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Estimate the Levels of Copeptin and Chromogranin A and Some Biochemical Parameters in Patients with Chronic Diseases

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ABSTRACT

The current study aimed to estimate the concentrations of copeptin and chromogranin A and some biochemical parameters in patients with chronic diseases. Eighty-five subjects reported different chronic diseases in Azadi Teaching Hospital and Al-Jumhuri Hospital from September 2023 to January 2024. Experimental work was carried out at the Laboratories of Al-Jumhuri Hospital in Kirkuk, Iraq. The volunteers in the current study were divided as follows: 30 healthy volunteers as a control group. 25 patients with chronic kidney disease. 30 patients with diabetes mellitus. 30 patients with heart failure diseases. The results showed some kidney functions in chronic kidney disease (CKD), diabetes mellitus (DM), and heart failure (HF) patients, where urea and creatinine levels in chronic kidney disease (CKD) patients significantly increased ($P \leq 0.05$) compared to the control group. In DM patients and HF patients, the urea and creatinine levels showed non-significant ($P > 0.05$) change compared to the control group. CRP percentage in CKD patients was (52.0 %). DM patients and HF patients were (50.0 %) and (46.7 %), respectively, compared to the control group, which was (0.0 %). On the other hand, the results showed copeptin levels in CKD, DM, and heart failure patients were significantly ($P \leq 0.05$) elevated compared to the control group. Chromogranin A (CgA) levels in CKD, DM, and heart failure patients significantly increased ($P \leq 0.05$) compared to the control group. Based on the results of the current study, both copeptin and chromogranin A can be considered an important indicator in the diagnosis of some chronic diseases.

Keywords: Copeptin, Chromogranin Diabetes, CKD, CVD.

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تقدير مستويات الكوبيتين والكروموكرانين أ وبعض المعايير الكيموحيوية لدى مرضى الأمراض المزمنة

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الملخص

هدفت الدراسة الحالية إلى تقدير تراكيز الكوبيتين والكروموكرانين أ وبعض المعايير الكيموحيوية في مرضى الأمراض المزمنة. تم اخذ 85 شخصًا لديهم أمراض مزمنة مختلفة في مستشفى آزادي التعليمي والمستشفى الجمهوري في الفترة من سبتمبر 2023 إلى يناير 2024. وتم إجراء العمل التجريبي في المختبرات الخاصة في كركوك، العراق. تم تقسيم المتطوعين في الدراسة الحالية على النحو التالي: 30 متطوعاً أصحاء كمجموعة سيطرة. 25 مريضا يعانون من مرض الكلى المزمن. 30 مريضاً بالسكري. 30 مريضا يعانون من الأمراض القلبية الوعائية. أظهرت النتائج بعض وظائف الكلى لدى مرضى الفشل الكلوي المزمن، مرض السكري، والأمراض القلبية الوعائية، حيث ارتفع مستوى اليوريا والكرياتينين لدى مرضى الفشل الكلوي المزمن ($P < 0.05$) مقارنة بمجموعة السيطرة. بينما أظهرت مستويات اليوريا والكرياتينين في مرضى السكري ومرضى الأمراض القلبية الوعائية تغيراً غير معنوي ($P < 0.05$) مقارنة بمجموعة السيطرة. كانت نسبة CRP لدى مرضى الفشل الكلوي المزمن (52.0 %). في حين كانت النسبة في مرضى السكري والأمراض القلبية الوعائية (50.0 %) و(46.7 %) على التوالي، مقارنة بمجموعة السيطرة التي كانت (0.0 %). من ناحية أخرى، أظهرت النتائج ارتفاع مستويات الكوبيتين في مرضى الفشل الكلوي المزمن، ومرضى السكري، والأمراض القلبية الوعائية بشكل معنوي ($P < 0.05$) مقارنة بمجموعة السيطرة. ارتفعت مستويات CgA في مرضى الفشل الكلوي، وداء السكري، والأمراض القلبية الوعائية بشكل معنوي ($P < 0.05$) مقارنة بمجموعة السيطرة. وبناء على نتائج الدراسة الحالية يمكن اعتبار كل من كوبيتين وكروموكرانين أ مؤشرا هاما في تشخيص بعض الأمراض المزمنة.

