonin receptors further complicates serotonin's role in IBS [11, 12].

The 5-HT3 and 5-HT4 receptors are particularly important in gut function. The 5-HT3 receptor mediates gut motility and sensation, while the 5-HT4 receptor primarily influences motility [13]. Medications targeting these receptors, such as alosetron for IBS-D and tegaserod for IBS-C, have been developed to manage symptoms [14].

Another area of interest is the interaction between CCK and other gut hormones and neurotransmitters, particularly serotonin. Both play crucial roles in gut motility and sensation. Earlier animal studies have revealed that serotonin and cholecystokinin (CCK) co-expressing EC cells can be seen in the small and large intestines.

Cholecystokinin (CCK) is one of the gastrointestinal hormones that play an essential role in the regulation of nutritional homeostasis. This hormone is peptide and synthesized and secreted from neuroendocrine I cell distributed throughout the mucosa in the proximal two- thirds of the small bowel. The gastrointestinal motility regulator Cholecystokinin (CCK) functions as a potent peptide hormone. The hormone activates gallbladder activity after meals and reduces stomach emptying as well as it impairs bowel transit [15]. Research investigations suggest that IBS pathogenesis involves changes in CCK release together with abnormal tissue reactions to this peptide. The scientific research reveals that the symptoms might stem from both excessive CCK secretion and increased tissue responsiveness to the hormone CCK [16].

Some studies suggest that IBS patients, particularly those with IBS-D, have elevated plasma CCK levels. This indicates that excessive CCK production or impaired clearance could play a role in symptom development [17, 18]. However, other studies have found lower CCK levels in IBS patients as compared to healthy controls. This inconsistency highlights the complexity and heterogeneity of IBS [15].

Research on CCK has led to investigations into potential therapeutic approaches. CCK receptor antagonists have been explored as possible treatments, particularly for IBS-D patients. These drugs aim to block CCK's effects on gut motility and sensitivity, potentially alleviating symptoms such as diarrhea and abdominal pain. Understanding their interactions may provide

deeper insights into IBS pathophysiology and lead to more targeted treatment options. While some studies have shown promising results, more research is needed to establish their efficacy and safety in IBS management [19].

The connection between CCK and IBS extends beyond direct physiological effects. CCK has been implicated in stress response modulation, which is known to exacerbate IBS symptoms. It activates the hypothalamic-pituitary-adrenal (HPA) axis, increasing cortisol release. It may contribute to the stress-related symptoms experienced by many IBS patients [17] The hormone CCK triggers smooth muscle contraction in the gallbladder along with the gastrointestinal tract and activates gland secretion in the pancreas, liver, small intestine, and other organs [20]. Previous research revealed that external CCK administration failed to modify either rectal movement or sensory perception. The rapid intermittent expansion of stomach size leads to increased abdominal pain in patients who have IBS [21] Research indicates that CCK-8 peptide increases colonic motility and causes abdominal pain in IBS patients, although scientists have not determined the underlying mechanism [17] Patel & Shackelford reported that patients with IBS-D exhibited both psychosomatic disorders and increased sensitivity of their internal organs. The pathogenesis of IBS-D potentially involves SERT and CCK in regulating the brain-gut axis while simultaneously affecting visceral sensitivity [22].

Understanding the complex interactions between serotonin, CCK, and other physiological factors is crucial for improving IBS diagnosis and treatment. Despite extensive research, many aspects of CCK's involvement in IBS remain unclear. The exact mechanisms through which CCK contributes to IBS symptoms require further investigation. This study examined the roles of serotonin, cholecystokinin (CCK), and selenium in the pathophysiology of irritable bowel syndrome (IBS) in men. We aimed to investigate the alterations in these biomarkers among IBS patients. Moreover, we examined their relationships with key physiological processes, including gastrointestinal motility and visceral sensitivity.

MATERIAL AND METHODS:

STUDY DESIGN AND PARTICIPANTS

This cross-sectional study was conducted at Falluja General Hospital from October 20,2023, to July 8, 2024. The study included 90 adult male patients diagnosed with irritable bowel syndrome (IBS) confirmed by a gastroenterologist. In addition, 40 age-matched healthy male individuals (ages 20-65 years) with no history of gastrointestinal disorders served as the control group.

