

The Role of the Hormones Copeptin, Cortisol, and the Immune Marker Acute Phase Protein C in the Case of Male and Female Hypertension and Hypertensive Patients

Shatha H. Shaker¹, Zaid M.M. Almahdawi²

¹College of Education for pure Sciences - Tikrit University – Salahaddin – Iraq

²College of Sciences - Tikrit University - Salahaddin – Iraq

Email : shatha.h.shaker@tu.edu.iq

Abstract :

This study was conducted on patients with hypertension and diabetes of both sexes in Salah al-Din Governorate. The study started from the beginning of December 2019 until the first of March 2020, and the study included 90 people distributed into six groups. Blood samples were collected from the patients and healthy subjects and then serum was separated for subsequent tests.

This study aimed to obtain more clarification of some hormonal and immunological varienns in patients with high blood pressure and diabetes, and to know the effect of this increase on the changes in the concentrations of the hormones copeptin and cortisol, as well as studying the role of the inflammational c-rp marker. The results of the study showed a "high significant increase ($p \leq 0.01$) in the concentration of the two hormones copeptin and cortisol in the blood serum of groups of hypertension, hypertension and diabetic patients compared with the healthy control group. A high significant increase ($p 0.01$) in the concentration of c-rp in serum of hypertension , hypertension and diabetic patients compared with healthy control groups.

1- Introduction .

Hypertension (HTN), [1] sometimes called hypertension, is a chronic condition in which the blood pressure in the arteries is high. This elevation requires the heart to work harder than usual in order to be able to push blood into the blood vessels. Blood pressure consists of two numbers, systolic pressure and diastolic pressure, and this depends on the pressure obtained and measured during the contraction of the heart muscle (systole) or relaxation between beats (diastole). Normal systolic blood pressure at rest ranges between 100-140 mm Hg (upper reading) and diastolic between 60-90 mm Hg (lower reading) [2]. Diabetes is a chronic (metabolic) disease characterized by an increase in the level of sugar in the blood hyperglycemia as a result of a relative or complete deficiency of the insulin hormone whose existence has not been truly known yet [3]. Diabetes is one of the most common chronic diseases, and the last report of the World Health Organization found about 415 million people in the world suffering from diabetes in the year 2015 [4], and reports indicate that the rate of diabetes in the world is affected by several factors, including the difference in sex [5]. The traditional view of hormones is that they move to their targets in the bloodstream after secretion from the glands that secrete them. This pattern of emptying (directly into the bloodstream) is called apocrine secretion. The meaning of the term hormone has been extended beyond the original definition of bloodborne secretions, to include similar regulatory substances that are distributed by diffusion across cell membranes rather than the blood system [6]. Copeptin is a glycopeptide that is bound to glucose and contains a pulp rich in leucine, and consists of 39 amino acids [7]. The hormone cortisol is a steroid hormone, secreted by the adrenal

cortex of the adrenal gland connected to the kidneys, as it is secreted in response to psychological or physical stress or a decrease in the level of glucocorticoid hormones in the blood [8]. There are many different conditions in which CRP is overproduced, so a high CRP level does not diagnose a specific disease. An elevated CRP level can support the presence of an inflammatory disease such as, rheumatoid arthritis, rheumatoid muscle pain, or large cell arteritis [9].

2- Materials and methods .

2-1- Samples collection / The study included (90) randomly selected samples belonging to the control group and patients with high blood pressure only and patients with high blood pressure and diabetes whose ages ranged from both sexes (30-70 years), where samples were collected from Health centers in (Al-Qadisiyah region, Al-Alam district, and Samra district). Blood samples were obtained from the humeral vein in a volume of (10ml) by means of a medical syringe in the early morning hours (Fasting) with taking some information concerning each of them, as the blood samples were placed in test tubes containing silicone, and left in a water bath at a temperature of (37). It was then separated in a centrifuge at a speed of 3500 cycles for 15 minutes to obtain blood serum, where it was placed in the Abendorf test tubes after being divided into 0.5 ml in each tube, then the samples were preserved at a temperature. (20-) M and all the information was recorded on it until it was used. After that, hormonal and biochemical tests were conducted in the consulting office of the College of Science / University of Tikrit.

