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Renoprotective effect of candesartan in patient with diabetes mellitus and hypertension

Sajad Moneim Al-Jubouri[1], Reem aljanabi[2]

[1]Ibn Sina University for Medical and Pharmaceutical Sciences, College of Medicine, Pharmacology Department, Email: Sajad.m.aljubouri@ibnsina.edu.iq.
[2]Ibn Sina University for Medical and Pharmaceutical Sciences / College of Medicine / Pharmacology Department, Email: Aljanabireem@ibnsina.edu.iq

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ABSTRACT

Patients with diabetes and hypertension often have renal function and blood pressure issues, which can increase the risk of cardiovascular events and kidney failure. Angiotensin receptor blockers (ARBs) like candesartan reduce blood pressure and may protect the kidneys. This 8-week study examined how candesartan affected renal function and blood pressure in diabetics and hypertensives. A control group (Group 1) and three diabetes and hypertension groups (Groups 2, 3, and 4) each had 30 participants in this cohort longitudinal study. Group 1 received no medication, whereas Groups 3 and 4 received 16 mg and 8 mg candesartan daily. Group 2 was untreated during the research. During the 8-week study, serum creatinine, GFR, blood pressure, and proteinuria were measured weekly. The findings showed that candesartan improved renal function and blood pressure. Serum creatinine and proteinuria decreased significantly (2.71±0.6 to2.06±0.54), (36.4±3.8 to 23.64±3.52) respectively in Group 3, which received more candesartan. GFR improved significantly (72±9.27 to 83± 6.85) in this group during the research. Group 4 showed statistically significant improvements with a reduced candesartan dose. Group 3 had a greater blood pressure drop than Group 4. All changes were found to be statistically significant, with p-values below 0.05. In conclusion, candesartan improves renal function and lowers blood pressure. In diabetics and hypertensives. The findings suggest that increasing dosage may have greater benefits. This study adds to the evidence that candesartan is useful in treating renal and cardiovascular risk individuals. Additional research is needed to determine the best medicine administration methods and long- term results.

Keywords: Candesartan, Renoprotective, Hypertension, Diabetes mellitus, serum creatinine.

INTRODUCTION

Diabetic nephropathy and hypertensive nephropathy are two distinct medical issues that have a close association, both causing damage to the kidneys through different biological mechanisms. In diabetic nephropathy, persistent hyperglycemia initiates a series of repercussions that result in damage to the glomeruli [1, 2]. At first, high blood sugar levels can lead to increased filtration and enlargement of the glomeruli, which in turn aggravates resistance in the renal blood vessels. Over time, this leads to the thickening of the glomerular basement membrane and mesangial expansion, and it ultimately results in the development of microalbuminuria, a key indicator of early diabetic nephropathy [3]. The disease advances as nodular glomerulosclerosis, or Kimmelstiel-Wilson lesions, develop and renal function gradually deteriorates [4]. However, hypertensive nephropathy mainly occurs due to long-term elevated blood pressure, which can cause harm to the blood vessels in the kidneys. Extended high blood pressure may result in impaired functioning of the blood vessel lining, hardening of small arteries, and eventually, damage to the kidney's filtering units [5].

The renin-angiotensin-aldosterone system (RAAS) is involved in both conditions, leading to glomerular hypertension and promoting renal fibrosis. It is worth noting that the presence of both diabetes mellitus and hypertension can significantly speed up the rate of progression of kidney damage [6].

Renal dysfunction is frequently the outcome of diabetes mellitus and hypertension, leading to further morbidity and mortality in affected individuals. Renal dysfunction is frequently occurring in diabetic nephropathy, this affects one third of diabetes Miletus patients [7]. Microalbuminuria which is considered a warning sign of renal damage is correlated with high risk of end-stage renal disease (ESRD) and cardiovascular complications. Similarly, elevated blood pressure in hypertension patients is a causative agent in progression of hypertensive nephropathy which lead to kidney damage. It is crucial to manage blood pressure as the uncontrolled elevated blood pressure is frequently associated with increased risk of gradual loss of kidney function [8, 9].

Having in mind that diabetes mellitus and hypertension are two common co-morbidities which are important factors in cardiovascular diseases and chronic kidney disease (CKD), Candesartan, as one of the most frequently used angiotensin II receptor blockers (ARBs), is proven to be very effective in the management of patients with these two conditions. And this is true because controlling blood pressure, reducing cardiovascular risk, and saving kidneys would lead to better care of these individuals [10, 11, 12].

Candesartan, which is a highly potent medication, helps lower the blood pressure. It works by precisely affecting and blocking angiotensin II type 1 (AT1) receptor leading to vasodilation and lowering resistance throughout the vascular system. This is one of the most critical counteractions against the complications in diabetes that are somehow related to hypertension [11, 13].

The development of cardiovascular disease is strongly affected by diabetes and hypertension. In this respect, Candesartan provides cardioprotective effects mainly through its anti-inflammatory and antioxidant actions [14]. It has been demonstrated that Candesartan helps to suppress systemic inflammation and oxidative stress, which contribute to atherogenesis and later cardiovascular consequences [15].

Its use in combination with other drugs is a regular prescription as it provides effective control of hypertension and diabetes. This drug has an excellent safety profile and minimal side effects, which remain almost non-sensitive even during a long-term treatment course. This combination extends the therapeutic flexibility of it [16].

Besides, another aspect of the anti-inflammatory properties of candesartan is related to its ability to suppress the pro-inflammatory cytokines and chemokines synthesis in the kidney tissue. This decreased inflammation leads to reduced renal damage and fibrosis, contributing to the preservation of renal function [17]. Furthermore, candesartan has antioxidant activity by decreasing reactive oxygen species (ROS) production and increasing endogenous antioxidant enzyme levels. Candesartan also takes care of cellular health in the kidneys by removing oxidative stress, which prevents apoptosis and results in the healthy functioning of the renal system as a whole [18, 19].

Candesartan possess ability which can affect the renal hemodynamics and as a result the both glomerular filtration rate (GFR) and renal blood flow are noticed to be enhanced. And this improvement consequently play role in lowering progression rate of chronic kidney disease (CKD) and preservation of renal function of kidney [20].

In addition, this drug encompasses the potential to directly counteract fibrosis by inhibiting the production and accumulation of proteins in the kidney, which may assist in hindering the formation of renal fibrosis [21].

