# Estimation Levels of Cholecystokinin, Gastrin and Secretin in Patients With Type 2 Diabetes Mellitus

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**ABSTRACT**

A diabetic patient with diabetes mellitus experiences high blood sugar levels as a result of low insulin levels or a resistance to the medication's effects. The tests were carried out at a medical laboratory using specialized kits, and the 45 patient samples and 45 healthy person samples from both sexes as a control group were dispersed based on the questionnaire form. In contrast to the non-significant rise in serum gastrin and secretin levels, the results demonstrated a substantial increase in cholecystokinin (CCK) levels between the patient and control groups and a significant increase in CCK levels according to gender, type of therapy, and disease history. In conclusion, individuals with diabetes mellitus type 2 may have aberrant blood CCK levels, which require concentration to assess the full scope of their impact on the individual.

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## 1. Introduction

One of the most frequent diseases in the world is type 2 diabetes. It is a chronic metabolic illness in which the patient has high blood sugar levels because there is no natural reaction to insulin, which is already present in minute quantities in the blood since the pancreas is unable to secrete it. The patient also suffers severe side effects including recurrent inflammatory wounds that require amputation [1,2]. The inability of β cells to function is one of the main factors that cause diabetes type 2, hence the strategy for treating or preventing the illness depends on what causes such functional failure to develop. The mechanisms underlying metabolic processes, such as the involvement of stress signals in the endoplasmic reticulum in the formation of β cells failing, form the pathophysiology of type 2 diabetes [3]. One in every eleven persons has diabetes, and 90% of those with diabetes have type 2 diabetes. These rates were particularly noticeable in Asian countries. Diabetes is the tenth most dangerous disease in the world [4]. The root causes of type 2 diabetes are multifactorial and linked to a variety of risk variables, including age, race, genetics, physical activity, diet, and smoking. One of the most important risk factors for vascular problems in type 2 diabetes mellitus is the level of HbAIc. Because they control their movement as well as the intestinal absorption of cholesterol, CCK receptors are present in the gallbladder and small intestine [5]. The gastrointestinal hormone cholecystokinin (CCK) enhances the release of pancreatic enzymes and intestinal acids, promotes tumorigenesis and neurogenesis, and participates in cellular functions such maintaining the islets of Langerhans and gastric mucosa. Additionally, it was shown that various tumor cells express the CCK receptor [6]. CCK receptors are abundant in various parts such as small intestine, pancreas, gallbladder and gastric mucosa, these receptors regulate gallbladder and small intestine motility also control the gastric, gallbladder and intestinal emptying [7]. Calcium-sensing receptors and G-protein-coupled receptors cause intestinal cells to produce CCK hormone in response to dietary proteins and lipids. The islets of langerhans response is influenced by this hormone's ability to preserve -cell and function as an incretin in various circumstances. It also targets vagal afferent neurons and recognizes them as a site for the association of nerve signals to control vagal afferent neurons' secretions and ingestion [8]. CCK is produced by pancreatic islets as well, and in rats, it prevents -cell apoptosis by reducing cytokine-induced β cell death [9]. The CCKAR and CCKBR receptors have a significant part in

appetite regulation and controlling food quantities, and these receptors may be specifically targeted in therapies based on activating them. This is done by utilizing the molecular basis underlying the receptors' selectivity. In order to perform its essential activities, such as controlling insulin secretion and sustaining beta-cell functioning [10]. The CCK hormone must connect to certain receptors that are found in the intestinal I-cells and neurons in the neurological system. In order to lower blood glucose levels in diabetic patients, CCK peptide analogues are created as a bioactive and stable version of the hormone with enzymatic activity [11]. A hormone that aids in digestion, secretin is a peptide produced by S cells in the duodenum. It promotes pancreatic secretions. Additionally, it is crucial for the fetus's brain development, and its receptors are expressed in several tissues to perform pleiotrophic tasks [12]. Secretin controls the secretion of several organs, such as the liver's biliary epithelium, where its receptors are expressed and which controls the secretion and proliferation of these cells as well as the maintenance of bile output [13]. Gastrin hormone is created by G cells in the stomach, where it promotes the formation of enterochromaffin-like cells and works as a growth factor in a variety of processes, including the preservation of the gastric mucosa and neoplastic conversion[14,15]. The objective of the current study is to assess the levels of the hormones CCK, Gastrin, and Secretin in people with type 2 diabetes and investigate the impact of various variables on these parameters in diabetic patients.