1. INTRODUCTION

Oxidative stress is defined as an imbalance between the production of reactive oxygen species (free radicals) and antioxidant defense systems [(1)]. Reactive oxygen species (ROS), which includes oxygen radicals and their peroxides, are often generated at low levels by cellular organelles such as mitochondria and normal cell reactions. Under these conditions, they participate in several cellular signaling pathways that mediate cellular proliferation and differentiation; however, overproduction of them induces oxidative damage[(2)].

Oxygen-free radicals by cellular stress-sensitive pathways have been related to insulin resistance and reduced insulin secretion [(3)]. Free radicals induce damage to macromolecules such as lipids, proteins, and DNA and have been identified as a risk factor in various diseases such as cardiovascular disease, neurodegenerative disorders, and cancer [(2)]. ROS are also linked to induce the expression of pro-inflammatory cytokines and decreased nitric oxide release that, in turn, cause endothelial dysfunction [(4, 5)].

Reactive oxygen species overproduction is also linked to the oxidation of low-density lipoprotein cholesterol (LDL-C) and lipid peroxidation, which refers to the oxidation of membrane polyunsaturated fatty acids such as arachidonic acid or linoleic acid by free radicals. It can alter the structure and function of biological membranes. Malondialdehyde (MDA) can be used to monitor the degree of oxidative damage in many diseases like diabetes, atherosclerosis, and chronic inflammation [(6, 7)]. Typically, a biomarker can be described as a defining characteristic, measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention [(8)].

Biomarkers can be derived from molecular, histologic, radiographic, or physiologic

characteristics of the disease. Moreover, several subtypes of biomarkers have been defined according to their putative applications[9]. Copeptin is a polypeptide that is produced by the hypothalamo-pituitary axis system and is classified as a pre-prohormone with neurophysin II and vasopressin. Due to its primary function in controlling water and electrolyte balance, this arginine vasopressin C-terminal derivative can be used to diagnose cardiac and renal failure [10]. chromogranin A (CgA) was suggested as a significant diabetes biomarker [11]. According to recent research, CgA is a useful biomarker for a number of stressful diseases, such as diabetes mellitus [12]. So, the current study aimed to estimate the concentrations of copeptin and chromogranin A and some biochemical parameters in patients with chronic diseases.

2. MATERIALS AND METHODS

2.1. Study population

Hundred fifteen subjects, 85 subjects reported different chronic diseases in Azadi Teaching Hospital and Al-Jumhuri Hospital from September 2023 to January 2024, and 30 healthy volunteers as a control group. Experimental work was carried out at private Laboratories in Kirkuk, Iraq. The volunteers in current study were divided as follow:

- 30 healthy volunteers as control group.
- 25 patients with chronic kidney disease.
- 30 patients with Diabetes mellitus.
- 30 patients with heart failure diseases.

2.2. Sample collection

Venous blood of (5 ml) was obtained from each patient using a sterile syringe, and the blood sample was placed into sterile gel tubes. The blood was separated by centrifuging it for (5–10 minutes) at 3000 rpm. The serum was then divided into four Eppendorf tubes and stored for two weeks in a deep freezer (-20℃) until it was needed.

2.3. Ethical approval

The native ethics group states that these trials were approved and that all participating patients provided informed consent and knowledge about the purpose of the investigation. The approval of the Sciences College, Tikrit, Azadi, and Kirkuk Teaching Hospitals was also obtained in document 582, dated 10/18/2023.

2.4. Measurements

Regarding the measurements related to the current study, urea, and creatinine were measured by using standard methods with reagents from BioMaghreb Company – Tunisia. CRP ELISA kit is a solid phase direct sandwich method. The assay was performed according to the steps described by the manufacturer (SUNLONG, China). The Human Copeptin kit is an Enzyme-Linked Immunosorbent Assay (ELISA). The assay was performed according to the steps described by the manufacturer (amsbio co., South Korea). Chromogranin A: Chromogranin A ELISA kit is a solid phase direct sandwich method. The assay was performed according to the steps described by the manufacturer (SUNLONG, China).

2.5. Statistical analysis

Statistical analysis was performed by statisticians with the SPSS 15.01 Statistical Package for Social Sciences and also Excel 2003. Data analysis was done using chi-square test for tables with frequencies, while we used an independent sample t-test for tables with means and standard deviations. a p-value of (≤ 0.05) was used as the level of significance. The correlation coefficient was used to find the correlation between studied markers by using Pearson correlation. Descriptive statistics for the clinical and laboratory results were formulated as mean and standard error.