MATERIALS AND METHODS

Study design: This study was conducted at Al Sader Teaching Hospital in Najaf, Iraq. The study aimed to assess the renoprotective effect of candesartan in patients with diabetes mellitus and hypertension. The study was conducted over a period of 8 weeks, with regular measurements and follow-up sessions started from first of December 2023 till the end of January 2024. For this study, a total of 120 participants were enrolled. 90 of them are patients who had a diagnosis of both diabetes mellitus (type 2) and hypertension. and 30 are healthy control individuals. Participants needed to be adults (aged 18 or above) with a confirmed diagnosis of diabetes and hypertension, and willing to take part in the study. Exclusion criteria involved individuals with a background of chronic kidney disease (CKD) stage 4 or higher, secondary causes of hypertension, pregnancy, or known intolerance to ARBs.

The study involved 120 participants who were divided into four groups, with each group consisting of 30 participants.

Group 1: 30 individuals serve as the control group, consisting of healthy individuals who did not undergo any treatment throughout the study period. This group is considered the standard for evaluating diabetes and hypertension progression and the effect of candesartan medication. Group 2 consisted of 30 patients who are diagnosed with diabetes and hypertension but not taking the target medication candesartan and this group is important for assessment of the renal function and comparing this with individuals receiving candesartan.

Group 3 included 30 patients who are received candesartan at dose of 16 mg foe one time per day during the 8 months of study. And the crucial role of this group is the valuable insights about the blood pressure and renoprotective effect of high dosage of candesartan. Group 4 consisted of 30 patients who were administered candesartan dose of 8 mg once daily for 8 weeks. This group help in evaluating the renoprotective effect of candesartan and its efficacy regarding blood pressure at lower dosage. The study compared this group with Group 3.

The patient's classification into the groups and determination of candesartan dosage is done by medical professionals. Professionals take in account the individual needs of each patient, medical history and the study design. The 120 participants in the study were asked to perform baseline evaluations in order to insure validity and consistency on data collection and the accuracy of the assessment of treatment effects.

This primary evaluation was performed through review of medical history and physical examination. Objective measures were done as Routine measurements of serum creatinine level, GFR, blood pressure, proteinuria conducted for 8 weeks.

Serum creatinine levels were used to assess kidney function and the glomerular filtration rate (GFR) which is important sign renal function as it measure the rate at which blood is filtered by the glomeruli. Proteinuria was evaluated at each week during the eight weeks of study to determine the presence of protein in urine samples as protein presence is indication that filtration barriers in the kidney is compromised and this may be a sign for progression of diabetic nephropathy. Each week, blood pressure reading was also recorded carefully to evaluate candesartan effect on hypertension management.

Every patient has a comprehensive medical history that includes their name, age, gender, region, weight, date, telephone number, history of any other diseases or treatments, blood pressure, and the date of their next follow-up appointment. The follow up visits are vital for ensuring that treatment plan is followed and for promptly monitoring any potential health issues.

that data acquired form the study were analyzed using SPSS software version 25.0 version. the analysis was conducted to evaluate the variation in renal functions among the groups. The software used to calculate mean and p-value to assess correlations and variations between groups to finally assess the renoprotective effect of candesartan in patients with diabetes mellitus and hypertension.

RESULTS

The average age of participants is relatively comparable among the groups, with Group 2 having the lowest mean age (49 ± 5.7 years) and Group 1 having the highest (51.6 ± 4.63 years). The Body Mass Index (BMI) exhibits significant variation, with Group 2 displaying the greatest average BMI (28.7 ± 7.2), whereas Group 4 has the lowest (23.4 ± 13.8). In terms of gender, there is a slight imbalance in the distribution, with Group 2 having a higher number of females (17), while Group 4 has a higher number of males (21), as presented in table 1.

Table 1: characteristics of individuals in all groups

		G1	G2	G3	G4
Age		51.6 ± 4.63	47.8 ±13	49 ±5.7	50.72 ± 3.2
BMI		23.4 ±13.8	28.7 ±7.2	28.68 ± 5.4	27.3 ± 2.7
Gender	Male	14	13	19	21
	Female	16	17	11	9

Serum creatinine levels in the four groups during the 8 weeks:

The serum creatinine data demonstrate a notable disparity in renal function among the four groups during 8- week duration. Table 2 and figure 1 show that, at the beginning of the investigation (Week 0), the control group (Group 1) had a serum creatinine level of 0.82 ± 0.09 mg/dL, which is within the normal range. Groups 2, 3, and 4, which included individuals with both diabetes mellitus and hypertension, exhibited significantly higher levels of serum creatinine, all above 2.6 mg/dL. The observed differences between these groups and the control group were statistically significant, as indicated by a p-value of less than 0.001 (***a).

Over the course of the initial three weeks, the levels of creatinine in Groups 2, 3, and 4 were rather constant, suggesting that both without therapy (Group 2) and with candesartan medication (Groups 3 and 4), the initial levels continuously above those of the control group. However, noticeable alterations became evident starting with Week 4. Group 3, who were administered a daily dose of 16 mg of candesartan, experienced a notable decrease in serum creatinine levels. The levels decreased from 2.71 ± 0.6 mg/dL at Week 0 to 2.35 ± 0.66 mg/dL. The rise persisted, with the amount reaching 2.06 ± 0.54 mg/dL by Week 8. The reductions in this category were statistically significant in comparison to Group 2 (*b' and **b), with p-values below 0.05 and 0.01, respectively, over many weeks.

Group 4, with a reduced dosage of candesartan (8 mg once day), likewise exhibited a reduction in serum creatinine levels, but to a smaller degree than Group 3. The readings exhibited a drop from an initial value of 2.69 ± 0.46 mg/dL to 2.27 ± 0.36 mg/dL at Week 8. The reductions observed in multiple weeks were statistically significant when compared to Group 2 (shown by *band **b), with p-values below 0.05 and 0.01.