## 2. Experimental part

The current investigation was carried out in the Iraqi province of Basra from February to May 2021. 90 samples were gathered and split into two groups of both sexes (45 type 2 diabetes patients and 45 healthy individuals as a control group), with each group's samples allocated into three age groups ranging from 40 to 70. It was taken into account that none of the two groups had any chronic illnesses that would have had an impact on the study's findings based on the questionnaire's format. Under the guidance of a specialist in internal medicine, samples were obtained from a medical laboratory, and the disease was determined based on the clinical symptoms and test diagnosis. Human ELISA tests were performed using the CCK (Bioassay technology laboratory), Gastrin (MyBioSource), and Secretin human ELISA kits, which were detached from serum samples and kept at -20 °C in the deep freezer (Lifespan Biosciences). SPSS is used for statistical analysis, with a statistical significance level of P 0.05. The variation in the values of these parameters between the control and patient groups was evaluated using the T-Test, a one-way ANOVA test. Data are given as mean standard deviation.

## 3. Results

The percentages of the study sample distribution by gender, age group, method of therapy, and history of disease are shown in Table 1. The current investigation discovered non-significant variations in blood gastrin and secretin levels between patients and controls, but a substantial rise in serum CCK concentration in diabetes patients as compared to the control group (Table 2) .

Table 1: Demographic information of the study samples.

| Gender | Patients (N=45) | |
|---|---|---|
| | Frequency | Valid Percent% |
| Male | 24 | 26.7 |
| Female | 21 | 23.3 |
| | Control (N=45) | |
| Male | 22 | 24.4 |
| Female | 23 | 25.6 |
| Age | Patients (N=45) | |
| | Frequency | Valid Percent% |
| 40-50 | 22 | 24.4 |
| 51-60 | 13 | 14.4 |
| 61-70 | 10 | 11.1 |
| | Control (N=45) | |
| 40-50 | 12 | 13.3 |
| 51-60 | 17 | 18.9 |
| 61-70 | 16 | 17.8 |
| Treatment | Patients (N=45) | |
| | Frequency | Valid Percent% |
| Insulin | 26 | 28.9 |
| Sugar regulator | 19 | 21.1 |
| History of disease (year) | Patients (N=45) | |
| | Frequency | Valid Percent% |
| 5-10 | 18 | 20.0 |

| | | |
|---|---|---|
| 15-11 | 27 | 30.0 |

Table 2: Comparison of study parameters among diabetic patients' group and control

| Serum parameter | Patients (n=45) | Control (n=45) |
|---|---|---|
| CCK(ng/L) | 141.56±50.23 | 55.64±28.07* |
| Gastrin (pg/ml) | 161.56±63.05 | 135.86±59.73 |
| Secretin (pg/ml) | 194.89±107.64 | 173.64±116.65 |
| *Significant at the (P≤0.05) | | |

The results revealed a non-significant increase in serum CCK level with age groups, but a significant increase in CCK level in female patients compared to male patients, a significant increase in diabetic patients receiving insulin therapy compared to those taking diabetes regulators, and a significant increase in diabetic patients who have a disease between 11 and 15 years compared to those who have a disease between 5-10 years (Table 3).

Table 3: Comparison of study parameters among diabetic patients according to the several factors.

| CCK(ng/L) | Gender | | |
|---|---|---|---|
| | Male(n=24) | Female(n=21) | |
| | 133.20±64.94 | 151.11±22.82* | |
| | Age | | |
| | (40-50 )years(n=22) | (51-60 )years (n=10) | (61-70 )years(n=13) |
| | 128.77±63.60 | 149.26±25.73 | 157.26±32.55 |
| | Treatment | | |
| | Insulin(n-=27) | Sugar regulator(n=18) | |
| | 152.81±16.27 | 124.68±69.05* | |
| | History of disease( year) | | |
| | 5-10 (n=18) | 11-15 (n=27) | |
| | 124.68±69.05 | 152.81±28.71* | |
| *Significant at the (P≤0.05) | | | |

