Article

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Following up on the repercussions on patients with high blood pressure and diabetes, including atherosclerosis

Ula Jabal Mohammed[1] and Basim M. Ali [2]

1.2Chemistry Department, Science, University Of Kufa, Al Najaf, Iraq;

$E_{mail;}$ ulaj.almaamori@student.uokufa.edu.iq; basimm.radhi@uokufa.edu.iq

Abstract

Background & objective: The current investigation examined the relationship between cortisol levels and adrenomedullin (ADM) in patients with type 2 diabetes mellitus (DMT2) and hypertension (HT). As DMT2 patients experience HT at a rate of (40–60)%, DMT2 is thought to be one of the known complications of HT. The combination of these two conditions can result in the development of stroke and myocardial infarction, which are the primary causes of death in Iraq due to the disease progressing to atherosclerosis and diabetic nephropathy.

Methodology: The study included sixty individuals with DMT2 and HT, ages 45 to 65 (36 males and 24 females). Samples were taken from the Al-Sadr Teaching Hospital's diabetic section in Najaf Al-Ashraf, Iraq. As a control group, however, thirty healthy individuals (15 men and 15 women) were chosen. The ELISA

technique was used to measure the levels of cortisol and ADM. This was a case-control study.

Results: In comparison to the control group, the ADM and cortisol concentrations in DMT2 patients were significantly higher, according to the data. The results of this study indicate that DMT2 and HT patients had significantly higher levels of cortisol and ADM than the control group did. Furthermore, high levels of ADM in patients are thought to be an early marker of DMT2 and HT disease detection, indicating the positive correlation between cortisol and these two diseases.

Conclusions: The discoveries of this exploration propose that those with atherosclerosis could display a certain immunity to cortisol, despite receiving therapy. While treatment persists, the quantities of ADM, ST2, cholesterol, and low-density lipoprotein appear to stay high in these individuals. In contrast, cortisol is considered a more sensitive marker for identifying atherosclerosis.

Abbreviations: type 2 diabetes mellitus-DMT2; hypertension- HT; ADM-Adrenomedullin; Stromelysin-2-ST2;HDL-high density lipoprotein; LDL-low density lipoprotein; TG-triglyceride; BMI-body mass index; matrix metalloproteinase-10- (MMP-10); hypothalamic-pituitary-adrenal -HPA.

Key Words: diabetes mellitus, hypertension, adrenomedullin, stromelysin-2, cortisol, hormone, enzyme, peptide

1.Introduction

As DMT2 patients experience HT at a rate of (40–60)%, DMT2 is thought to be one of the known complications of HT. The combination of these two conditions can result in the development of stroke and myocardial infarction, which are the primary causes of death in Iraq due to the disease progressing to

atherosclerosis and diabetic nephropathy [1]. Peripheral vascular resistance and the volume of circulating fluid interact to regulate blood pressure. The force of myocardial contraction and the volume of blood fluid in circulation control each other [2]. The equilibrium between the storage and excretion of sodium and myocardium [3] Sympathetic nervous system activity and heart function regulate force [4] . Vascular remodeling, renin-angiotensin system-related vasoactive factors, and vascular tone all control peripheral vascular resistance [5]. This suggests that the kidney's salt excretion is increased at pressure levels above the threshold [6]. In cases of severe salt sensitivity, blood pressure rises, and thus sodium is excreted through the urine. Moreover, high blood pressure causes the inception to shift to a level higher than normal, excretion of salt through the kidneys into the urine leads to complications of chronic kidney disease, especially in elderly patients, and when HT combines with DMT2 it can lead to serious[7] . The most important of these diseases is atherosclerosis, which is preceded by endothelial dysfunction, vascular remodeling, oxidative stress, inflammation, vasoactive substances, cytokines, and chemokines, [8] in addition to growth factors, as these factors interact with each other and can cause and lead to Advanced development and defect in the lining of blood vessels, resulting in damage to various organs of the body [9].