2-2- Distribution of the studied samples into six groups:

- The first group: male patients with high blood pressure and diabetes included (18) persons, their ages ranged between (30-70) years.
- The second group: the male patients with high blood pressure only and their number (18) persons, their ages ranged between (30-70) years.
- The third group: female patients with high blood pressure and diabetes included (18) females whose ages ranged between (30-70) years.
- The fourth group: only female patients with high blood pressure included (18) females whose ages ranged between (30-70) years.
- The fifth group: the control group of healthy males included (9) persons whose ages ranged between (30-70) years.
- The sixth group: the control group of healthy females included (9) females whose ages ranged between (30-70) years.

2-3- To estimate the concentration of the hormone copeptin in the blood serum, the ELISA test kit used the Sandwich-ELISA technique.

2-4- To estimate the concentration of the hormone cortisol in the blood serum, the ELISA test kit used the Sandwich-ELISA technique.

2-5- To estimate the concentration of c-rp in serum, the ELISA test kit used the Sandwich-ELISA technique.

3- Statistical analysis.

The results were analyzed statistically using Analysis of Variance (ANOVA). The arithmetic means of the parameters were compared using Duncan's multiple range test at a significant level ($p < 0.01$) [10].

4- Results and discussion.

4-1- Serum level of the hormone Copeptin in hypertensive and diabetic patients (male) and in hypertensive and diabetic patients (female) and hypertensive patients only (males) and hypertensive patients only (females).

The results of the current study, shown in Figure (4-1), showed that there was a high level of significance at a significant level ($P < 0.01$) for the level of copeptin in the blood serum of the two groups of patients with hypertension and diabetes, of males and females, compared to the control groups of males and females. Significant ($P \leq 0.01$) in the level of copeptin between the two groups of patients with stress only, male and female, compared to the control groups of males and females, and there were no significant differences between the two groups of patients with blood pressure and diabetes, male and female, and between the two groups of patients with pressure only, male and female. And there were no significant differences between the group of stress-afflicted females only and between the two control groups of males and females according to the values mentioned in Table (3) (21.06 ± 152.32), (10.28 ± 153.34), (27.61 ± 168.06) and (11.61 ± 142.42) and (10.15 ± 133.19) and (7.72 ± 138.68) respectively.

Copeptin is derived from cleavage of arginine vasopressin precursor (AVP), which is produced in equal proportion in the hypothalamus and processed during axial transport. AVP is an unstable peptide with a short half-life of 5 to 20 minutes. Unlike AVP, copeptin is a stable and easily measured molecule [11]. He indicated [11] that increased levels of copeptin were associated with worse outcomes in various clinical cases of hypertensive patients, and this is in agreement with the current study, where the results showed a high significant increase in the group of male hypertensive patients only.

Copeptin increases peripheral resistance, and in so doing increases arterial blood pressure. This increases the burden on the heart, as the heart is forced to exert more effort to counteract the peripheral resistance as heart disease increases in development, and this in turn reduces arterial pressure, which in turn stimulates more secretion of copepeptin [12]. The current study showed a high significant increase in the group of hypertensive and diabetic patients from both groups of males and females in the level of copeptin. [13] indicated an increase in the level of copeptin in the serum of patients with diabetes and obesity who suffer from high blood pressure. [14], [15] indicated that an increase in the proportion of copeptin leads to an increase in vasopressin secretion, which causes high blood pressure (systemic and glomerular) because it leads to increased narrowing of blood vessels.