Inclusion Criteria:

- Adult males aged **20-65 years**.
- IBS diagnosis confirmed by clinical symptoms

Exclusion Criteria:

- Patients with a history of **hematologic disorders, oncologic conditions, malnutrition,** or **acute or chronic inflammatory diseases**.
- Participants with a history of major psychiatric disorders or neurological diseases affecting gut function.

SAMPLE COLLECTION AND BIOCHEMICAL ANALYSIS

Serum levels of serotonin, cholecystokinin, and selenium were measured using standard laboratory procedures. Informed consent from all participants was obtained. 5 mL of venous

blood was collected from each subject in the morning after an overnight fast (8-12 hours). Blood samples were collected in sterile vacutainer tubes without anticoagulants. Samples were allowed to clot at room temperature for 30 minutes. centrifugation at 3,000 rpm for 10 minutes was performed to separate the serum. The serum was then aliquoted into Eppendorf tubes and stored for analysis.

STATISTICAL ANALYSIS

Statistical analysis was conducted using IBM SPSS v27.0. Descriptive statistics included mean, standard deviation (SD), and standard error of the mean (SEM). These were calculated for all variables. Differences between IBS patients and controls were assessed using independent samples t-tests, with statistical significance set at $p < 0.05$.

Correlation analysis was performed using Pearson's correlation coefficient to examine relationships between serotonin, CCK, and selenium levels. A Receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of each biomarker. It was performed with the area under the curve (AUC), and sensitivity, specificity, and confidence intervals (CI) were reported.

All statistical tests were two-tailed, and p-values below 0.05 were considered statistically significant.

RESULTS:

Table 1 presents a comparison of serotonin, cholecystokinin (CCK), and selenium levels between IBS patients and controls. The data was analyzed using t-tests, with p-values provided to indicate statistical significance. CCK levels in IBS patients (312.5878 ± 53.5100) were significantly higher than in controls (105.8670 ± 25.6366), with a t-test value of -16.723 and a p-value of <0.0001 as shown in **Figure 1**. Elevated CCK levels may be associated with abnormal digestive processes and appetite regulation in IBS patients.

Table 1: Mean and SD of serotonin, cholecystokinin, and selenium in studied groups

Parameters	Patients	Control	t-test	P-value
Serotonin	70.356 ± 14.470	176.1133 ± 26.4595	9.6531	P<0.0001
CCK	312.5878 ± 53.5100	105.8670 ± 25.6366	-16.723	P<0.0001
Selenium	16.2653 ± 4.1460	26.6227 ± 4.3278	10.340	P<0.0001

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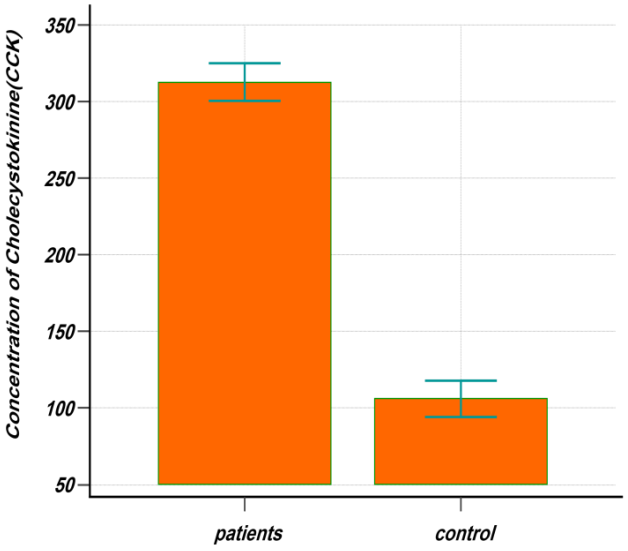