Table 2: level of serum creatinine in groups in the 8 weeks of study

	G1	G2	G3	G4
Start (W0)	0.82 ±0.09	2.69± 0.57*** a	2.71±0.6*** a	2.69±0.46*** a
W1	0.83±0.12	2.71±0.55 *** a	2.71 ±0.59*** a	2.68±0.57*** a
W2	0.84±0.10	2.71±0.54*** a	2.73±0.47*** a	2.71± 0.45*** a
W3	0.86±0.11	2.72±0.53*** a	2.72±0.55*** a	2.71± 0.39*** a
W4	0.79±0.11	2.69±0.52*** a	2.35±0.66*** a, *b	2.67±0.52*** a, *c

W5	0.81±0.13	2.72±0.56*** a	2.27±0.49*** a, *b	2.54±0.55*** a, **b, *c
W6	0.83±0.15	2.73±0.57*** a	2.23±0.61*** a, *b	2.48±0.48*** a, *b
W7	0.82±0.12	2.75±0.61*** a	2.15±0.35*** a, **b	2.33±0.44*** a, **b, *c
W8	0.85±0.15	2.76±0.59*** a	2.06±0.54*** a, **b	2.27±0.36*** a, **b, *c

*** = p<0.001. ** = p<0.01. * = p<0.05. a: Versus G1 . b: Versus G2, c: Versus group 3.

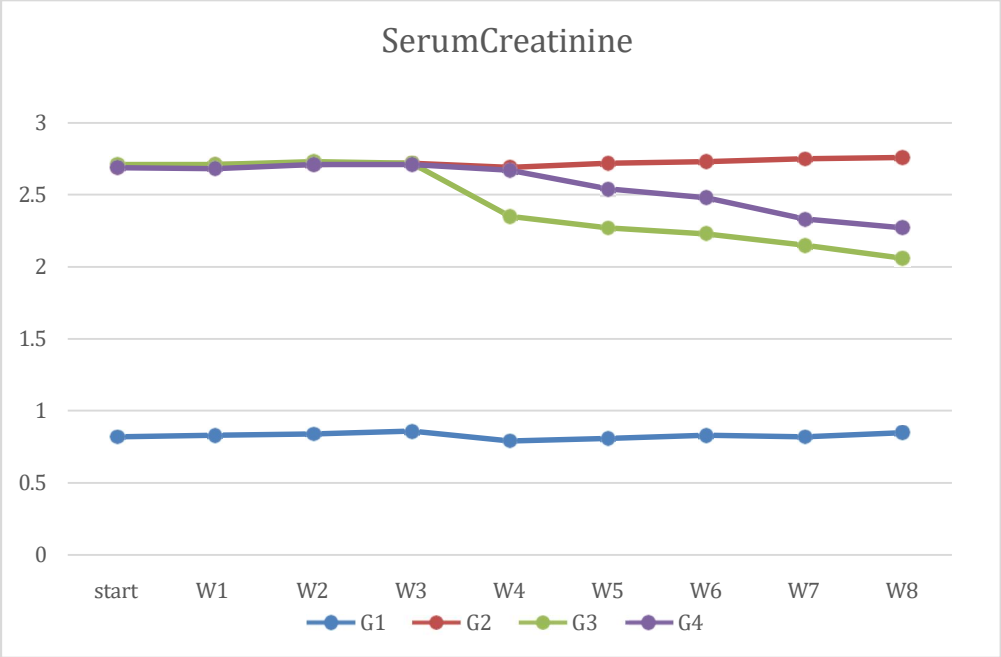

Figure 1: variations in serum creatinine levels among groups of participants during weeks of study glomerular filtration rate (GFR)

Table 3 and figure 2 display data on glomerular filtration rate (GFR) during an 8-week duration, examining the impact of various dosages of candesartan on renal function in patients with diabetes mellitus and hypertension. Initially, at the start of the study (Week 0), the control group (Group 1) had a glomerular filtration rate (GFR) of 94±5.12 mL/min/1.73 m², which is a measure of normal kidney function. Conversely, the baseline glomerular filtration rates (GFRs) of the remaining groups (Groups 2, 3, and 4) were notably lower, varying from 72 to 74 mL/min/1.73 m². The observed differences were statistically significant, as indicated by p-values below 0.001 when comparing to Group 1.

During the first three weeks, Group 1 consistently maintained a constant glomerular filtration rate (GFR), whereas Groups 2, 3, and 4, which had lower initial GFRs, exhibited few fluctuations. The consistent stability observed in the control group, in contrast to the reduced glomerular filtration rates (GFRs) observed in the other groups, highlights the significant influence of diabetes and hypertension on renal function. Throughout this period, the GFR values in Groups 2, 3, and 4 consistently differed considerably from those in the control group. Starting from Week 4, significant improvements were noted in Groups 3 and 4, Group 3,experienced a rise in their glomerular filtration rate (GFR) to 77±6.45 mL/min/1.73 m². Over the following weeks, their GFR continued to improve, reaching 83±6.85 mL/min/1.73 m² by Week 8. This increase signifies a noteworthy enhancement, with p-values below 0.01 and 0.001 when compared to Group 2.

Group 4, exhibited a steady rise in GFR, but to a lesser extent compared to Group 3. By Week 8, the glomerular filtration rate (GFR) in Group 4 had risen to 80±6.34 mL/min/1.73 m². The observed enhancement was statistically significant when compared to Group 2.

Table 3: GFR during weeks of study among groups of participants

	G1	G2	G3	G4
Start (W0)	94±5.12	73±2.76*** a	72±9.27*** a	74±6.77 *** a
W1	99±4.83	76± 3*** a	73± 6.26*** a	74± 3.86*** a
W2	95±7.25	72± 5.67*** a	71± 5.63*** a	73± 2.55*** a
W3	93±5.37	70± 3.71*** a	72± 2.74*** a	75± 3.17*** a, *b
W4	92±6.45	68±2.85*** a	77± 6.45*** a, *b	75± 6.28*** a, **b
W5	93±4.63	69± 5.92*** a	79± 3.81*** a, **b	76± 1.76*** a, **b, *c

W6	95±5.88	67± 7.12*** a	81±5.94*** a, **b	78± 4.23*** a, **b, *c
W7	92±4.92	66 ± 6.33*** a	82 ± 3.51** a, ***b	79± 5.66*** a, ***b, *c
W8	94±5.04	66± 5.16*** a	83± 6.85** a, ***b	80± 6.34** a, **b, *c