Adrenomedullin(ADM) primarily functions as a vasoactive hormone, and a number of cardiac conditions as well as illnesses like hypertension, chronic renal failure, and congestive heart failure are associated with elevated plasma concentrations of ADM. Research indicates that ADM is crucial for maintaining cardiac control as well as fluid and electrolyte balance [16] . From a physiological standpoint, ADM regulates vascular tone and has a potent, long-lasting hypotensive impact. ADM maintains the physiological equilibrium of the heart, blood vessels, and kidneys in addition to its vasodilating action. These effects are

mediated by an increase in the glomerular filtration rate. Moreover, ADM stimulates the relaxation of nitric oxide-dependent vascular arteries and prevents the production of angiotensin II and endothelin-1 [17]. Research has demonstrated that raising the concentration of ADM causes renin activity to rise significantly, which in turn causes the production of aldosterone to be increased by angiotensin II. This suggests that ADM dilates the renal blood vessels by releasing nitric oxide [18]

Another member of the matrix metalloproteinase family is called stromelysin-2 (ST2), or matrix metalloproteinase-10 (MMP-10). Similar to other matrix metalloproteinases, ST2 plays a role in the extracellular matrix's remodeling and disintegration. Numerous cell types, such as macrophages, epithelial cells, and fibroblasts, generate ST2. It must be activated in order to release its enzymatic activity after being secreted as an inert zymogen [19]. Type II collagen is the primary substrate for ST2, and it is a crucial part of cartilage. It can also break down other elements of the matrix, including elastin, gelatin, and type IV collagen. Apart from its function in tissue remodeling, ST2 has been connected to other physiological and pathological processes, such as inflammation, cancer metastasis, wound healing, and embryogenesis.

The adrenal cortex produces cortisol, which is the primary stress hormone in humans. The hypothalamic-pituitary-adrenal (HPA) axis controls and secretes cortisol. Corticotropin-releasing hormone (CRH) is secreted by the hypothalamus in response to stress. CRH then triggers the pituitary gland to release adrenocorticotropic hormone (ACTH), and the bloodstream then carries ACTH to the adrenal gland, specifically in the cortex, where it produces cortisol [22].Being a glucocorticoid hormone, cortisol can have a major impact on the onset and course

of hypertension by altering the body's fluid and electrolyte balance and encouraging the kidneys to retain more salt and water, which increases blood volume. Elevated blood volume may be a factor in hypertension. Additionally, cortisol increases blood vessel sensitivity to vasoconstrictors like angiotensin II. Blood pressure and peripheral resistance are raised as a result of this elevated vascular tone. Insulin resistance is linked to the development of high blood pressure and can be brought on by cortisol. The vasodilatory effects of insulin are impeded by insulin resistance, which raises blood pressure. Angiotensin II and aldosterone production can rise when the renin-angiotensin-aldosterone system (RAAS) is activated, which is a response to cortisol. Strong vasoconstrictor angiotensin II is present, and aldosterone encourages the retention of salt and water, both of which can increase blood pressure. Cortisol has the ability to increase sympathetic nervous system activity, which raises peripheral resistance, heart rate, and contractility. Elevated sympathetic activity has the potential to exacerbate hypertension [(23)].Being a glucocorticoid hormone, cortisol can have a major impact on the growth and development of DMT2 because it decreases glucose uptake and utilization in peripheral tissues like muscles and adipose tissue and increases gluconeogenesis—the liver's process of producing glucose from non-carbohydrate precursors. Cortisol's activities raise blood glucose levels. Cortisol causes insulin resistance, which impairs the ability of target tissues to respond to insulin, which leads to decreased insulin sensitivity and thus decreased cell absorption of glucose, which contributes to high blood sugar. Chronic exposure to high levels of cortisol can impair the function and secretory capacity of pancreatic beta cells and this can lead to decreased insulin production, further exacerbating the development of DMT2. Visceral fat storage in the abdomen is facilitated by cortisol and is closely linked to the development of DMT2 and insulin resistance. One of the main risk factors for DMT2 and metabolic

syndrome is excess abdominal fat. Because of its anti-inflammatory properties, cortisol may be partly responsible for the low-grade chronic inflammation seen in DMT2. This inflammatory illness has the potential to It might impede glucose homeostasis and insulin sensitivity [24].

2. METHODOLOGY

This is a case-control study. The present study included sixty patients with DMT2 and HT (36 males and 24 females), and a control group of thirty healthy individuals. Their ages ranged from 45 to 65 years. Each patient was registered at Al-Sadr Teaching Hospital in Najaf, Iraq, under the Diabetes and Hypertension Unit. Using a blood pressure monitor and Hb A1c test, all patients were diagnosed. As a control group, thirty healthy individuals (15 males and 15 females) were selected and were chosen because their age ranges were close to the patients' group. All subjects were not smokers and did not suffer from thyroid diseases.