From previous studies, it was found that excessive VP release (caused by, relative dehydration, stress or genetics) in diabetics and from both sexes stimulates the HPA axis and raises glucocorticoid levels leading to the development of a mild phenotype similar to Cushing's syndrome with overweight, obesity, and insulin resistance. [16], and it is one of the reasons that explain the high level of copeptin in the two groups with hypertension and diabetes of both sexes in this study. The reason for the absence of significant differences between the group of women with hypertension and the two groups of healthy

men and women is attributed to this group taking antihypertensive drugs such as copeptin inhibitors [17]. Finally, when comparing groups of male and female patients, the results of the study showed that there is a significant difference in the effect of sex on the level of the hormone copeptin, and it was higher in males than in women, while [18] indicated that there was no significant difference in the effect of sex on the level of copeptin.

*** The different letters on the columns mean that there is a significant difference in the studied groups at a significant level (P <0.01).**

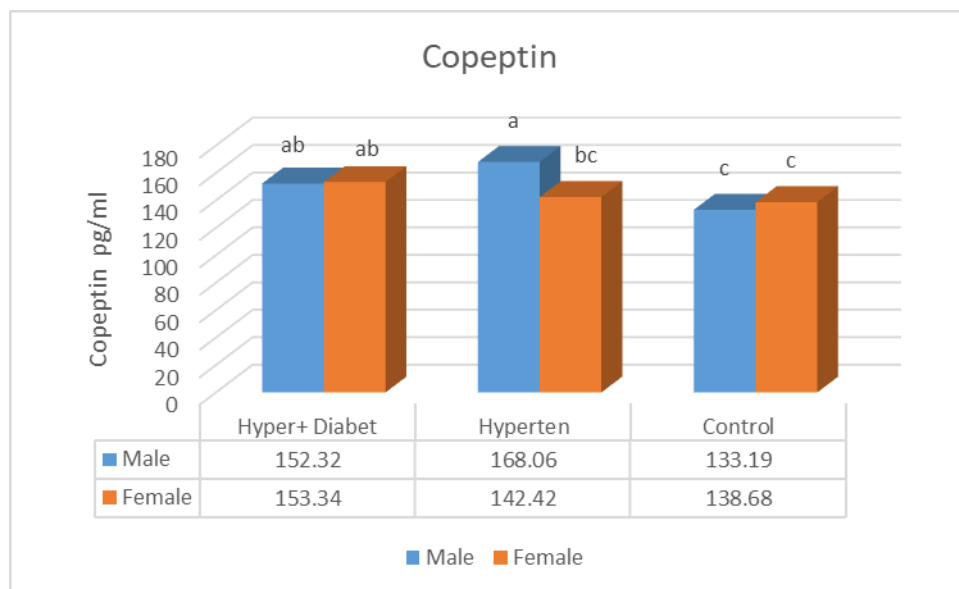


Figure (1-4) The level of copeptin in the blood of patients with hypertension and diabetes (male), hypertensive and diabetic (female), hypertensive patients only (males), hypertensive patients only (females), and the two healthy groups (males and females)

4-2- The level of Cortisol in the blood serum of hypertensive and diabetic patients (male) and in hypertensive and diabetic patients (female) and hypertensive patients only (males) and hypertensive patients only (females).

The results of the current study, shown in Figure (4-2), showed that there was a high significant increase in the level of cortisol at a significant level ($P \leq 0.01$) for the level of cortisol in the blood serum of the two groups of patients with hypertension and diabetes, of males and females, compared to the control groups of males and females, and the presence of high morale at the level Significant ($P \leq 0.01$) in the level of cortisol between the two groups of patients with pressure only, male and female, compared to the control groups of males and females, and there were no significant differences between the two groups of patients with blood pressure and diabetes, males and females, and between the two groups of patients with blood pressure only male and female, according to the mentioned values In Table (3) (3.228 ± 58.46), (4.43 ± 55.25), (6.89 ± 57.93), (6.05 ± 56.26), (4.81 ± 51.58) and (6.08 ± 49.76), respectively.

