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Physiological and immunological study of hypertensive patients treated with candesartan

Salah Abd Ali[1]*, Suha Abdul-Khaliq Al-Jowari [2]
[1] *Department of Biology, College of Science University of Baghdad, Karbala, Iraq*
[2] *Department of Biology, College of Science University of Baghdad, Baghdad, Iraq*

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Abstract

Hypertension is the primary cause of cardiovascular disease and early mortality globally, it is a complex feature Determined by many factors endogenous mechanisms, genetic factors, physiological systems and environmental exposures variances. In recent years, there has been growing scientific interest and research focused on the immunological aspects of antihypertensive medications. Among these, Candesartan has emerged as a prominent subject of study. It has been demonstrated to reduce the inflammatory reactions associated with hypertension. The present study was conducted at Imam Hussein Teaching Hospital in the holy city of Karbala from December 20, 2022 to May 22, 2023. There were three distinct groups in the study which are (G1) healthy people, (G2) those receiving medication other than candesartan for their hypertension and (G3) patients receiving candesartan treatment for hypertension to evaluate various physiological parameters in order to ascertain the impact of candesartan on these samples such as serum sodium, serum potassium, and Adiponectin, as well as the investigation of some immunological markers like Interleukin1(IL-1), Interleukin18(IL-18) and Tumor Necrosis Factor(TNF). The study findings showed statistically significant differences in the mean levels of TNF, Interleukin-1, Interleukin-18, serum sodium, serum potassium, and adiponectin between the study groups. The current study was designed to obtain more clarification of some physiological and Immunological parameters in Iraqi hypertensive patients treated with candesartan, and determine the essential role of some physiological parameters such as, (serum sodium, serum potassium, and adiponectin), and Immunological parameters such as, [pro- inflammatory cytokines like, Interleukin-1(IL-1), Interleukin-18, and Tumor Necrosis Factor alpha (TNF-α)]. The result of physiological parameters showed a high significant increasing ($P<0.05$) in the concentration of serum potassium level in group of hypertension patients treated with candesartan (G3) while the concentration of serum sodium and adiponectin showed a significant decreasing ($P<0.05$) in the same group (G3) compared with control healthy group(G1), and positive control group (G2). The results of Immunological parameters including Interleukin-1, Interleukin 18 and Tumor necrosis factor- alpha showed that there was a high significant increasing ($P<0.05$) in the concentration of control healthy group(G1), and positive control group (G2) compared with hypertension patients treated with candesartan (G3).

Keywords: Hypertension, Candesartan, Adiponectin, Tumor Necrosis Factor, serum sodium and potassium.

*Email: salah.abd1102a@sc.uobaghdad.edu.iq

دراسة فسيولوجية ومناعية لمرضى ارتفاع ضغط الدم المعالجين بالكانديسارتان

صلاح عبد علي[1]*, سهى عبد الخالق الجواري [2]

[1]قسم علوم الحياة، كلية العلوم، جامعة بغداد، كربلاء، العراق

[2]قسم علوم الحياة، كلية العلوم، جامعة بغداد، بغداد، العراق

الخلاصة:

ارتفاع ضغط الدم هو السبب الرئيسي لأمراض القلب والأوعية الدموية والوفيات المبكرة على مستوى العالم، وهو سمة معقدة تحددها عوامل كثيرة منها عوامل داخلية وعوامل وراثية وعوامل بيئية ومجموعة من الانظمة الفسيولوجية. في السنوات الأخيرة، كان هناك اهتمام علمي متزايد وأبحاث تركز على الجوانب المناعية للأدوية الخافضة للضغط. ومن بين هذه المواضيع، برزعقار الكانديسارتان كموضوع مهم للدراسة. لقد ثبت الدراسات أنه يقلل من التفاعلات الالتهابية المرتبطة بارتفاع ضغط الدم. أجريت الدراسة الحالية في مستشفى الإمام الحسين التعليمي في مدينة كربلاء المقدسة في الفترة من 20 كانون الأول 2022 إلى 22 أيار 2023. تم تقسيم الاشخاص المشاركين في الدراسة الى ثلاث مجموعات وهي (G1) الأشخاص الأصحاء، (G2)افراد مصابين بارتفاع ضغط الدم الذين يتلقون أدوية أخرى غير الكانديسارتان و (G3) افراد مصابين بارتفاع ضغط الدم و يتلقون علاج الكانديسارتان وذلك لتقييم بعض المؤشرات الفسيولوجية المختلفة مثل قياس تركيز الصوديوم والبوتاسيوم والاديبونكتين اضافة الى قياس بعض المؤشرات المناعية مثل الانترلوكين 1(IL−1) و الانترلوكين 2 (IL−18) وعامل نخر الورم (TNF−α).