2.1. Blood sample collection

Five milliliters of venous blood samples were drawn using a disposable needle and plastic syringes from each patient and control subjects without a tourniquet , in the morning who had fasted for 10 hours . Samples were transferred into a gel tube these samples were separated by a centrifuge at 3000 rpm for 15 minutes.

2.2. Serum level of enzyme and hormones

ADM and ST2 were measured by ARS BIOCHEM company (China), and cortisol was measured by DRG company (Germany) in serum enzymatically by ELISA technique.

2.3. Serum level of lipid profile

While Using a spectrophotometer approach, the levels of cholesterol, triglycerides, HDL, and LDL were measured. A specific kit from the Spinreact company was used for each parameter (in Spanish).

2.4. Statistical analysis

Using statistical software, the conclusions drawn from analyzing biochemical data were statistically calculated (SPSS 26). The F-distribution analysis's mean, variance, and conclusions were discovered. Using Microsoft Excel (2016) and SPSS 26, a significant value or probability assessment below 0.05 ($p<0.05$) was found [8] .

3. RESULTS

3.1. Demographic characteristics

Table 1 shows the demographic characteristics of the study population. The mean age of patients with atherosclerosis was 59.000 ± 7.882, which was very close to that of controls (59.933 ± 7.35) with no significant difference. Also, the two groups were comparable BMI with no significant differences.

Table 1: Comparative demographic data of the study population

Variables	Patient Mean±SD	Control Mean±SD	p-value
Age	**59.0±7.88**	**59.9±7.35**	**0.637**
BMI(kg/m^2)	**28.9±2.59**	**30.0±3.01**	**0.147**

Data presented as Mean ± SD

3.2. Hormonal and enzyme profile

Table 2 shows the levels of the cortisol, ADM and ST2 in patients compared to the control group, as it shows a significant increase in the levels of cortisol in patients compared to the control group.

Table 2: Hormonal and Enzyme profile in patients and controls

	Patient		Control		
	Mean±	S.D	Mean±	S.D	P-value
Cortisol	99.99±	42.88	79.59±	32.77	0.043
ADM	16.4312 ±	4.39	15.37 ±	3.22	0.292
ST2	1.5189 ±	0.279	1.51 ±	0.39	0.963

Data presented as Median (Range); P < 0.05 considered as significant

3.3. Lipid profile and atherogenic index

Table (3) appearances significant increase ($p<0.05$) in total TG and LDL in patients as compared with the control group. In addition, the results shows significant decrease in HDL between two groups , no significant change in cholesterol as compared with the control group.

Table 3: Lipid profile in patients and controls

	Patients		Control		Total		
	Mean±	S. D	Mean	±S. D	Mean±	S. D	P-value
TG	206.9±	98.60	133.26	±27.90	170.091±	80.87	0.001
HDL	33.8±	14.56	40.28	±8.76	37.07±	12.35	0.043
CHO	170.06±	63.74	152.03	±37.42	161.05±	52.61	0.187
LDL	111.52 ±	46.52	89.89	±33.61509	100.70±	41.69	0.044
VLDL	41.38±	19.72	6.6	5±5.58123	34.01±	16.17	0.001

IndexI	**3.96702**	**3.92 ±1.23**	**5.11± 3.144**	**0.003**
	6.28±			
IndexII	**3.51264**	**2.30 ±0.94028**	**2.76692**	**0.002**
	4.43±		**3.36±**	
IndexIII	**±5.00**	**±1.06**	**4.09453**	**0.001**
	7.38	**3.46**	**5.42±**	

Data presented as Median (Range); P < 0.05 considered as significant

3.3. Correlation between all variables in patients

Spearman's correlation test was used to explore the possible correlation of all parameters in patients and controls. Cortisol displayed a significant positive correlation with parameters ST2 and LDL, Cortisol showed a significant negative correlation with HDL . On the other hand , ADM appearance positive correlation with TG and VLDL,as well as ST2 showed a significant positive correlation with cortisol as shown in (Table 4)