Since most cells in the body contain cortisol receptors, they affect many different functions in the body. Cortisol can help control blood sugar levels, regulate metabolism, help reduce inflammation, and aid in memory formation. It has a controlling effect on salt and water balance and helps control blood pressure. In women, cortisol also supports fetal growth during pregnancy. All of these functions make cortisol an important hormone for

protecting public health [19]. Hypertension is one of the most common and alarming features of the disease. Its severity is mainly related to the duration and severity of elevated cortisol levels in the blood serum as cortisol narrows the arteries, while the hormone epinephrine increases your heart rate. By working together, they force your blood to pump harder and faster. This leads to high blood pressure [20], which is in agreement with the current study, where the two groups of hypertensive men and women showed high levels of cortisol. It was indicated [21] that the odds of developing depression in diabetics (high increases of cortisol level) were twice that of the non-diabetic comparison groups and that there was no difference according to gender or type of diabetes. When the adrenal glands secrete cortisol into the bloodstream, the hormone leads to the flow of glucose, which provides an immediate source of energy as it prevents the production of insulin, so glucose will not be stored, but will be available for immediate use, and this was also agreed with this study, as the two groups of patients with hypertension and diabetes, male and female, showed a high "high significant" levels. Cortisol. The stress hormone (cortisol) is associated with higher blood sugar levels in individuals with type 2 diabetes (T2D), indicating that cortisol plays a harmful role in contributing to blood sugar in this population. The high incidence of Coronavirus Disease 2019 (COVID-19) has been shown to be stressful for individuals most at risk of dying from the disease, including those with underlying conditions such as diabetes [22].

- The different letters on the columns mean that there is a significant difference in the studied groups at a significant level (P <0.01).

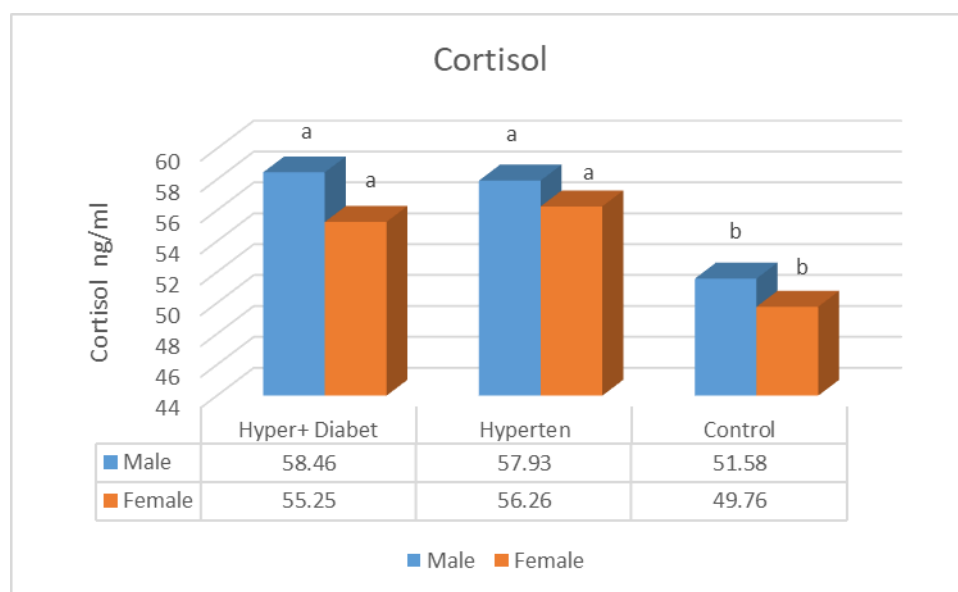


Figure (2-4) The level of cortisol in the blood of patients with hypertension and diabetes (male), hypertensive and diabetic (female), hypertensive patients only (males), hypertensive patients only (females) and the two healthy groups (males and females)

4-3 - The level of C-reactive protein (c-rp) in the blood serum of hypertensive and diabetic patients (male) and in hypertensive and diabetic patients (female) and hypertensive patients only (males) and hypertensive patients only (females).