## 4. Discussions

High levels of CCK are commonly seen in diabetic individuals. The role of CCK in controlling insulin sensitivity was highlighted in an experimental study showing that CCK gene knockout mice have normal glucose and insulin levels in response to arginine, that CCK functions to increase body fats after eating a high-fat meal, and that the absence of CCK causes glucose intolerance [16]. The increased levels of plasma neuropeptide Y in postmenopausal diabetic women compared to healthy women, as well as the substantial association between CCK and insulin and leptin, imply a role for neuropeptides in the metabolic circumstances that lead to type 2 diabetes [17]. A possible effect of CCK hormone on insulin secretion was found in a study that examined the role of oral glucose in controlling plasma CCK levels in non-insulin-dependent diabetes mellitus patients. Additionally, the body's release of this hormone in response to glucose levels in diabetic patients with well-controlled disease did not differ significantly from that of healthy subjects [18]. High cholesterol and poor CCK sensitivity were found to be correlated; both conditions are linked to diabetes and obesity. In addition, obese individuals and diabetic patients showed an association between lower cholesterol and normal weights, a drop in triglycerides, and an increase in high density lipoprotein [19,20]. By storing triglycerides in the white adipose tissue, CCK plays a crucial role in maintaining the tissue's homeostasis. In addition, CCK receptors in the white adipose tissue improve insulin response. Postprandial CCK hormone facilitates the storage of fatty acids like triglycerides by regulating the LPL/ANGPTL-4 axis by directly acting on CCK receptors in the white adipose [21]. Due to its impact on insulin, CCK receptors have been targeted in medications either alone or in combination with insulin-tropic gut hormones, such as in the treatment of diabetes mellitus. The CCK receptors are expressed in numerous organs of the body and the bioactive CCK peptides work on islet cell growth and the secretion of insulin and glucagon [22]. Compared to patients with noninsulin-dependent diabetes mellitus, healthy individuals had elevated plasma CCK after the meal. Only in these individuals did blood glucose rise, but after administering CCK to patients, blood glucose did not increase. This demonstrates a function for CCK in controlling hyperglycemia in males after meals, and diabetic individuals also experience changes in CCK levels that might affect hyperglycemia [23]. Food intake is regulated by the CCK1 receptor, and pancreatic endocrine function is regulated by the CCK1 and CCK2 receptors. The

genes that encode these receptors may be candidate genes in the development of the disease, and these receptors may potentially function as therapeutic targets in diabetes mellitus. These receptors' polymorphism may contribute to type 2 diabetes [24]. When the CCK hormone is eliminated from mice in an experiment, it inhibits the development of β-cells and increases their death since it is only expressed in the β-cells in obese or insulin-resistant persons. Since it was shown that employing CCK receptor agonists as a therapy has an impact on body weight and the body's reaction to blood insulin and protects -cells from apoptosis, it follows that CCK generated from β-cells is helpful in protecting these cells from death [25]. According to the current data, women had significantly higher blood CCK levels than men. The physiological differences between men and women are still unclear, but depending on the gender, the differences can be seen in the nuclear receptors that control many functional pathways in the alimentary canal. These differences can also be seen in the body's capacity to secrete the right hormones in response to the nutrition received, where the nuclear receptors have an impact on metabolism [26]. H. Gilliam-Vigh et al. [27] found no discernible difference between diabetes patients and healthy controls in the density of CCK cells and CCK mRNA in the small intestine and at a lower level in the large intestine. The production of pancreatic enzymes and digestive juices may be affected in individuals with diabetes mellitus type 2 if their serum CCK levels are aberrant. To determine the extent of this influence on the patient, concentrations of serum CCK must be collected. ).

## 4. Conclusions

Patients with type 2 diabetes who have pancreas dysfunction, which is clearly linked to numerous complications that affect various organs, may also exhibit abnormalities in serum CCK levels that affect the hormone's many functions. These include regulating pancreatic enzyme secretion and gallbladder contact action, which are likely to be present in these patients and must be taken in concentration to determine the full extent of its effects.

## References

[1] A. H. Al-Rikabi, D.J. Tobin, K. Riches-Suman, M. J. Thornton, Dermal fibroblasts cultured from donors with type 2 diabetes mellitus retain an epigenetic memory associated with poor

wound healing responses, Sci. Rep., 11(2021)1-13, https://doi.org/10.1038/s41598-020-80072-z

[2] U. Galicia-Garcia, A. Benito-Vicente, S. Jebari, A. Larrea-Sebal, H. Siddiqi, K. B. Uribe, C. Martín, Pathophysiology of type 2 diabetes mellitus, Int. J. Mol. Sci., 21(2020)2-34, https://doi.org/10.3390/ijms21176275

[3] D. L. Eizirik, L. Pasquali, M. Cnop, Pancreatic β-cells in type 1 and type 2 diabetes mellitus: different pathways to failure, Nat. Rev. Endocrinol., 16(2020)349-362, https://doi.org/10.1038/s41574-020-0355-7

[4] Y. Zheng, S.H. Ley, F. B. Hu, Global aetiology and epidemiology of type 2 diabetes mellitus and its complications, Nat. Rev. Endocrinol., 14(2018)88-89, https://doi.org/10.1038/nrendo.2017.151