Table 4: Spearman's correlation of variables in patients

		TG	HDL	LDL	CHO	VLDL	Cortisol	ST2	ADM
TG	r	1	-.338	.487**	.721**	1.000**	.182	.168	.532**
	p		.068	.006	.000	.000	.336	.376	.002
HDL	r	-.338	1	-.559**	-.425*	-.338	-.546**	-.208	-.114
	p	.068		.001	.019	.068	.002	.270	.550
LDL	r	.487**	-.559**	1	.446*	.487**	.428*	.231	.269
	p	.006	.001		.014	.006	.018	.220	.150
CHO	r	.721**	-.425*	.446*	1	.721**	.128	.232	.332
	p	.000	.019	.014		.000	.501	.218	.073
VLDL	r	1.000**	-.338	.487**	.721**	1	.182	.168	.532**
	p	.000	.068	.006	.000		.336	.376	.002
Cortisol	r	.182	-.546**	.428*	.128	.182	1	.549**	.083
	p	.336	.002	.018	.501	.336		.002	.663
ST2	r	.168	-.208	.231	.232	.168	.549**	1	-.194
	p	.376	.270	.220	.218	.376	.002		.305
ADM	r	.532**	-.114	.269	.332	.532**	.083	-.194	1
	p	.002	.550	.150	.073	.002	.663	.305	

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

4.Discussion

The results in Table (1) indicate no change in age and body mass index (BMI) between the patient and control groups. When comparing the patient group with the control group in the cortisol analysis in table(2), the relationship was found to be significant (p value = 0.004). This is due to increased glucose levels in diabetics, which leads to increased insulin resistance, which in turn leads to activation of the HPA axis and increased secretion of cortisol. As for the effect of cortisol on HT, it is due to the fact that cortisol enhances the secretion of vascular hormones such as angiotensin, which leads to contraction of blood vessels and thus increased blood pressure. Also, HT and DMT2 are always accompanied by an increase in psychological and physiological stress, which leads to chronic stress, thus stimulating the HPA axis and thus releasing cortisol[25] . The same

table also shows that there is no statistically significant relationship in the level of ADM (P value = 0.296) and ST2 (P value = 0.926) between the two groups of patients and control. This may be due to DMT2 and HT being considered low-inflammatory diseases, as well as individual differences and the need for a larger number of patients to know the effect of these two vital compounds on DMT2 and HT disease, in addition to the use of treatments that affect the work of the ADM hormone and the ST2 enzyme. All of these factors lead to the appearance of non-significant results for these two compounds [(21)]. One of the hallmarks of DMT2, a complicated metabolic disease, is an observably elevated blood glucose level. This elevated level raises the risk of several conditions, such as vascular and metabolic diseases, particularly when diabetes is coupled with hypertension and dyslipidemia (10). Insulin resistance and a defect in insulin secretion, or relative insufficiency in insulin secretion, are thought to be the primary causes of blood vessel remodeling, which in turn causes disruption of the pancreatic ß-cells and impairs insulin production (11). Insulin resistance in DMT2 causes ß-cells to secrete more insulin, which results in a deficiency in ß-cell function, since ß-cell function is thought to be both sufficient and essential for the disease's development. Diabetes is frequently not identified for a long time, which causes ß-cell function to decline by 50% (12). Both hyperglycemia and hyperinsulinemia can encourage vascular remodeling in the early stages of diabetes. Vascular remodeling occurs gradually, which increases peripheral artery resistance to eventual collapse under high blood pressure. The loss of pancreatic cells and subsequent attenuation of insulin release due to advanced stages of vascular remodeling reduce insulin's ability to reabsorb salt (13).One of the most frequent complications for diabetics is high blood pressure. Over time, high blood pressure might result from diabetes-related blood vessel damage. Diabetes and high blood pressure both significantly raise the risk of major health issues, such as impaired

kidney function from high blood pressure in diabetics resulting in diabetic nephropathy, which can cause kidney failure. The risk of vision loss increases when small blood vessels in the eye are damaged by high blood pressure retinopathy. Diabetes and high blood pressure both contribute to cardiovascular disease, which increases the risk of heart attacks, strokes, and other cardiovascular problems (14).Nerve damage is more likely to occur and worsen with high blood pressure in people with diabetes, causing peripheral neuropathy. Careful management of both high blood pressure and diabetes through lifestyle changes, medications, and regular monitoring is essential to reduce the risk of these devastating diabetes complications. Maintaining blood pressure, blood sugar and other key health markers within recommended levels can greatly improve outcomes for people with both conditions (15). ST2 supports the growth, regeneration, and repair of a variety of tissues. Because this enzyme is linked to both the process of metabolism and the chronic inflammation that is associated with diabetes, studies have revealed a rise in ST2 levels in DMT2 patients. Insulin resistance may occur as a result of chronic inflammation. Additionally, ST2 compromises blood vessel integrity and plays a role in the emergence of blood vessel-related disorders associated with diabetes, such as cardiovascular disease. Furthermore, ST2 can be utilized as a biomarker for the diagnosis or monitoring of diabetic patients (20). Regarding HT's impact on ST2, studies show that this enzyme contributes to the formation of high blood pressure by assisting in the organization and reconstruction of the extracellular matrix, which modifies the characteristics and makeup of blood vessel walls and directly affects high blood pressure. Thus, the risk of cardiovascular disease is increased by vascular hypertension (21).