*** = p<0.001. ** = p<0.01. * = p<0.05. a: Versus G1. b: Versus G2, c: Versus group 3.

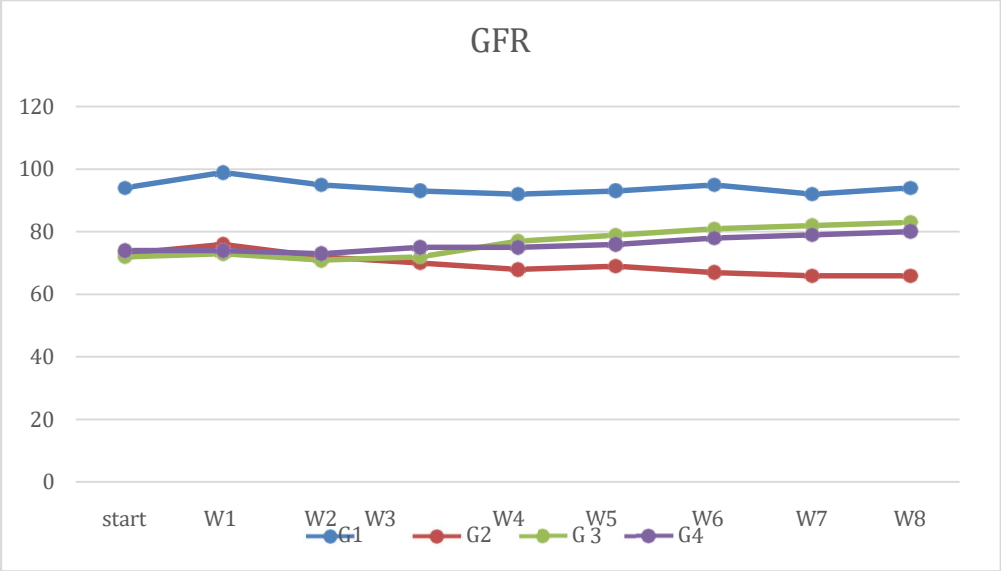

Figure 2: levels of GFR among groups during the 8 weeks of study

Blood pressure

Table 4, figure 3 and 4 represent the blood pressure data that demonstrates the effect of candesartan medication on both systolic and diastolic blood pressure in patients with diabetes mellitus and hypertension within an 8- week timeframe. Initially, at Week 0, the control group (Group 1) had a normal blood pressure, with systolic and diastolic readings of 120±5.4 mmHg and 80±3.6 mmHg, respectively. Conversely, the blood pressure levels of the other groups (Groups 2, 3, and 4) were notably higher, with systolic readings above 155 mmHg and diastolic readings reaching 88 mmHg. The observed variations from the control group were consistently present in all the treatment groups, with p-values < 0.001 (***a).

Groups 3 and 4, which received varying doses of candesartan, experienced significant decreases in blood pressure during the initial three weeks. Group 3, who were given a daily dose of 16 mg, experienced a significant decrease in systolic blood pressure. By Week 1, it declined from 155±8.62 mmHg to 135±6.25 mmHg. By Week 8, systolic pressure continued to decrease, reaching 125±8.52 mmHg. Candesartan medication caused statistically significant blood pressure changes compared to Group 2. Candesartan medication clearly reduced blood pressure, as shown by the p-values below 0.001.

Group 4, given 8 mg daily, also reduced systolic BP, but less than Group 3. In Group 4, systolic BP decreased from 160±4.28 mmHg at baseline to 140±6.81 by Week 1 and 125±4.7 at Week 8. The decrease was consistently significant compared to Group 2 and varied with candesartan dosage.

The diastolic blood pressure exhibited a comparable trend, as Group 3 observed a decrease from 92±7.53 mmHg at the beginning to 78±4.06 mmHg at Week 8. Group 4 experienced a decrease in blood pressure from 90±2.91 mmHg to 78±3.41 mmHg by Week 8, which was significantly different from Group 2.

Table 4: systolic and diastolic pressure records during the 7 weeks

		G1	G2	G3	G4
Start	systolic	120±5.4	160±11.4 ***a	155± 8.62***a	160± 4.28***a
	diastolic	80±3.6	88± 5.17 **a	92± 7.53***a, *b	90± 2.91***a, *b, *c
W1	systolic	125±7.2	165± 8.66***a	135± 6.25**a, ***b	140± 6.81***a, ***b, *c
	diastolic	80±2.5	88± 3.65***a	85± 4.5***, *b	88± 3.85 ***a, *c
W2	systolic	122±8.3	160± 9.51***a	130± 12.65 **a, ***b	140± 6.92 **a, ***b, **c
	diastolic	78±3.26	88± 4.47***a	88± 5.84***a	88± 9.63***a
W3	systolic	118±7.4	150± 14.3***a	140± 8.58***a, **b	135± 7.54**a, **b, *c
	diastolic	80±4.31	90±5.71***a	84±3.7*a, **b	86±3.9**a, *b, *c
W4	systolic	120±8.6	155± 3.68***a	135±9.5**a, **b	140±12.04**a, **b, *c
	diastolic	80±3.8	92±7.33***a	83±2.81***b	85±3.27*a, *b

W5	systolic	115±7.67	160± 9.77***a	130±10.3***a, ***b	137± 7.3**a, ***b, *c
	diastolic	83±6.04	85± 3.6***a	80±4.57*a, **b	82±4.27*b
W6	systolic	118± 7.6	165± 8.46***a	128±8.23**a, ***b	133±8.36***a, ***b, *c
	diastolic	80±4.7	90±2.8***a	81± 3.75**b	80±3.25***b
W7	systolic	122±8.27	160±8.09*a**	125±7.4*a, ***b	130±7.91*a, ***b, **c
	diastolic	80±5.27	90±3.16***a	80±3.61**b	80±2.93***b
W8	systolic	120± 9.52	155± 9.16***a	125± 8.52*a, ***b	125±4.7**a, ***b, *c
	diastolic	80±3.18	88±3.71***a	78±4.06*a, ***b	78±3.41**a, ***b