***Figure 1**: Mean & SD of CCK in studied groups*

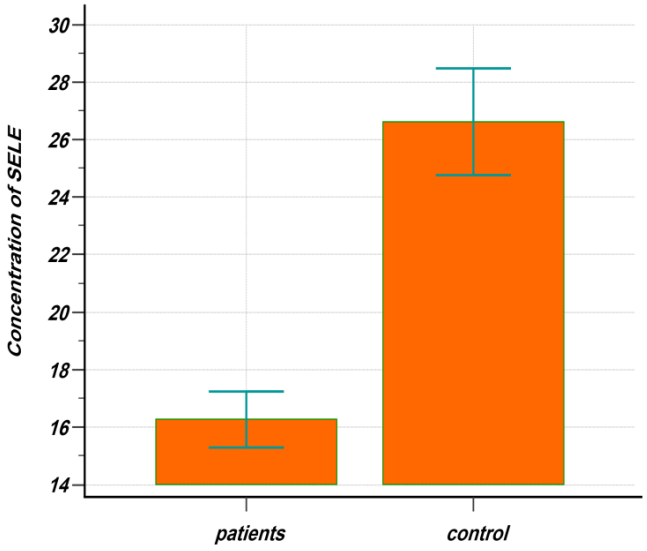

***Figure 2**: Mean & SD of SELE in studied groups*

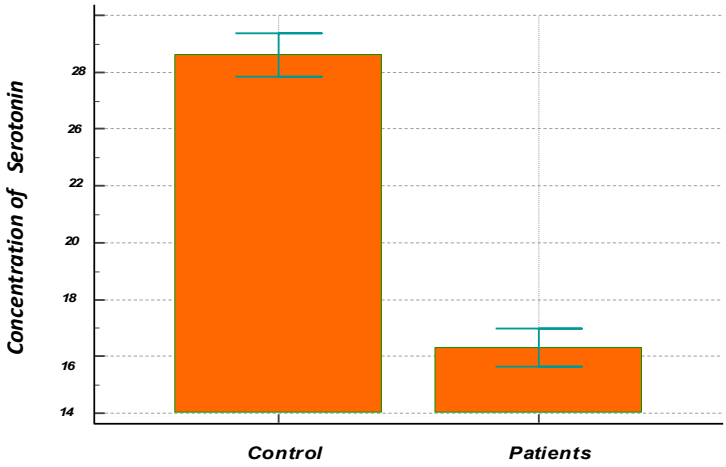

***Figure 3**: Mean & SD of Serotonin in studied groups*

Serotonin levels in IBS patients (70.356 ± 14.470) were significantly lower than in controls (176.1133 ± 26.4595), with a t-test value of 9.6531 and a p-value of <0.0001. Given serotonin's role in regulating mood, appetite, and gut motility, this reduction may contribute to IBS symptoms such as altered bowel habits and abdominal discomfort as shown in **Figure 3**. Selenium levels in IBS patients (16.2653 ± 4.1460) were significantly lower than in controls (26.6227 ± 4.3278), with a t-test value of 10.340 and a p-value of <0.0001 as shown in **Figure 2**. These findings suggest that serotonin, CCK, and selenium may serve as potential biomarkers for IBS, warranting further research.

Table 2 presents a correlation matrix for serotonin, cholecystokinin (CCK), and selenium (SELE). The matrix provides correlation coefficients, significance levels (p-values), and the sample size (n) for each pairwise comparison.

As shown in **Figure 4**, a moderate positive correlation was observed between CCK and serotonin ($r = 0.51$, $p = 0.0444$). This suggests that as CCK levels increase, serotonin levels also tend to rise. However, the strength of this correlation indicates that additional factors likely

influence this relationship.

A strong negative correlation was found between CCK and selenium (r = -1.597, p < 0.0001). This result suggests an inverse association between these two biomarkers. However, the magnitude of this coefficient exceeds the conventional range of -1 to 1, indicating a possible data anomaly or the need for non-linear analysis. Similarly, a significant negative correlation was identified between serotonin and selenium (r = -0.91, p = 0.02233). This suggests that higher serotonin levels are associated with lower selenium concentrations (**Figures 5** and **6**).