3. RESULTS AND DISCUSSION

3.1. Socio-demographic characteristics

3.1.1. Gender

The gender of patients was non-significant statistically at ($P \leq 0.05$) between males and females. The percentage of male patients at (57.6 %). Whereas the percentage of female patients at (42.4 %) (Table 1).

Table 1: Distribution of sample study according to Gender in patients

Gender	No	Percentage (%)
Male	49	57.6
Female	36	42.4
Total	85	100 %
P-value	---	0.093 NS
NS: Non-Significant.		

3.1.2. Residence

The residence of patients, were non-statistically significant at ($P \leq 0.05$) between rural and urban. The percentage of rural patients at (56.5 %). Whereas, the percentage of urban patients at (43.5 %) (Table 2).

Table 2: Distribution of sample study according to Residence in patients

Residence	No	Percentage (%)
Rural	48	56.5
Urban	37	43.5
Total	85	100 %
P-value	---	0.083 NS
NS: Non-Significant.		

3.1.3. Types of disease

The type of disease in patients, was non-significant statistically at ($P \leq 0.05$) between CKD, diabetes and heart failure. The percentage of CKD at (29.4 %). the percentage of diabetes at (35.3 %). In addition, the percentage of heart failure at (35.3 %) (Table 3).

Table 3: Distribution of sample study according to type of disease

Disease stage	No	Percentage (%)
Renal failure	25	29.4
Diabetes mellitus	30	35.3
Heart failure	30	35.3
Total	85	100 %

3.1.4. Kidney functions

Table 4 shows some kidney functions in CKD, DM and HF patients, where urea levels (86.7 ± 17.68) in CKD patients significantly increased ($P \leq 0.05$) compared to control group (32.07 ± 7.94). while, in DM patients (32.38 ± 7.39) and HF patients (34.35 ± 7.64), the urea levels showed non-significant ($P \leq 0.05$) change compared to control group. on the other hand, the creatinine levels (2.184 ± 0.627) in CKD patients significantly increased ($P \leq 0.05$) compared to control group (0.566 ± 0.121). while, in DM patients (0.726 ± 0.094) and HF patients (0.756 ± 0.104), the creatinine levels showed non-significant ($P \leq 0.05$) change compared to control group.

Table 4: Kidney functions in studied groups

Groups Parameter	Urea mg/dl	Creatinine mg/dl
Control (50)	32.07 ± 7.94 b	0.566 ± 0.121 b
Kidney disease	86.7 ± 17.68 a	2.184 ± 0.627 a
Diabetes mellitus	32.38 ± 7.39 b	0.726 ± 0.094 b
Heart failure	34.35 ± 7.64 b	0.756 ± 0.104 b

The results showed a significant increase in the screening or diagnostic tests of renal function (urea and creatinine) ($P < 0.05$), as shown in the Table (4). The serum urea increasing in chronic hemodialysis is proportional to the progression of the disease, which is highly influenced by a catabolic state or excessive protein ingestion, leading to a higher production of other waste substances of protein catabolism [13]. In contrast, the increase in creatinine level in the serum of patients with CRF is attributed to the decrease in the number of functioning nephrons, which would reduce the GFR, which causes major decrease in renal excretion of water and solutes [14] these results are compatible with Khalidah [15].

The Cr is cleared from the body by the kidneys; when the kidney functions abnormally, Cr concentration increases in the blood because a small amount of it is released through the urine, so there is a significant reduction in the CrCl [16]. In this present study, the comparison of urea and creatinine plasma levels in diabetes mellitus patients and a control group. Research by Blessing et al., [17]. Shows that plasma creatinine level in type 2 diabetes mellitus is increased in males and females compared with their levels in apparently healthy non-diabetic controls.

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3.1.5. CR protein

Table 5 shows CRP positive percentages in CKD, DM and HF patients, where CRP percentage in CKD patients was (52.0 %). while, in DM patients and HF patients (34.35 ± 7.64) was (50.0 %) and (46.7 %) respectively, compared to control group which was (0.0 %).