Table (3) shows that there is a statistically significant relationship in TG (p value = 0.001) when comparing patients and control groups. There is also a

significant relationship in the levels of LDL (p-value=0.044), VLDL (p-value=0.001), and HDL (p-value=0.001), because lipid level plays a crucial role in individuals with type 2 diabetes (DMT2) and high Blood pressure (HT), as the results showed a significant increase in TG, LDL.C, and VLDL.C levels, and a significant decrease in HDL.C levels due to metabolic syndrome in patients with diabetes. High blood pressure mainly affects fat metabolism, which Underscores the need for management strategies designed to effectively assess cardiovascular risk in these patients and correlate carbohydrate metabolism with lipid metabolism, leading to disruption of lipid metabolism. Therefore, dyslipidemia in patients with hypertension and DMT2 is an indicator of coronary artery disease. The results of this study concluded that there is a positive relationship between patients with DMT2 and high blood pressure and high lipid levels, supporting the hypothesis that dyslipidemia is an important complication of patients with type 2 diabetes and high blood pressure. Several previous studies have also indicated the relationship between hyperlipidemia and hypertension. Eating saturated fats, cholesterol and other sources of calories daily, and disturbances in lipid levels, leads to high levels of triglycerides in the blood and high levels of cholesterol, which causes high blood pressure [26] [27].

The table (4) shows that there is a positive and significant relationship (r = 0.532) between ADM and TG (p value = 0.002). This is due to insulin resistance, oxidative stress, and endothelial cell injury, which contribute to higher ADM and TG levels in DMT2 and HT patients. DMT2 patients have high triglycerides, which are associated with obesity, hyperlipidemia, and hyperglycemia, all of which are major causes of cardiovascular disease, and both of which are associated with chronic inflammatory conditions [28] thus increasing ADM production. The concentration of TG also increases due to insulin resistance, which leads to an increase in the production of TG in the liver, a decrease in the

body's use of TG, and an increase in its production in the liver, thus increasing the concentration of TG in the bloodstream [29].In the same table, there is a significant and positive relationship (p-value = 0.018) (r=0.481) between cortisol and LDL levels. The reason for this is that cortisol secretion increases in the case of HT due to increased stress and stress, and high cortisol levels lead to the liver producing cholesterol, especially LDL. As for DMT2, increased cortisol concentration increases insulin resistance, thus reducing the removal of LDL from the blood and increasing its production in the liver. Increased cortisol also stimulates the liver to produce LDL and reduces the activity of the receptors responsible for removing LDL from the bloodstream, as some studies have confirmed. While cortisol is related to HDL, the relationship (r = -0.546) between them was found to be negative (p value = 0.002). The reason for this inverse relationship is that cortisol reduces the enzymes responsible for manufacturing HDL in the liver. It also increases the removal of HDL from the circulatory system through by stimulating the catabolism of molecules, it also prevents the entry of HDL into the liver again for reuse. Oxidative stress and increased inflammation in patients with DMT2 and HT also lead to a deterioration in HDL function [30].The same table also shows that there is a positive and significant relationship (r = 0.53) between cortisol and ST2 (p value = 0.002). The reason for this relationship is the ability of cortisol to stimulate ST2 production in many cell types, such as vascular cells and inflammatory cells, in addition to activating intracellular signaling pathways and stimulating pathways associated with oxidative stress. These pathways lead to increased gene transcription of the ST2 enzyme [31].

5.Conclusions

The discoveries of this exploration propose that those with atherosclerosis could display a certain immunity to cortisol, despite receiving therapy. While treatment

persists, the quantities of ADM, ST2, cholesterol, and low-density lipoprotein appear to stay high in these individuals. In contrast, cortisol is considered a more sensitive marker for identifying atherosclerosis.

6. Data availability

The numerical data generated during this research is available with the authors.

7. Acknowledgments

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