[5] H.H. Wang, P. Portincasa, M. Liu , P. Tso, D.Q. H. Wang, An Update on the Lithogenic Mechanisms of CCK a Receptor (CCKAR), an Important Gallstone Gene for Lith13. Genes, 11(2020)2-22, https://doi.org/10.3390/genes11121438

[6] Q. Zeng, L. Ou, W. Wang, D.Y. Guo, Gastrin, CCK, signaling, and biological activities in cellular processes, Front. Endocrinol., 11 (2020)1-16, https://doi.org/10.3389/fendo.2020.00112

[7] H. H. Wang, P. Portincasa, D.Q.H. Wang, Update on the molecular mechanisms underlying the effect of cholecystokinin and cholecystokinin-1 receptor on the formation of cholesterol gallstones, Curr. Med. Chem., 26(2019) 3407-3423, https://doi.org/10.2174/0929867324666170619104801

[8] G. J. Dockray. Cholecystokinin, Curr. Opin. Endocrinol. Diabetes Obes., 19 (2012) 8-12 . DOI: 10.1097/med.0b013e32834eb77d

[9] H.T. Kim, A. H. Desouza, H. Umhoefer, J. Han, L. Anzia, S.J. Sacotte and D.B. Davis, Cholecystokinin attenuates β-cell apoptosis in both mouse and human islets, Transl. Res., 243(2022) 1-13, https://doi.org/10.1016/j.trsl.2021.10.005

[10] X. Zhang, C. He, M., Wang, Q. Zhou, D., Yang, Y. Zhu, W. Feng, H. Zhang, A. Dai, X. Chu, J. Wang, Z. Yang, Y. Jiang, U. Sensfuss, Q. Tan, S. Han, S. Reedtz-Runge, H. Eric Xu, S. Zhao, M-W. Wang, B. Wu, Q. Zhao, Structures of the human cholecystokinin receptors bound to agonists and antagonists, Nat. Chem. Biol., 17(2021)1230-1237., https://doi.org/10.1038/s41589-021-00866-8

[11] V. Pathak, P.R. Flatt, N. Irwin, Cholecystokinin (CCK) and related adjunct peptide therapies for the treatment of obesity and type 2 diabetes, Peptides, 100 (2018) 229-235, https://doi.org/10.1016/j.peptides.2017.09.007

[12] J.Y.S. Chu, W.H. Yung, B.K.C. Chow, Secretin: a pleiotrophic hormone, Ann. N. York Acad. Sci., 1070(2006) 27-50, https://doi.org/10.1196/annals.1317.013

[13] S. Afroze, F. Meng, K. Jensen, K. McDaniel, K. Onori, P. Rahal, P. Onori, E. Gaudio, G. Alpini, S.S. Glaser, The physiological roles of secretin and its receptor, Ann. Transl. Med., 1 (2013) 29, doi: 10.3978/j.issn.2305-5839.2012.12.01

[14] E. Rozengurt, J.H. Walsh, Gastrin, CCK, signaling, and cancer, Annu. Rev. Physiol., 63(2001) 49-76, https://doi.org/10.1146/annurev.physiol.63.1.49

[15] G. Dockray, R. Dimaline, A. Varro, Gastrin: old hormone, new functions, Pflügers Archiv, 449 (2005) 344-355 https://doi.org/10.1007/s00424-004-1347-5

[16] M. Lo, S. Obici, H.H. Dong, M. Haas, D. Lou, D.H. Kim, M. Liu, D. D'Alessio, S. C. Woods, P. Tso, Impaired insulin secretion and enhanced insulin sensitivity in cholecystokinin-deficient mice, Diabet, 60(2011) 2000-2007, https://doi.org/10.2337/db10-0789

[17] A. Milewicz, E. Mikulski, B. Bidzińska, Plasma insulin, cholecystokinin, galanin, neuropeptide Y and leptin levels in obese women with and without type 2 diabetes mellitus, Int. J .Obes. Relat. Metab. Disord, 24(2000) S152- S152. https://doi.org/10.1038/sj.ijo.0801310

[18] H. Hasegawa, H. Shirohara, Y. Okabayashi, T. Nakamura, M. Fujii, M. Koide, M. Otsuki, Oral glucose ingestion stimulates cholecystokinin release in normal subjects and patients with non-insulin-dependent diabetes mellitus, Metab, 45 (1996) 196-202, https://doi.org/10.1016/S0026-0495(96)90053-0