Table 2: correlation coefficient of Serotonin, cholecystokinin and selenium in studied groups

Parameter	**CCK**	**SERO**	**SELE**
CCK	1	0.51	**-1.597**
		P = 0.0444	**P < 0.0001**
		n = 90	**n = 90**
SERO	0.51	1	**-0.91**
	P = 0.0444		**P = 0.02233**
	n = 90		**n = 90**
SELE	-1.597	-0.91	**1**
	P < 0.0001	P = 0.02233	
	n = 90	n = 90	

All correlations were calculated based on a sample size of 90

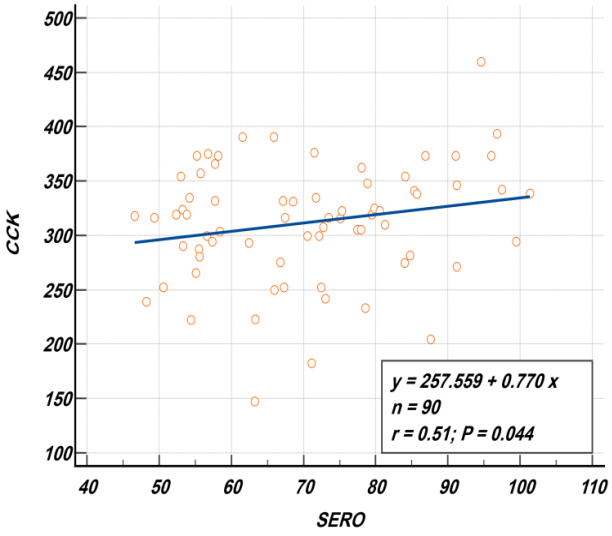

***Figure 4**: Correlation coefficient between CCK and SERO in patients' group*

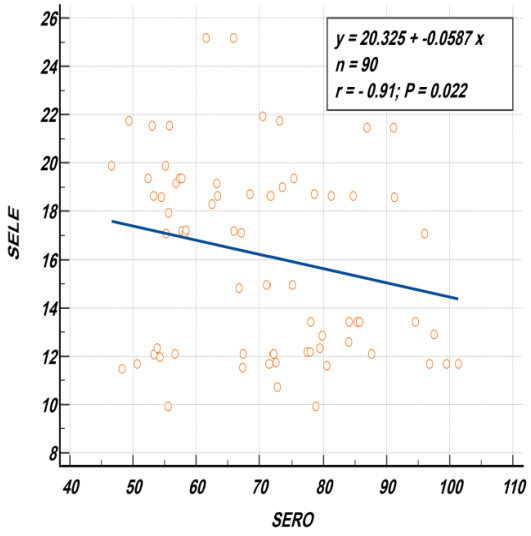

***Figure 5**: Correlation coefficient between SELE and SERO in patients' group*

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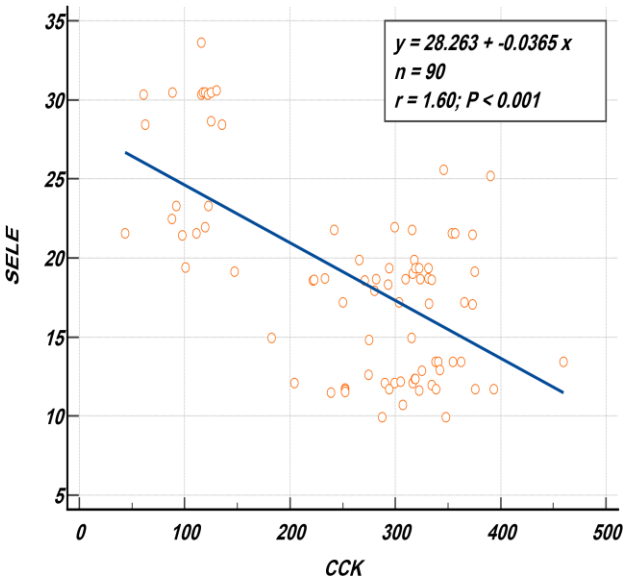

***Figure 6**: Correlation coefficient between SELE and CCK in patients' group*

These findings highlight a complex regulatory interplay between serotonin, CCK, and selenium, which may be relevant for IBS pathophysiology. The positive correlation between serotonin and CCK could reflect their interconnected roles in gastrointestinal function, while the negative correlations with selenium suggest its potential involvement in neurotransmitter balance or oxidative stress regulation.

Table 3 presents the results of a Receiver Operating Characteristic (ROC) curve analysis for three parameters: cholecystokinin (CCK), serotonin (SERO), and selenium (SELE). ROC curve analysis is a powerful statistical tool used to evaluate the diagnostic performance of biomarkers in distinguishing between patient and control groups.