*** = p<0.001. ** = p<0.01. * = p<0.05. a: Versus G1. b: Versus G2, c: Versus group 3.

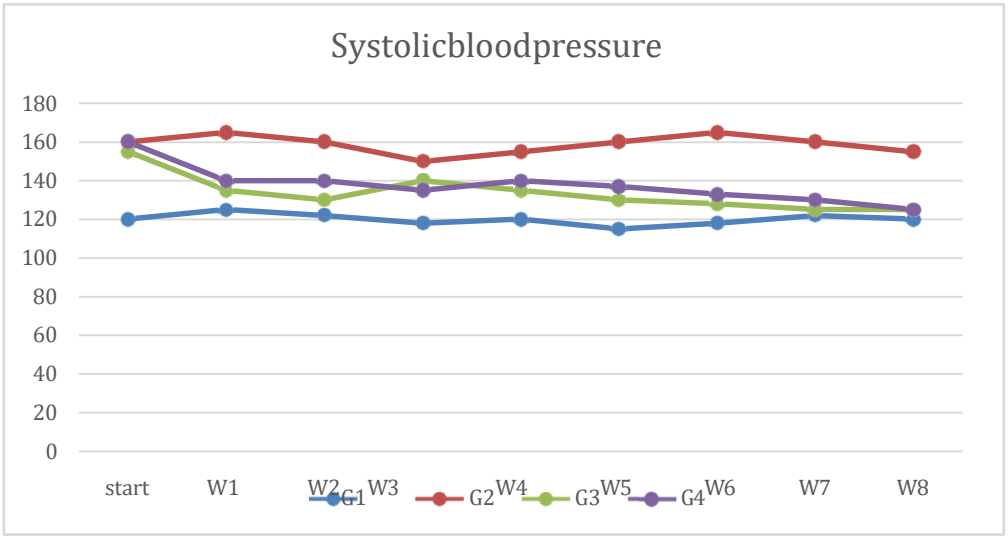

Figure 3: systolic blood pressure records among groups during the 8 weeks.

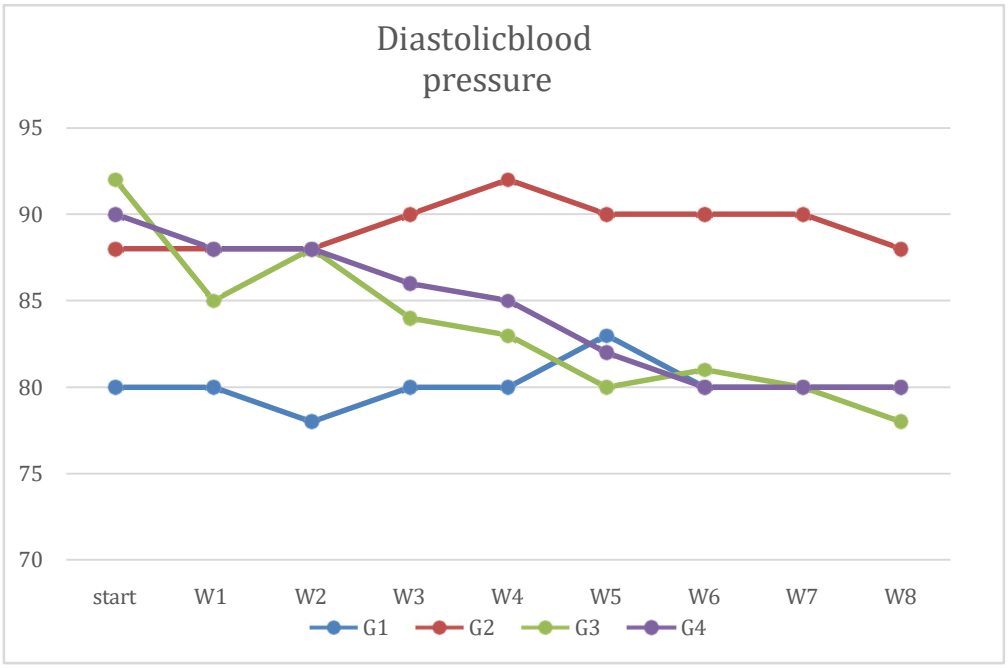

Figure 4: Diastolic blood pressure records among participants during weeks of study.

Proteinuria

Initially, at the start of the study (Week 0), the control group (Group 1) had proteinuria levels of 4.52 ± 0.9 mg/dL, which suggested that their kidney function was normal. However, proteinuria levels were significantly higher in Groups 2, 3, and 4, which consisted of diabetic and hypertensive patients. Group 2, which did not receive candesartan, had proteinuria levels of 35.15 ± 5.65 mg/dL. In contrast, Groups 3 and 4, which were

treated with different doses of candesartan, had proteinuria levels of 36.4 ± 3.8 mg/dL and 35.71 ± 6.13 mg/dL, respectively. The values in these groups were significantly higher than those in the control group, with statistical significance ($p < 0.001$, ***a).

During the trial, the levels of proteinuria in Groups 2, 3, and 4 remained elevated, however, individuals treated with candesartan (Groups 3 and 4) started to exhibit decreases. By Week 4, Group 3, which received a dosage of 16 mg of candesartan, experienced a significant decrease in proteinuria to 28.61 ± 2.41 mg/dL. In comparison, Group 4, which received a dosage of 8 mg of candesartan, reduced proteinuria to 30.17 ± 4.24 mg/dL. The decreases were found to be statistically significant in comparison to Groups 2 and3 ($p < 0.05$, *b, *c). By Week 8, the protective effects of candesartan on the kidneys were more noticeable. In Group 3, the amount of protein in the urine decreased to 23.64 ± 3.52 mg/dL, and in Group 4, it decreased to 25.82 ± 6.22 mg/dL. Once again, these differences were shown to be statistically significant when compared to Group 2 ($p < 0.01$, **b) as table 5 and figure 5 illustrate.

Table 5: proteinurea during the 8 weeks of study

	G1	G2	G3	G4
Start (W0)	4.52 ±0. 9	35.15±5.65 *** a	36.4±3.8*** a	35.71±6.13*** a
W1	4.48±0.83	35.42±4.86*** a	36.22 ±4.09*** a	35.37±4.5*** a
W2	5.02±1.03	36.13±7.6*** a	35.42±6.15*** a	34.94± 7.32*** a
W3	4.62±0.92	35.75±8.55*** a	35.17±4.85*** a	34.26± 3.3*** a
W4	4.79±0.81	35.59±6.5*** a	28.61±2.41*** a	30.17±4.24*** a ,*b
W5	5.01±0.9	36.64±7.14*** a	27.85±4.73*** a, *b	29.57±6.63*** a, **b, *c
W6	4.52±0.9	36.81±5.57*** a	25.31±3.45*** a, *b	28.62±5.71*** a, **b, *c
W7	4.46±1.02	37.25±6.1*** a	24.18±5.7*** a, **b	26.27±3.81*** a, **b
W8	4.51±8.04	37.46±4.71*** a	23.64±3.52*** a, **b	25.82±6.22*** a, **b, *c