[19] J.F. Rehfeld, Measurement of CCK in plasma with reference to nutrition related obesity studies, Nutr. Res, 76 (2020) 1-8. https://doi.org/10.1016/j.nutres.2020.01.003

[20] S.D. Thapa, K.C Shiva Raj, S. Gautam, D. Gyawali, Dyslipidemia in type 2 diabetes mellitus, J. Pathol. Nepal, 7(2017) 1149-1154. https://doi.org/10.3126/jpn.v7i2.17978

[21] A. Plaza, B. Merino, V. Cano, G. Domínguez, J. Pérez-Castells, M.S. Fernández-Alfonso, M. Ruiz-Gayo, Cholecystokinin is involved in triglyceride fatty acid uptake by rat adipose tissue, J. Endocrinol., 236(2018) 137-150, https://doi.org/10.1530/JOE-17-0580

[22] J.F. Rehfeld, Premises for Cholecystokinin and Gastrin Peptides in Diabetes Therapy, Clin. Med. Insights: Endocrinol. Diabet., 12 (2019) 1-6, https://doi.org/10.1177/1179551419883608

[23] R.A. Rushakoff, I.D. Goldfine, L.J. Beccaria, A. Mathur, R. J. Brand, R.A. Liddle, Reduced postprandial cholecystokinin (CCK) secretion in patients with noninsulin-dependent diabetes mellitus: evidence for a role for CCK in regulating postprandial hyperglycemia, J. Clin. Endocrinol. Metab., 76(1993) 489-493, https://doi.org/10.1210/jcem.76.2.8432795

[24] S. Marchal-Victorion, N. Vionnet, C. Escrieut, F. Dematos, C. Dina, M. Dufresne, D. Fourmy, Genetic, pharmacological and functional analysis of cholecystokinin-1 and cholecystokinin-2 receptor polymorphism in type 2 diabetes and obese patients, Pharmacogenet. Genomics, 12(2002) 23-30. DOI: 10.1097/00008571-200201000-00004

[25] J.A., Lavine, C.R. Kibbe, M. Baan, S. Sirinvaravong, H.M. Umhoefer, K.A. Engler, D. B. Davis, Cholecystokinin expression in the β-cell leads to increased β-cell area in aged mice and protects from streptozotocin-induced diabetes and apoptosis, Am. J. Physiol. Endocrinol. Metab., 309(2015) E819-E828 https://doi.org/10.1152/ajpendo.00159.2015

[26] A.E. Dean, F. Reichardt, S. Anakk, Sex differences feed into nuclear receptor signaling along the digestive tract, Biochim. Biophys. Acta- Mol. Basis Dis., 1867(2021) 166211 https://doi.org/10.1016/j.bbadis.2021.166211

[27] H. Gilliam-Vigh, T. Jorsal, J.F. Rehfeld, J. Pedersen, S.S. Poulsen, T. Vilsbøll, F.K. Knop, Expression of Cholecystokinin and its Receptors in the Intestinal Tract of Type 2 Diabetes, J. Clin. Endocrinol. Metab., 106 (2021)2164-2170., https://doi.org/10.1210/clinem/dgab367

# دراسة فسلجية للتغيرات في مستوى الكوليسيستوكينين في مرضى السكري من النوع 2

دلال فلاح العقابي

**قسم تقنيات المختبرات الطبية ، كلية الكنوز الجامعية ، البصرة ، العراق**

**المستخلص**

مرض السكري هو مرض استقلابي حيث يعاني مريض السكري من ارتفاع مستويات السكر في الدم بسبب انخفاض مستويات الأنسولين أو مقاومة تأثيره. اشتملت الدراسة الحالية على 45 عينة من المرضى و 45 عينة من الأصحاء كمجموعة سيطرة من كلا الجنسين ، وزعت المجاميع بالاعتماد على استمارة الاستبيان خاصة ، وأجريت الفحوصات في مختبر طبي باستخدام كتات خاصة . أظهرت النتائج زيادة معنوية في مستوى الكوليسيستوكينين بين المرضى والسيطرة ، وزيادة غير معنوية في مستوى الكوليسيستوكينين حسب الجنس ونوع العلاج وتاريخ المرض ، بينما لوحظ زيادة غير معنوية في الجاسترين و السكرتين في الدم. في الختام ، قد يعاني مرضى السكري من النوع 2 من شذوذ في مستويات الكوليسيستوكينين في الدم يجب أن يؤخذ في نظر الاعتبار لتحديد مدى تأثيره على المريض.