The results of the current study shown in Figure (4-3) showed that there was a high significant increase in the level of c-rp at the level of (P≤0.01) in the blood serum of the

two groups of patients with hypertension and diabetes, of males and females, compared to the control groups of males and females, and the presence of high morale at Significant level ($P \leq 0.01$) in the c-rp level among the group of patients with stress only of males compared to the control groups of males and females, and the presence of a high significant level ($P \leq 0.01$) in the level of c-rp among the group of patients with pressure only from females. Compared to a control group of males, There were no significant differences between groups of patients with hypertension, diabetes, and hypertensive patients only and from both sexes, and there were no significant differences between the group of patients with pressure only from females compared to the control group from females according to the values mentioned in Table (3) (64.1 ± 292.4) and (65.9 ± 323.8), (66.2 ± 295.1), (52.0 ± 278.7), (21.26 ± 196.9) and (84.6 ± 247.8) respectively.

C-RP is a substance that the liver produces in response to inflammation. Other names for C-RP are highly sensitive C-reactive protein (hs-CRP) and highly sensitive C-reactive protein (us-CRP). A high level of C-RP in the blood is a sign of inflammation, and it can be caused by a variety. Of cases, from infection to cancer [23]. High levels of C-reactive protein can also indicate inflammation of the heart arteries, which may mean a higher risk of heart attack. However, the C-RP test is a very nonspecific test, and C-RP levels can be elevated in any inflammatory condition [23].

He indicated [24] that high c-rp was associated with an increased risk of developing T2DM type II diabetes for both sexes of patients with hypertension and diabetes in Tikrit, and the results of his study show a strong relationship between C-RP and T2DM. T2DM is classified as a chronic disease that develops over time and is affected differently by many factors, including genetics and lifestyle. Another study conducted by [25] demonstrated that there is no significant association between C-RP and hypertension in perimenopausal or postmenopausal women, and this is in agreement with the results of the current study, whose results showed close to normal ratios in the group of women with stress only. Comparison with a control group.

The study published by Tanno-Sobetsu, as a prospective cohort study conducted in Japan, showed that there is no relationship between elevated C-RP alone and the increased development of hypertension in both men and women and this is what I disagree with this study. However, most studies suggested that C-RP was positively associated with hypertension [26].

- **The different letters on the columns mean that there is a significant difference in the studied groups at a significant level ($P < 0.01$).**