Table 5: CRP percentages in studied groups

GROUPS	+ VE	%	- VE	%	Total
Diabetic	15	50.0 %	15	50.0 %	30
Heart Failure	14	46.7 %	16	53.3 %	30
Kidney Failure	13	52.0 %	12	48.0 %	25
Control	0	0.0 %	5	100 %	5
Total	42	46.7 %	48	53.3 %	90
	Ns **Chi-Square = 4.795 P-Value = 0.187**				

Measurement of CRP has become virtually a gold standard as a predictor of morbidity and mortality in CKD patients as an independent marker. Among the biochemical parameters most reliable and studied are the serum total proteins and serum albumin levels, but few studies correlate them with the levels of CRP to understand its co-relational significance [18]. This study showed that inflammation, as measured by CRP level, increases with declining renal function in CKD patients, similar to previous reports [19]. The current study showed an association between CRP and diabetes, as indicated by Pradhan et al. [20], who observed elevated CRP levels in diabetic middle-aged women compared to the healthy control, supporting a possible role of inflammation in the pathogenesis of T2DM. Furthermore, Han et al. reported sex differences in the association of elevated CRP levels with the incidence of T2DM [21]. This strong association in women may be explained by the hormone differences and the higher adiposity percentage [22]. in the study by Marques-Vidal et al. [23], higher CRP levels were associated with all T2DM and IR markers, and these associations persevered after multivariate adjustment. Similarly, the study showed that participants with impaired glucose tolerance had higher CRP levels than euglycemic subjects, although this difference became nonsignificant after BMI adjustment.

3.1.6. Copeptin & Chromogranin A (CgA)

Table 6 shows copeptin levels in CKD, DM and HF patients, where copeptin levels (5.193 ± 0.491) in CKD patients high significantly ($P \leq 0.05$) elevated compared to control group (3.562 ± 0.256). while, in DM patients (4.851 ± 0.42) and HF patients (4.761 ± 0.502), the copeptin levels showed significant ($P \leq 0.05$) elevated compared to control group. CgA levels (2.591 ± 1.051) in CKD patients significantly increased ($P \leq 0.05$) compared to control group (1.223 ± 0.729). while, in DM patients (3.155 ± 0.793) and HF patients (2.998 ± 0.751), the CgA levels showed high significant ($P \leq 0.05$) change compared to control group.

Table 6: Copeptin and chromogranin A levels in studied groups

Groups Parameter	Copeptin (pmol/L)	Chromogranin A (ng/ml)
Control	3.562 ± 0.256 b	1.223 ± 0.729 c
Kidney disease	5.193 ± 0.491 a	2.591 ± 1.051 b
Diabetes mellitus	4.851 ± 0.42 a	3.155 ± 0.793 a
Heart failure	4.761 ± 0.502 a	2.998 ± 0.751 ab

Copeptin is co-secreted with the arginine vasopressin (AVP) upon hemodynamic or osmotic stimuli. Unlike the AVP, copeptin is stable in serum and plasma at room temperature and can be measured as a marker for AVP secretion [24]. In our study, serum copeptin levels were significantly higher in diabetic patients than healthy non-diabetic group; this agrees with Zhu et al. [25], who found that serum copeptin elevation is associated with type-2 diabetes mellitus and diabetic complications, suggesting a role for AVP/copeptin in the pathogenesis of type-2 diabetes mellitus.

Similarly, Asferg et al. [26] found that serum copeptin is associated with insulin resistance, obesity, and metabolic syndrome. In the current study, the mean plasma copeptin level was statistically significantly higher in the CKD group as compared to the control group. Also, it was significantly higher in diabetic patients. These

findings are supported by Bjornstad et al.[27], who reported that copeptin was significantly higher in patients with stages 2 to 5 of CKD in comparison with stage 1 CKD patients. In addition, plasma copeptin is significantly higher in type 1 diabetic patients with albuminuria compared with normoalbuminuric group. Several studies have shown that copeptin levels can predict outcomes in adults with heart failure [28, 29].

In a study of 268 adult patients with advanced heart failure, Stoiser et al. [30] showed that copeptin has a better ability to predict death compared to BNP. Similarly, in a large cohort of adult patients with all the stages of heart failure, Neuhold et al. [31] showed that copeptin has a similar predictive ability of all-cause mortality compared to BNP, but when both were combined, the predictive ability improved.

4. CONCLUSIONS

Based on the results of the current study, both copeptin and chromogranin A can be considered an important indicator in the diagnosis of some chronic diseases.

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