Introduction

Hypertension, or high blood pressure, is a major global health concern with far-reaching consequences. It is a primary contributor to a staggering 8.5 million deaths worldwide each year. These fatalities result from a range of serious conditions directly linked to hypertension, including stroke, ischemic heart disease, various other cardiovascular disorders, and kidney disease [1]. Usually, there are no symptoms associated with high blood pressure. It is commonly detected during a routine primary care visit [2]. The most popular methods for diagnosing hypertension are at-home 24-hour blood pressure monitors or sphygmomanometers in hospital settings. Internationally, it is estimated that over 30% of adults have been diagnosed [3]. Ninety-five percent of cases lack recognized primary causes of hypertension; nonetheless, factors such as genetics, obesity, inactivity, inflammation, alcohol intake, poor diet, low potassium diet, and high salt diet have all been associated with hypertension[4]. Human hypertension patients' kidneys and arteries have been shown to include immune cells. Humans with hypertension have higher levels of several inflammatory biomarkers, such as high sensitivity C-reactive protein, several cytokines, and complement system products[5].

When a patient is diagnosed with hypertension, the first course of action usually involves making lifestyle modifications, such as eating a nutritious diet, cutting back on sodium, consuming less alcohol, and engaging in more physical exercise. While lifestyle modifications are often the first line of defense against hypertension, they may not always be sufficient to achieve optimal blood pressure control [6].There are various pharmacological treatment options available in these circumstances. Medication alternatives for pharmacological treatment include angiotensin II receptor blockers, calcium channel antagonists, ACE inhibitors, and diuretics. Numerous recent large-scale clinical trials have demonstrated that angiotensin II type 1 receptor blockers (ARBs) are either more effective than typical

antihypertensive drugs or just as beneficial in avoiding organ damage caused by hypertension[7].

Candesartan is a common antihypertensive medication used in clinical practice that selectively blocks the angiotensin II type I (AT1) receptor. Preclinical studies have shown that candesartan treatment lowers blood pressure and has anti-inflammatory, antioxidant, and anti-cancer effects. Furthermore, candesartan has been demonstrated in clinical trials to be safe and well-tolerated in individuals with renal disease [8]. The antihypertensive drug candesartan has a molecular structure like a biphenyl derivative and inhibits the angiotensin II receptor [9]. The angiotensin receptor (AT1) for angiotensin II (AT II) at level 1 of the renin-angiotensin aldosterone system (RAAS) is blocked by the active mechanism of candesartan. During a RAAS reaction, AT II's vasoconstrictor effects are most pronounced [10]. Candesartan reduces the release of vasoconstrictors, which enhances arterial elasticity and mitigates the adverse effects of angiotensin II endothelium. When compared to other conventional antihypertensive drugs such as calcium channel blockers (CCBs), β-blockers, and diuretics (Ds), candesartan exhibits a distinct benefit in terms of improving arterial flexibility[11]. When treating hypertension, angiotensin II type 1 receptor blockers (ARBs), such as candesartan, are the first-choice antihypertensive medications. Bradykinin release was enhanced by candesartan, which significantly decreased the expression of inflammatory mediators including TNF-α, IL-1β, IL-6 and IL18 [12].

Adiponectin has been investigated as a marker of cardiovascular risk as well as a therapeutic target because of its positive effects on cardiovascular health. Reduced plasma levels of adiponectin are linked to increased cardiovascular risk and genetic variations[13]. The possibility of a protective effect of high circulating adiponectin in healthy individuals is lost (or even reversed) in severe cardiovascular disease states such as heart failure. Decreasing plasma adiponectin levels increase the risk for diabetes mellitus. Adiponectin deficiency has been associated with hypertension and increasing the risk of stroke [14]. Angiotensin II type 1 receptor blockers like candesartan, which reduces adipocyte dysfunction, may also enhance adiponectin as one of their positive effects in the treatment of hypertension [15].