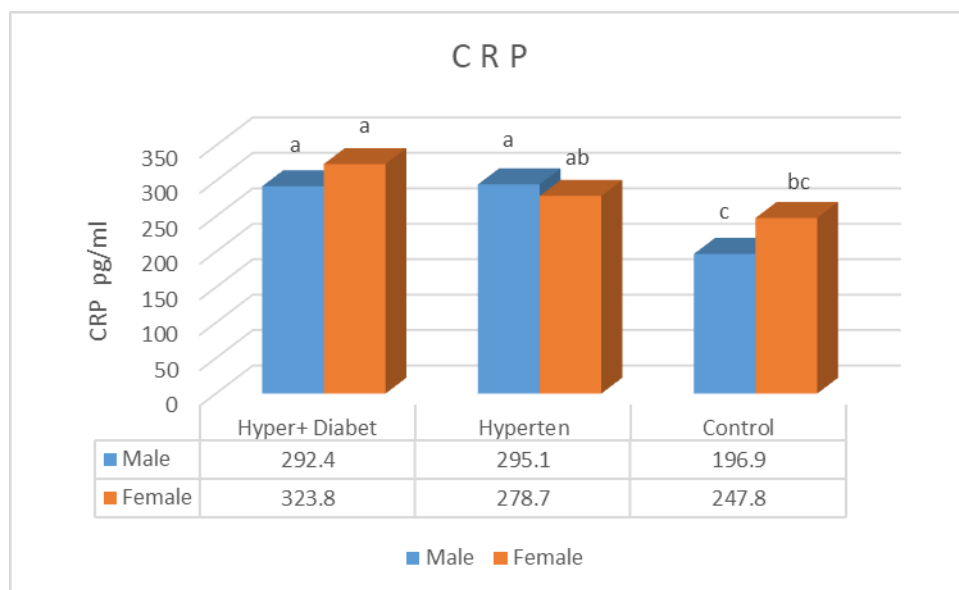


Figure (3-4) The level of (c-rp) in the blood of patients with hypertension and diabetes (males), hypertensive and diabetic patients (females), hypertensive patients only (males), hypertensive patients only (females), and the two healthy groups (males and females)

5- Conclusion .

There was a significant increase in the level of Copeptine and cortisol in people with high blood pressure, people with high blood pressure and diabetes, and of both sexes, compared to healthy people of both sexes. There was a significant increase in the level of C-reactive protein in men with high blood pressure and people with high blood pressure and sugar of both sexes compared to healthy people of both sexes, and there were no significant differences between women with stress only with the group of healthy people of both sexes in the level of Acute phase protein c-rp.

Reference :-

- 1- World Health Organization(2013). A global brief on hypertension . Report ,April 2013. Contract No.: WHO/DCO/WHD/2013.2.
- 2- Al-Alouji, Sabah Nasser 2014). Physiology. Dar Al-Fikr for printing and publishing.
- 3-Nicholson, G. and Hall, G.M. (2016).Diabetes mellitus :New drugs for anew epidemic .Brj , Anaesth , 107:65-73.
- 4-Zimmet, P.; George-Alberti, K. Magliano, D. and Bennet, P.(2016). Diabetes mellitus statistics on prevalence and mortality facts and fallacies.Nat .Rev. Endocrinol ., 12:616-622.
- 5-Baynest , H.W. (2015) . Classification , Pathophysiology , Diagnosis and Management of Diabetes Mellitus. J Diabetes Metab. 6 : 541-49 .
- 6-Rabinstein, A.A.(2018). Optimal blood pressure after intracerebral hemorrhage: still a moving target. Stroke., 49:275-276. 10.1161/ STROKEAHA .117.020058.
- 7-Spanakis, E. K.; Wand, G. S.; Ji, N. and Golden, S. H. (2016). Association of HPA axis hormones with copeptin after psychological stress differs by sex. Psychoneuroendocrinology, 63: 254-261.
- 8-Hoehn, K.;and Marieb, EN., (2010). Human Anatomy & Physiology. San Francisco: Benjamin Cummings. ISBN 978-0-321-60261-9.