Table 3: Roc curve for Serotonin, cholecystokinin and selenium in studied groups.

Parameter	AUC	Standard Error	95% Confidence Interval	Z Statistic	Specificity (%)	Sensitivity (%)	p-value
CCK	1.000	0.0000	0.959 - 1.000	-	100.0	100.0	<0.0001
SERO	0.997	0.0010	0.959 - 1.000	-	93.7	100.0	<0.0001
SELE	0.967	0.0159	0.906 - 0.993	29.377	80.0	91.4	<0.0001

The ROC analysis in Table 3 indicates that CCK exhibits perfect discrimination (AUC = 1.000), with both sensitivity and specificity reaching 100% as shown in **Figure 7**. This suggests that CCK is an ideal biomarker for distinguishing between IBS patients and controls. Similarly, serotonin demonstrates near-perfect discrimination (AUC = 0.997), with 100% sensitivity and 93.7% specificity. Selenium, while slightly less precise, still shows excellent diagnostic accuracy

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(AUC = 0.967). It displayed sensitivity and the specificity values of 91.4% and 80.0%, respectively (**Figure 8** and **Figure 9**).

These findings suggest that CCK, serotonin, and selenium could serve as valuable diagnostic biomarkers for IBS. However, it had the unusually high diagnostic performance. Therefore, further validation in larger and more diverse populations is warranted to confirm the robustness of these results.