*** = p<0.001. ** = p<0.01. * = p<0.05. a: Versus G1. b: Versus G2, c: Versus group 3.

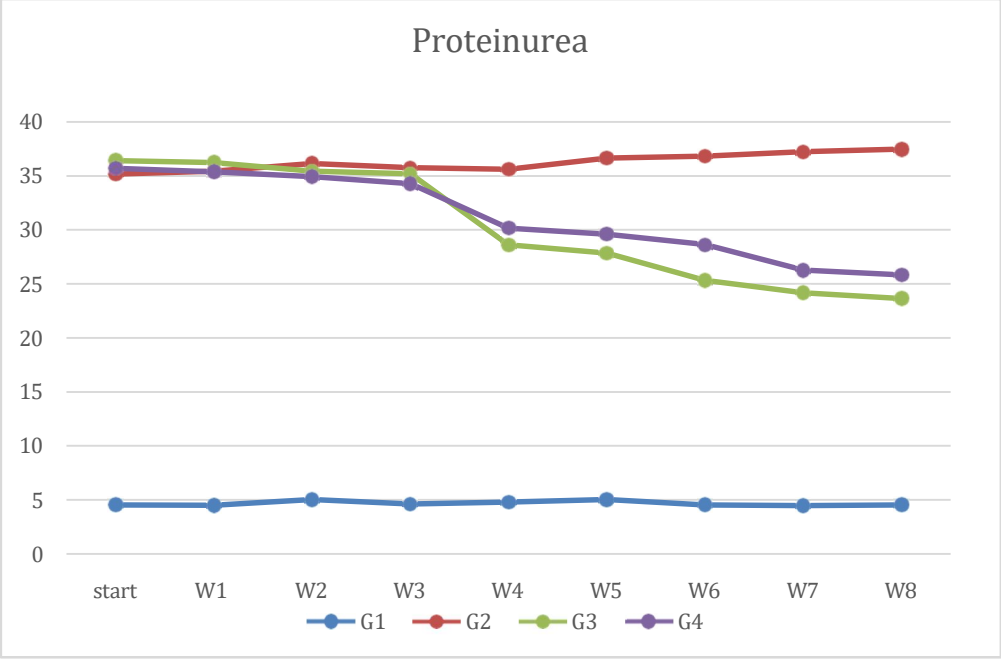

Figure 5: levels of proteinuria in the 8 weeks.

DISCUSSION

Renal dysfunction, a commonly observed clinical change, is strongly linked to diabetes mellitus and hypertension. Diabetes mellitus is the primary cause of most cases of end-stage renal diseases diagnosed in the United States [22].

Group 2 has the lowest average age of 49 ± 5.7 years in the present study, whereas Group 1 has the highest average age of 51.6 ± 4.63 years. There are significant variations in Body Mass Index (BMI) amongst different groups. Group 2 exhibits the greatest mean BMI of 28.7 ± 7.2, while Group 4 displays the lowest at 23.4 ± 13.8. In terms of gender distribution, Group 2 has a higher number of females (17), whereas Group 4 has a higher number of males (21).

These findings are consistent with recent research that suggest women with impaired glucose tolerance and diabetes had a higher prevalence of hypertension compared to males with identical glucose abnormalities. Furthermore, hypertension is predominantly prevalent among individuals between the ages of 45 and 75 [23]. Individuals diagnosed with hypertension typically have advanced age, increased body weight, greater accumulation of abdomen fat, and display elevated levels of both systolic and diastolic blood pressure, as well as a higher pulse rate. Similarly, a gradual rise in BMI over a period of time is a noteworthy and separate factor that can indicate the likelihood of developing hypertension. Moreover, an increase in BMI throughout the monitoring period is a significant indicator of the development of diabetes [24].

The incidence of diabetes in India is 7.3% among women and 7.8% among men. The rates vary according on age, ranging from 2.4% among males aged 18 to 25 to 14.0% among men over 65. The prevalence of hypertension is higher among men (27.4%) compared to women (23.6%). Additionally, the likelihood of developing hypertension increases with age, ranging from 9.2% among women aged 18 to 25 to 48.6% among women over 65. Among those aged 40 and above residing in rural areas the prevalence of diabetes is 5.9%, whereas the prevalence of hypertension is 30% [25].

The prevalence of hypertension is significantly greater among individuals under the age of 45 in India compared to the figures published by the WHO/NCD-RisC for South Asia [26, 27].

Studies reveal that a substantial percentage of individuals who are overweight or obese, ranging from 60% to 76%, also suffer from hypertension, highlighting the strong correlation between high blood pressure and obesity [28]. This indicates that even among those who fall within the normal and overweight categories, a gradual rise in Body Mass Index (BMI) is linked to an elevated susceptibility to hypertension and cardiovascular disease (CVD) [29,30].

Individuals with borderline abnormal glucose tolerance or type 2 diabetes have increased arterial stiffness in comparison to individuals with normal glucose tolerance. The heightened rigidity of the arteries may be caused by the synergistic impact of heightened glucose and insulin levels, potentially resulting in an earlier occurrence of hypertension and other cardiovascular complications in individuals with type 2 diabetes [31].

Additionally, a significant association was identified between gender and the occurrence of diabetes, with men exhibiting a higher susceptibility to developing diabetes, especially between the ages of 35 and 69. Furthermore, this may have an impact on the development of additional complications and outcomes related to diseases such as hypertension [32]

The current study showed that creatinine levels in diabetic and hypertensive individuals' groups 2,3 and 4 was (>2.6 mg/dL) compared to (0.82 ± 0.09 mg/dL) in control group. Groups 3, 4 given candesartan showed drop in it but it was more considerable in group 3 with a dose of 16mg of candesartan compared to 8mg in group 4.

The present study compared serum creatinine levels during eight weeks in four groups. Group 1 was the control and had a normal creatinine level. High values were found in diabetes and hypertension groups 2, 3, and 4. Group 3, given 16 mg of candesartan daily, had a considerable drop in creatinine after eight weeks, but Group 4, given 8 mg, had a lower reduction.

Various studies have demonstrated that elevated blood glucose levels have detrimental effects on nephrons, hence impairing the kidneys' capacity to regulate fluid and electrolyte equilibrium. Elevated levels of serum creatinine frequently suggest the presence of renal failure [33].