The control of hypertension, osmolality, and the regulation of plasma volume are only a few of the physiological activities that are supported by the elements sodium and potassium [16].Potassium and sodium are closely related to kidney function and cardiovascular health4. Numerous studies have shown evidence for the relationship between blood pressure and dietary potassium and sodium. One of the main risk factors for hypertension is a diet high in sodium and low in potassium. An increase in salt and potassium consumption from diet may cause blood levels of potassium and sodium to rise [17] There is a significant positive correlation between sodium-to-potassium ratio consumption and blood pressure. Hyperkalemia is a common side effect of medications used to treat high blood pressure, such as ABC. Candesartan is an ARB drug has an effective effect on the channels that transmit potassium. It is necessary to conduct potassium level checks in people with high blood pressure who are taking candesartan [18].The study aims to clarify the effectiveness of candesartan and its importance in treating blood pressure by studying some physiological and immunological parameters.

Materials and Methods

The study design involved a total of 120 participants. These individuals were systematically divided into three distinct groups, with each group comprising 40 participants. Two distinct tests were administered to each of these groups: three immunological tests (interleukin 18, interleukin 1, and tumor necrosis factor) and three physiological tests (serum sodium, serum

potassium, and adiponectin). 5 ml of peripheral whole blood was drawn using a disposable plastic syringe from each patient and control group. The blood sample was transferred to a gel-coated tube and incubated in a water bath at 37°C for 10 minutes to allow clotting. Next, the tube was centrifuged for ten minutes at 3000 rpm. The clear serum was then extracted and frozen at −20°C until needed for experimentation with immunological and hormonal parameters. The decomposed samples were discarded [19]. The totals that the current study has adopted are as follows:

Group 1: This group (negative control) consisted of people who did not appear to have hypertension and were in good health.

Group 2: This group, which consisted of hypertensive patients receiving treatment with a medication other than candesartan, serves as a positive control.

Group 3: This group comprised those undergoing candesartan therapies for hypertension.

Determination of Serum interleukin-1 (IL-1)

The concentration of Interleukin - 1 in serum of study groups was determined depends on kit procedure is an Enzyme-Linked Immunosorbent Assay (ELISA) from Bioassay Technology, China. (Koma BIOTICH Korea. Human IL-6 ELISA Kit, K 023294: 8).

Determination of Serum Interleukin-18 (IL-18)

The serum concentration of Interleukin-18 (IL-18) was measured for all participants across the study groups depends on kit procedure is an Enzyme-Linked Immunosorbent Assay (ELISA) from Koma BIOTICH, Company (Korea) (Koma BIOTICH Korea. Human IL-1B ELISA Kit, K0131231:8).

Determination of Tumor Necrosis Factor – Alpha

(TNF-) in serum Tumor necrosis factor – alpha (TNF-) concentration in serum study groups was estimated depends on kit procedure is an Enzyme-Linked Immunosorbent Assay (ELISA) from Koma BIOTICH, Company (Korea) (Koma BIOTICH Korea. Human TNF- ELISA Kit, K 013594: 8).

Determination of Serum Sodium and Potassium

Level of serum sodium and potassium concentration of study groups was estimated depends on procedure of Elabscience® Electrolytes Colorimetric Assay Kit (No：E-BC-K207-M).

Determination of Adiponectin Concentration

A diponectin concentration in serum of study groups was estimated depends on kit procedure is an Enzyme-Linked Immunosorbent Assay (ELISA) from Bioassay Technology Laboratory (Human Adiponectin, ADP ELISA Kit No. E1550Hu).

Statistical Analysis

The mean and standard deviation (SD) were calculated to summarize the data. Statistical analysis was performed variances (one-way ANOVA) was used to compare more than two means. using SPSS version 26. Analysis of The Fissure exact test and the Chi-square were used to see if there was a significant difference in demographic data between the two sets of categorical data.

Results and Discussion

The results of physiological parameters for each study group are displayed in Table (1). Analysis of the data revealed a statistically significant difference ($p < 0.05$) in potassium concentrations among the study groups. Group 3 exhibited markedly elevated potassium levels (10.57±0.72 mg/L) compared to both Group 1 (4.11±0.51 mg/L) and Group 2 (3.18±0.24

mg/L). This substantial increase in potassium concentration in Group 3 was found to be statistically significant when compared to the other two groups. The study revealed a statistically significant ($p < 0.05$) increased in sodium concentration in G2 (180.6±14.9mg/l) compared with G1 (145.2±6.13mg/l) and G3 (145.05±6.86mg/l). Finally, the current study showed a significant ($p < 0.05$) decrease in adiponectin levels for G2 (3.64±4.73ng/l) compared with G1 (11.97±3.93ng/l) and G3 (12.59±4.28ng/l, respectively).