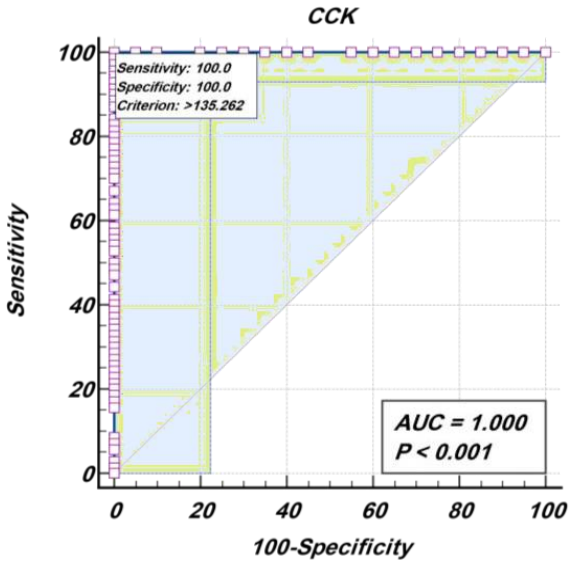

Figure 7: *ROC-Curve for CCK in studied groups*

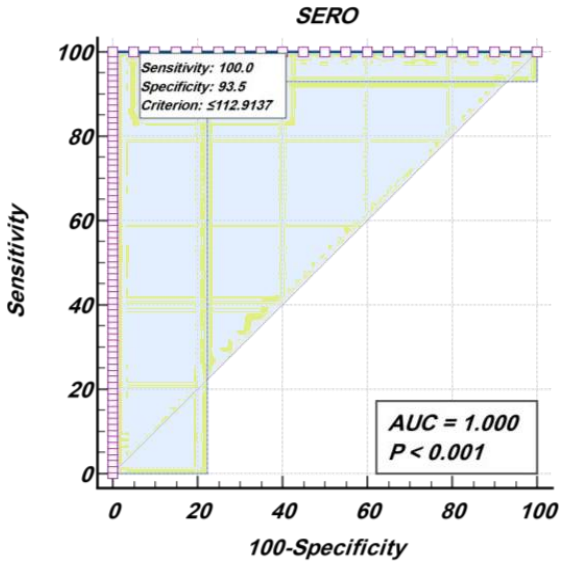

Figure 8: *ROC-Curve for SERO in studied groups*

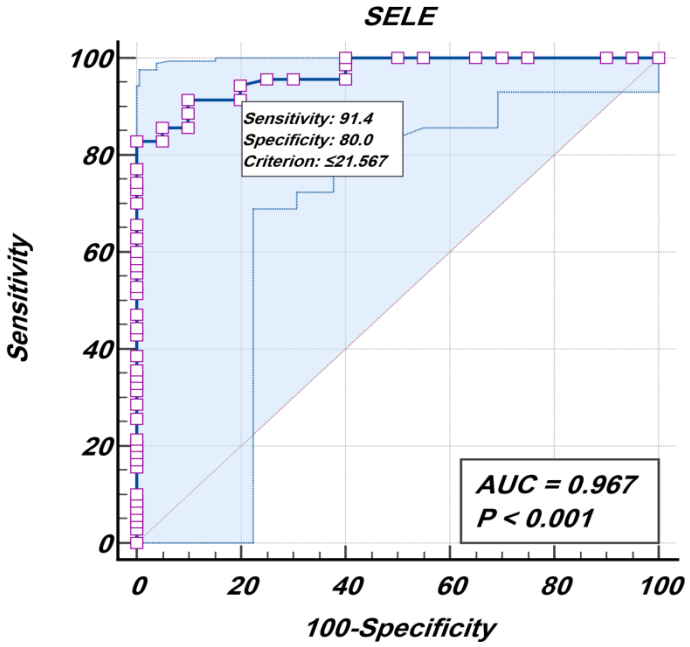

Figure 9: *ROC-Curve for SELE in studied groups*

Table 4: Pairwise Comparison of AUCs for Serotonin, Cholecystokinin, and Selenium

Comparison	Difference Between Areas	Standard Error	95% Confidence Interval	Z Statistic	Significance Level (p)
CCK ~ SERO	0.000	0.000	0.000 - 0.000	-	1.0000
CCK ~ SELE	0.0332	0.0159	0.00207 - 0.0644	2.090	0.0366
SERO ~ SELE	0.0332	0.0159	0.00207 - 0.0644	2.090	-

Table 4 presents a pairwise comparison of the Areas Under the Curve (AUC) for cholecystokinin (CCK), serotonin (SERO), and selenium (SELE) to assess differences in their diagnostic performance. The comparison between CCK and SERO indicates no significant difference in AUC values, with a reported difference of 0.000, a standard error of 0.000, and a 95% confidence interval of 0.000 to 0.000. The corresponding p-value of 1.0000 confirms that both biomarkers exhibit statistically identical discriminatory power.

In contrast, the comparison between CCK and SELE reveals a small but statistically significant difference in AUC values. The difference between areas is 0.0332, with a standard error of 0.0159. The 95% confidence interval (0.00207 to 0.0644) excludes zero, indicating a meaningful distinction between these parameters. A z statistic of 2.090 and a p-value of 0.0366 ($p < 0.05$) confirm that CCK demonstrates superior diagnostic performance relative to SELE.

Similarly, the comparison between SERO and SELE yields identical statistical values to the CCK vs. SELE comparison, suggesting a significant difference in diagnostic performance. However, the p-value for this comparison is not explicitly reported in the table. These findings suggest that while CCK and SERO are equally effective as diagnostic markers, both outperform SELE in distinguishing between the studied groups.

DISCUSSION:

The gut-brain axis is a bidirectional communication network between the central nervous system and the gastrointestinal tract. It plays a crucial role in regulating serotonin levels and the manifestation of IBS symptoms. Psychological factors, including stress and emotional disturbances, are well-documented triggers of IBS and can significantly influence serotonin signaling and gut function. This connection explains why psychological interventions such as cognitive-behavioral therapy (CBT) and mindfulness-based stress reduction have demonstrated effectiveness in managing IBS. These therapies aim to mitigate stress and enhance coping mechanisms, potentially normalizing serotonin levels and improving gut function [23, 24, 25].

Dietary factors also influence serotonin levels and IBS symptoms. Certain foods can stimulate serotonin release in the gut, exacerbating symptoms in sensitive individuals. The low FODMAP diet, which restricts fermentable carbohydrates, has been shown to alleviate IBS symptoms by reducing gas production and bloating, both of which can affect serotonin signaling [26]. Additionally, emerging research suggests that probiotics may help modulate serotonin levels, offering another potential therapeutic avenue for IBS management [27].