- 9-Sindhu, S.; Singh, H.K.; Salman, M.T.; Fatima, J.; and Verma, V.K. (October 2011). "Effects of atorvastatin and rosuvastatin on high-sensitivity C-reactive protein and lipid profile in obese type 2 diabetes mellitus patients". *Journal of Pharmacology & Pharmacotherapeutics*. 2 (4): 261–5.
- 10-Al-Rawi, Khashi Mahmoud. (2000). *Introduction to Statistics, Second Edition*, College of Agriculture and Forestry, Mosul.
- 11-Tasevska, I.; Enhörning, S.; Christensson, A.; Persson, M.; Nilsson, P.M.; and Melander, O. (2016). Increased Levels of Copeptin, a Surrogate Marker of Arginine Vasopressin, Are Associated with an Increased Risk of Chronic Kidney Disease in a General Population. *Am J Nephrol.*;44:22–8.
- 12-Yavcin, O.; Askin, L.; Secen, O.; Turkmen, S.; Akturk, E.; Tanriverdi, O. and Necati Dagli, M. (2019). Copeptin levels in patients with coronary artery ectasia. *Interventional Medicine and Applied Science*, 11(2), 112-116.
- 13- Al-Amin, Raghad Tahseen Thanoun Ahmad (2020). The role of plasminogen activator 1, vasvatin and related measures as predictive indicators of risk of arterial thrombosis and related criteria in obese men with diabetes and non-patients, Tikrit University, College of Science.
- 14- Halawa, M.R.; Gaafar, A.A. and Abdullah, A.A. (2017). Study of the level of Copeptin in patients with Diabetic Retinopathy. *The Egypt. J. Hosp. Med.* 69(1): 1757-63.
- 15-Abd El Dayem, S.M.; Battah, A.A.; Abo El Magd, El Bohy. (2019). Copeptin as a Biomarker of Atherosclerosis in Type 1 Diabetic Patients. *J Med Sci.* 13:1-4.
- 16- Rashad, N.M.; Ezzat, T.M.; Allam, R.M.; Ashour, W.M.; Ali, A.E.; and Soliman, M.H.(2019). Serum copeptin as a diagnostic and prognostic biomarker of coronary artery disease among patients with type 2 diabetes mellitus. *Egypt J Intern Med*;31:696-702.
- 17-Zhang, P.; Zhu, L.; Cai, J.; Lei, F.; Qin, J.J.; Xie, J., et al. (2020). Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin ii receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res.*;126:1671–81.
- 18- Al-Jumaili, Wissam Subhan Khalaf Muhammad (2019). Partial purification of the copeptin hormone and its relationship to some biochemical variables in patients with chronic renal failure in the city of Kirkuk. PhD thesis, College of Education for Pure Sciences, University of Tikrit.
- 19-Nieman, L.K.; Biller, B.M.K.; Findling, J.W.; Murad, M.H.; Newell-Price, J.; Savage, M.O.; et al.(2016). Treatment of cushing's syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.*100:2807–31. doi: 10.1210/jc.2015-1818.
- 20-Hardeveld, F.(2014) . Increased cortisol awakening response was associated with time to recurrence of major depressive disorder. *Psychoneuroendocrinology* ;50:62–71.
- 21-Hasan, S.S.; Clavarino, A.M.; Mamun, A.A.; and Kairuz, T. (2014). Incidence and risk of diabetes mellitus associated with depressive symptoms in adults: Evidence from longitudinal studies. *Diabetes Metab. Syndr. Clin. Res. Rev.* ;8:82–87.
- 22-Dias, J.P.; Joseph, J.J.; Kluwe, .B and et al.(2020) . The longitudinal association of changes in diurnal cortisol features with fasting glucose : MESA . *Psychoneuroendocrinology* . Published online,. doi:10. 1016/j. psyneuen. 2020.104698.
- 23-Dongway , A.C.; Fagged , A.S.; Zaki , H.Y. and Abdulla , B.E (2015). C- reactive protein is associated with low density lipoprotein – cholesterol and obesity in type 2 diabetes Sudanese . *Diabetes Metab . Syndro . obes* ; 8: 427- 35 .
- 24-Taha, Muhannad Imad Majeed (2018). Evaluating the role of a number of physiological and immunological factors in type 2 diabetics in Tikrit city. College of Science, University of Tikrit.

25-Ebong, I.A.; Schreiner, P.; Lewis, C.E.; Appiah, D.; Ghelani, A.; and Wellons, M.) 2016.(
The association between high-sensitivity C-reactive protein and hypertension in women of
the CARDIA study. *Menopause.*;23(6):662–8.

26-Wang, Z.; Chen, Z.; Zhang, L.; Wang, X.; Hao, G.; Zhang, Z.; Shao, L.; Tian, Y.; Dong,
Y.; and Zheng, C.(2018). Status of hypertension in China: results from the China
hypertension survey, 2012-2015. *Circulation.*;137(22):2344–56.