Table 1: Comparison between studied groups in sodium, potassium and adiponectin levels

Groups	Serum sodium concentration (mg/l)	Serum potassium concentration (mg/l)	Adiponectin level (ng/l)
G1	145.2±6.13B	4.11±0.51B	11.97±3.93A
G2	180.6±14.9A	3.18±0.24C	3.64±4.73B
G3	145.05±6.86B	10.57±0.72A	12.59±4.28A
P value	0	0	0
LSD	4.48	0.234	1.91

Similar latters indicate, No significant difference while different letters indicate significant difference of ($P \leq 0.05$)

Maintaining potassium balance and the role of potassium in managing hypertension have become clinically significant issues, especially with regard to treatments for preventing heart disease and high blood pressure, which may increase potassium retention. The most prevalent antihypertensive drugs that affect serum potassium levels and/or total body potassium are angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β blockers like candesartan [19]. Candesartan selectively prevents angiotensin II from binding to the AT1 receptor in a variety of tissues, including the adrenal gland and vascular smooth muscle, hence inhibiting the vasoconstrictor and aldosterone-secreting effects of angiotensin II. As a result, its activity is not affected by the pathways involved in angiotensin II synthesis [20]. Because it inhibits oxidative stress and maintains sodium levels while slowing the glomerular filtration rate, reducing albuminuria, reducing intraglomerular pressure, and reducing hyper- filtration, as a result candesartan releases potassium into the collecting duct, which causes a reduction in aldosterone levels and sodium transport to the distal nephron [21]. Certain studies suggest that antihypertensive medications belonging to the Angiotensin Receptor Blocker (ARB) class, including Telmisartan, Olmesartan, and Candesartan, lowers aldosterone secretion by inhibiting the production of angiotensin II, which in turn raises potassium levels by restricting potassium excretion. This explains the reason for the increase in potassium levels when using a class of antihypertensive drugs such as candesartan, this increase in potassium levels is expressed in the term hyperkalemia. The kidney plays an important role in the long-term control of blood pressure and is the major organ involved in the regulation of sodium homeostasis [22]. The main pressor of the renin-angiotensin system, angiotensin II causes vasoconstriction, increases aldosterone production and release, stimulates the heart, and causes the kidneys to reabsorb sodium [23]. Candesartan selectively prevents angiotensin II from binding to the AT1 receptor in a variety of tissues, including the adrenal gland and vascular smooth muscle, hence inhibiting the vasoconstrictor and aldosterone-secreting effects of angiotensin II. As a consequence, its activity remains unaffected by the pathways involved in the synthesis of angiotensin II. Because it suppresses oxidative stress and maintains sodium levels while slowing the glomerular filtration rate, lowering albuminuria, decreasing intra-glomerular pressure, and decreasing excessive filtration, candesartan is therefore regarded as one of the most significant antihypertensive medications. In collecting duct cells, aldosterone binds to a receptor and opens a sodium channel, increasing the amount of sodium reabsorption across the luminal membrane[24]. As sodium is reabsorbed, the lumen becomes more

electronegative, which makes the conditions perfect for potassium secretion through a potassium channel [25]. Candesartan is one ARB medicine that reduces the function of angiotensin II hormone by raising the quantity of circulating adiponectin. The hormone adiponectin, which is secreted by adipocytes, plays a significant role in blood cholesterol levels, insulin resistance, and cardiovascular disease, particularly hypertension. Peroxisome proliferator activator receptors (PPARs) are a subfamily of nuclear receptors that are ligand-activated transcription factors that have been shown to affect the expression of adiponectin. It plays a significant part in controlling insulin sensitivity and enhances lipid profiles [9]. A study administering candesartan to hypertensive patients found that the angiotensin receptor blocker significantly augmented PPAR concentrations compared to baseline levels after a treatment duration of three months. Candesartan raises adiponectin levels as a result. The study's findings, which are being presented, seem to support Several previous studies that compared candesartan-treated hypertension patients with negative controls found significant increases in adiponectin levels[26].