The administration of Candesartan at a dosage of 5 mg per kilogram of body weight resulted in a decrease in blood creatinine levels and alleviated symptoms of diabetic nephropathy (DN) after four weeks of treatment [34]. A separate trial demonstrated that the administration of candesartan medicine resulted in a decrease in blood creatinine levels by an average of 0.004 ± 0.09 mg/dL, indicating its efficacy in enhancing kidney function [35].

An Uzbik study revealed that candesartan medication decreased serum creatinine levels contributing in boosting and improvements in renal function [11]. In Egypt, at Zagazig University an investigation showed that four weeks of administration of candesartan medication of rats experiencing diabetic nephropathy, the level of serum creatinine dropeed from 2.72 to 2.12 [20].

A study conducted in 2008 explored the complications and advancement in kidney diseases in diabetic individuals found that diabetic patients who received candesartan treatment experienced a less decline in renal function compared to those who did not receive the treatment [36]. A supplementary proof was presented in an old study in 2003 which demonstrated that increased dose of candesartan from 8mg to 16 mg showed a notable decrease of serum creatinine level which support that dosage is considered a crucial factor in renal function improvements [37]

In this investigation glomerular filtration rate (GFR) changes over eight weeks. Group 1 (control) maintained a consistent GFR of 94 ± 5.12 mL/min/1.73 m², while Groups 2, 3, and 4—having diabetes and hypertension— had lower GFRs (72–74 mL/min/1.73 m²). starting from Week 4, improvements in GFR was observed in group 3,4 who are treated with candesartan.

Many studies have investigated the GFR and the effect of many parameters and medications on it. Aligning with the findings of the present study, in the early-stage diabetic and hypertensive patients, the average of glomerular

filtration rate (GFR) was observed to be 65 ± 26.7 mL/min per 1.73 m² [38].This phenomenon can be explained based on the glomerular hyperfiltration theory, the rise in blood osmotic pressure caused by hyperglycemia and the increase in blood volume trigger the excessive secretion of atrial natriuretic peptide (ANP), resulting in the expansion of glomerular afferent arterioles [34].

In diabetic rats that have been given candesartan, there has been a discernible increase in the glomerular filtration rate (GFR) over the course of time [20]. An Indonesian study conducted in 2021 reported that glomerular filtration rate (GFR) showed an elevation in patients with diabetic nephropathy medicated by candesartan [39]. Moreover, studies reported that inducing mesangial constriction and boosting the glomerular filtration coefficient by angiotensin receptor blockers (ARBs) including candesartan can result in increased glomerular filtration rate (GFR) [40]

In the context of blood pressure, in the present study in week 0 both systolic and diastolic blood pressures in the control group showed to be in the normal range, 120±5.4 and 80±3.6 mmHg, respectively. Groups 2, 3, and 4 had hypertension, characterized by systolic blood pressure measurements exceeding 155 mmHg and diastolic blood pressure measurements approaching 88 mmHg. Groups 3 and 4, who received different amounts of candesartan, experienced notable decreases in blood pressure by Week 8. Specifically, Group 3 (16 mg) had a greater drop in blood pressure compared to Group 4 (8 mg).

Consistent with these findings, many studies explored that effect of candesartan on blood pressure. In a study comparing two groups, one group treated with ARBs and the other serving as a control, there was no significant difference in the average systolic and diastolic blood pressure values. The ARB-treated patients had a systolic pressure of 130 ± 6 mmHg, while the control group had a systolic pressure of 132 ± 5 mmHg (P = 0.54). Similarly, the ARB-treated patients had a diastolic pressure of 69 ± 4 mmHg, while the control group had a diastolic pressure of 67 ± 5 mmHg (P = 0.32) [36].

A 2022 study found that among individuals with hypertension, the mean systolic and diastolic pressures before treatment were 142.50±6.62 mmHg and 94.34±5.25 mmHg, respectively. After treatment of candesartan for a three-months course, blood pressure was decreased. Both systolic and diastolic dropped to 127.60±6.15 mmHg and 83.54±5.34 mmHg respectively and this reduction was significant (p- value <0.001) [41].

Additionally, ameta-analysis conducted in 2021 showed that candesartan dose variation result in varied blood pressure reductions. A decrease in systolic blood pressure was seen, with a systolic blood pressure of -3.3 ± 18.6 mmHg at 64 mg and -4.0 ± 12.4 mmHg at 128 mg, respectively. When compared to candesartan 16 mg, which resulted in a drop in systolic blood pressure of -0.6 ± 11.6 mmHg, this found to be significantly lower [42].

At the beginning of this study (Week 0), the control group (Group 1) exhibited proteinuria levels within the normal range (4.52 ± 0.9 mg/dL), but Groups 2, 3, and 4, which consisted of individuals with diabetes and hypertension, showed significantly higher proteinuria levels, exceeding 35 mg/dL. Throughout the study, Groups 3 and 4, which received candesartan treatment, experienced substantial decreases in proteinuria levels by Week 4, followed by additional declines by Week 8.

These findings align with the results of other investigations. A study conducted in Italy investigated the effect of high blood pressure on kidney function in diabetic individuals. The study indicated that for every 5 mmHg increase in blood pressure, there was a 19% higher risk (P < 0.0001) of developing hypertension and a 5% higher risk (P = 0.008) of worsening proteinuria. Individuals with blood pressure levels over 12.8 mmHg were found to have a 50% higher likelihood of developing hypertension and an approximately 20% elevated chance of experiencing worsening proteinuria, in comparison to those with blood pressure levels below 6.9 mmHg [43]. A separate study found that the presence of protein in the urine increased as systolic blood pressure rose, further confirming the connection between hypertension and higher proteinuria [44]. Another investigation revealed that in the group receiving candesartan, there was a substantial reduction in proteinuria levels from 0.95±0.51 to 0.39±0.12 g/day (p=0.033). However, proteinuria levels remained unaltered in the control group [11]. A different study demonstrated a notable decrease in proteinuria following 12 weeks of administering candesartan, in comparison to the control group [36].

Furthermore, research on the dosage of candesartan has demonstrated that increasing the amount of medication results in more significant decreases in proteinuria. Doses of 64 mg and 128 mg resulted in a reduction of proteinuria by -22.23 ± 6.17 and -36.95 ± 7.05, respectively, compared to a reduction of -7.59 ± 5.69 at a dose of 16 mg [42]. A study on high dosages of candesartan found that starting at 16 mg or 32 mg and gradually increasing to 96 mg resulted in a gradual decrease in proteinuria, with the reduction being directly proportional to the dose [45].