Despite this comprehension of the role of serotonin in IBS, addressing this issue has proven difficult to treat. IBS is highly heterogeneous. Hence, treatment must be individualized, as patients have a different set of symptoms and triggers. There is ongoing research towards the identification of biomarkers that will predict how an individual will respond to certain therapies,

thus facilitating more tailored and more effective treatments [28, 29]. Interactions of serotonin with a variety of receptors have important regulatory roles in the gastrointestinal tract concerning motility, secretion, and sensation. The interrelationship between serotonin and the gut-brain axis is thus important because it highlights the need for a holistic approach to IBS management that combines dietary modification, psychological therapies, and pharmacological treatment. While research continues to uncover serotonin's role in IBS, this may suggest new, more effective, and more personalized therapeutic approaches to help patients [30].

Another area of interest is the interaction between CCK and other gut hormones and neurotransmitters implicated in IBS. In the past few years, researchers have also studied the role of CCK in IBS pathogenesis. Research indicates that CCK stimulates interactions with serotonin, which functions as a vital controller of gastrointestinal motor function and sensation. The study of these intricate relationships can lead to better knowledge about IBS pathophysiology that may help develop more effective treatment approaches. The cardinal feature of IBS is recurrent abdominal pain and altered bowel habits (diarrhea, constipation, or a mixed picture). The etiology of IBS is still unknown but is thought to be multifactorial. It includes gut motility dysfunction, visceral hypersensitivity, and brain-gut axis dysregulation [31].

Numerous research studies showed that CCK participates in the biological process of IBS development. It is largely because of its effects on gastrointestinal motility and visceral sensitivity. The delayed gastric emptying, as well as the promotion of intestinal transit effects of CCK, may explain why IBS patients exhibit different bowel routines. Furthermore, CCK is also involved in increased visceral sensitivity. This may result in increased pain sensitivity in the abdominal region [32]. Reports have been made of abnormal CCK levels or altered responsiveness to CCK in IBS patients. Elevated plasma CCK concentrations have been found in some studies, especially in IBS-D patients. These results suggest that excessive CCK production or impaired clearance may lead to IBS symptoms. However, these findings are not consistent. Some studies have reported no significant CCK level differences between IBS patients and healthy controls [33, 34]. These findings demonstrate the complexity and heterogeneity of the disorder.

Investigations into therapeutic interventions targeting this hormone in IBS have been based on the potential role of CCK in this disorder. In this regard, CCK receptor antagonists have been evaluated as a possible treatment, especially in IBS-D. Hence, these agents attempt to block the effects of CCK on gut motility and visceral sensitivity in order to relieve such symptoms as diarrhea and abdominal pain. Preliminary studies have shown promising results. However, further research is required to demonstrate the efficacy and safety of CCK receptor antagonists for IBS [35, 36].

The regulatory process of stress involves CCK as one of its components. Many research studies recognize CCK as one of the elements that intensify IBS symptoms [15, 17, 36, 38]. When CCK activates the hypothalamic-pituitary-adrenal (HPA) axis, it leads to elevated cortisol production. The mechanism potentially leads to stress-related symptoms among patients with IBS. Evidence from research supports the link between psychological elements and IBS symptom development [36].

This study sought to identify potential diagnostic markers and explore their intercorrelations. This research compared serum levels of CCK, serotonin, and selenium between IBS patients and healthy controls. These findings contribute to a better understanding of IBS pathogenesis. Moreover, it supports the development of targeted diagnostic and therapeutic strategies aimed at improving patient outcomes.

CONCLUSIONS:

This study highlights the significant roles of serotonin, cholecystokinin, and selenium in the

IBS pathophysiology. These biomarkers show strong relationships to IBS symptoms, which makes them promising options for both diagnosis and therapeutic development. The diagnostic performance of all three parameters reaches exceptional levels because CCK and serotonin exhibit nearly perfect discrimination ability. The research confirms their use potential as effective biomarkers for medical diagnosis and screening purposes. However, the unusually high performance, particularly of CCK, warrants further validation. The diagnostic performance results indicate CCK and serotonin could become better options than selenium for medical applications. The obtained results establish a solid basis for future investigations about the mechanistic mechanisms between these parameters and their potential clinical applications. Future investigation must establish their roles in disease development and confirm their use as valid diagnostic markers for clinical practice. Given the heterogeneity of IBS, future research should focus on larger, more diverse populations to confirm these findings.

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