Table 2: Comparison between studied groups in IL-1, IL-18 and TNF-α levels

Groups	IL-1 level (ng/l)	IL-8 level (ng/l)	TNF-α level (ng/l)
G1	10.5±6.58B	13.82±5.68B	7.45±2.85B
G2	37.97±14.3A	25.87±12.9A	56.98±12.04A
G3	7.92±3.78B	9.86±2.06C	8.90±8.92B
P value	0	0	0
LSD	4.14	3.65	3.90

Similar latters indicate, No significant difference while different letters indicate significant difference of ($P \leq 0.05$)

The primary active renin-angiotensin system component, angiotensin II, is necessary for the vascular and functional changes that hypertension causes. Moreover, angiotensin II hormone, which is assumed to be an inflammatory mediator and essential for the inflammatory process, is inhibited by ARBs such as candesartan. As a result, proteins that inhibit inflammatory cytokines like tumor necrosis factor (TNF) and interleukin-1 (IL-1) were less activated, including lipopolysaccharide (LPS), interferon (IFN), and nuclear factor kappa B (NF-B)[27]. Systemic inflammation brought on by hypertension increases levels of a number of inflammatory markers, including TNF, IL-1, IL-6, IL-8, IL-18, and IL23. Bradykinin levels may rise and bradykinin degradation may be halted by the antihypertensive medication ABRs. By increasing the release of bradykinin, candesartan greatly lowered the production of inflammatory mediators such TNF-α, IL-1β, IL-6, and IL-18[28]. Several research studies have linked IL-18 to hypertension and obesity. Furthermore, elevated levels of IL-18 were seen in those with these conditions, particularly high blood pressure. Because it promotes the generation of superoxide and ROS from mechanical stress-mediated NADPH oxidase, which affects the vascular wall and raises the production of IL-18, it is thought that IL-18 contributes to the hypertension brought on by Ang II [29]. While many antihypertensive medications, like ABRs, have anti-inflammatory qualities, relatively little study has looked at how these treatments impact IL-18 levels. According to recent experimental research, ATII increases the expression of IL-18 in vascular smooth muscle cells, while ATII receptor antagonists can decrease IL-18 expression in blood arteries and cardiomyocytes. Consequently, certain antihypertensive medications, particularly those that target angiotensin II, such candesartan, may cause a drop in interleukin-18 levels [30]. Studies show that cytokines like TNF- and IL-1 are present in higher concentrations in the blood plasma of hypertension patients than in the blood plasma of healthy people. These studies have demonstrated the interaction between the inflammatory cytokines TNF- and IL-1 and the blood pressure-regulating systems, including

the Renin-Angiotensin system. Via B1 and B2 receptors, bradykinin lowers blood pressure, increases vascular permeability, and has a vasodilator effect [31]. Via B1 and B2 receptors, bradykinin lowers blood pressure, increases vascular permeability, and has a vasodilator effect. It has a significant impact on cardiovascular function as well. Two other significant inflammatory responses to bradykinin via the B2 receptor are pain and fever. Bradykinin acts on the B2R to stimulate the production of renin, which in turn influences the levels of certain inflammatory indicators by lowering interleukin-1 and TNF levels. Bradykinin also stimulates protein kinase C [32]. Candesartan exhibits potent inhibitory action on lipopolysaccharide (LPS), which triggers TNF-α production. By reducing T cell release of CD25 and IL-2 as well as phagocyte production of reactive oxygen compounds (ROIs) like superoxide (O2), hydrogen peroxide (H_2O_2), and hydroxyl radical . candesartan lowers TNF levels [33].

Conclusion

Candesartan helps regulate sodium levels, which contributes to its blood pressure-lowering effect. At the same time, no drug is without some side effects and transparency, represented by the level of high potassium, which can lead to the occurrence of a condition known as hyperkalemia. Indicators of the safety and suitability of this medication for use in a variety of disorders, particularly hypertension, include the decline in the concentrations of immunological parameters IL-1,IL-18 and TNF.

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Ethical responsibilities of authors

We declare that we are the author of this paper entitled “Physiological and immunological study of a sample of hypertensive patients treated with candesartan” and we confirm that the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of College of Science/ University of Baghdad.

Disclosure and conflict of interest

The authors declare that they have no conflicts of interest.”

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