CONCLUSION

Candesartan has the ability to effectively enhance renal function by decreasing proteinuria, and blood creatinine levels and elevating glomerular filtration rate (GFR). Greater doses of candesartan were associated with more significant enhancements in renal function and blood pressure, revealing a response that is depending on the dosage. The study provides evidence for the efficacy of candesartan as a medication for managing both kidney dysfunction and hypertension in individuals with diabetes. The study emphasizes the significance of

targeted therapy in enhancing patient outcomes and suggests that additional research should investigate the ideal dosage and long-term impacts. This study contributes to the growing body of evidence that supports the advantageous role of candesartan in the management of complicated health issues.

REFERENCES

1. Samsu N. Diabetic nephropathy: challenges in pathogenesis, diagnosis, and treatment. BioMed research international. 2021 Jul 8;2021.
2. Carriazo S, Vanessa Perez-Gomez M, Ortiz A. Hypertensive nephropathy: a major roadblock hindering the advance of precision nephrology. Clinical kidney journal. 2020 Aug;13(4):504-9.
3. Pelle MC, Provenzano M, Busutti M, Porcu CV, Zaffina I, Stanga L, Arturi F. Up-date on diabetic nephropathy. Life. 2022 Aug 8;12(8):1202.
4. Thomas MC. Targeting the pathobiology of diabetic kidney disease. Advances in Chronic Kidney Disease. 2021 Jul 1;28(4):282-9.
5. Stompor T, Perkowska-Ptasińska A. Hypertensive kidney disease: a true epidemic or rare disease. Pol Arch Intern Med. 2020 Feb 27;130(2):130-9.
6. Banerjee D, Winocour P, Chowdhury TA, De P, Wahba M, Montero R, Fogarty D, Frankel AH, Karalliedde J, Mark PB, Patel DC. Management of hypertension and renin-angiotensin-aldosterone system blockade in adults with diabetic kidney disease: Association of British Clinical Diabetologists and the Renal Association UK guideline update 2021. BMC nephrology. 2022 Dec;23:1-31.
7. Akhtar M, Taha NM, Nauman A, Mujeeb IB, Al-Nabet AD. Diabetic kidney disease: past and present. Advances in anatomic pathology. 2020 Mar 1;27(2):87-97.
8. Martínez MM, Causillo TC, Agüero JE, Silva MG. Microalbuminuria as a marker of kidney damage in patients with diabetes mellitus. J Clin Med Rev. 2022;1(1):2836-330.
9. Patel DM, Bose M, Cooper ME. Glucose and blood pressure-dependent pathways–the progression of diabetic kidney disease. International journal of molecular sciences. 2020 Mar 23;21(6):2218.
10. Mukoso FN, Wembonyama SO, Gakuru AN, Katembo JL, Séverin AJ, Nkodila AN, Mbala CK, Pwo AK, Tsongo ZK. Heart failure: News on pathophysiology and innovative treatments to prevent it in diabetic patients. A study based on literature. Kivu Medical Journal. 2023 Nov 20;1(2).
11. Mustafaqulo‘g NT. Antihypertensive Efficacy Of Candesartan In Patients With Arterial Hypertension. World Bulletin of Public Health. 2023 Nov 20;28:54-61.
12. Vijay K, Neuen BL, Lerma EV. Heart failure in patients with diabetes and chronic kidney disease: challenges and opportunities. Cardiorenal medicine. 2022 Nov 19;12(1):1-0.
13. De Ciuceis C. Microvascular alterations in diabetes: focus on small resistance arteries. Microcirculation in Cardiovascular Diseases. 2020:149-64.
14. Mohammed SH, Hussein RH. Anti-hypertensive and anti-oxidant activities of walnut almond oil, and corn and candesartan on L-NAME induced hypertensive rats. J ZankoySulaimani. 2020 Dec 20;22:43-54.
15. Ashcheulova T, Gerasimchuk N, Kovalyova O, Kompaniiets K, Honchar O. Antihypertensive treatment effects on systemic inflammation, oxidative stress and proinflammatory cytokines.
16. Hanna SM, Rabea HM, Abdelrahim ME, Mahmoud HB. Safety and efficacy of candesartan versus valsartan combined with amlodipine on peripheral and central blood pressure. Hipertensión y Riesgo Vascular. 2024 Feb 28.
17. Moratal C, Laurain A, Naïmi M, Florin T, Esnault V, Neels JG, Chevalier N, Chinetti G, Favre G. Regulation of monocytes/macrophages by the renin–angiotensin system in diabetic nephropathy: State of the art and results of a pilot study. International Journal of Molecular Sciences. 2021 Jun 2;22(11):6009.
18. Atwa AM, Abd El-Ghafar OA, Hassanein EH, Mahdi SE, Sayed GA, Alruhaimi RS, Alqhtani HA, Alotaibi MF, Mahmoud AM. Candesartan attenuates cisplatin-induced lung injury by modulating oxidative stress, inflammation, and TLR-4/NF-κB, JAK1/STAT3, and Nrf2/HO-1 signaling. Pharmaceuticals. 2022 Oct 2;15(10):1222.
19. Vargas F, Wangesteen R, Rodríguez-Gómez I, García-Estañ J. Aminopeptidases in cardiovascular and renal function. Role as predictive renal injury biomarkers. International Journal of Molecular Sciences. 2020 Aug 5;21(16):5615.
20. Moety Da, Alaa I, Mahmoud Ma, Ebtesam Mi. Protective Effect of Angiotensin II Type 1-Receptor- Blocker on Diabetic Nephropathy in Rats: Role of Nephrin. The Medical Journal of Cairo University. 2020 Dec 1;88(December):2081-9.
21. Sinha SK, Nicholas SB. Pathomechanisms of Diabetic Kidney Disease. Journal of Clinical Medicine. 2023 Nov 27;12(23):7349.
22. Wang M, Li J, Li Y, Yao S, Zhao M, Wang C, Wu S, Xue H. The effects of hypertension and diabetes on new-onset chronic kidney disease: a prospective cohort study. The journal of clinical hypertension. 2020 Jan;22(1):39-46.

23. Jia G, Sowers JR. Hypertension in diabetes: an update of basic mechanisms and clinical disease. Hypertension. 2021 Nov;78(5):1197-205.
24. Tsimihodimos V, Gonzalez-Villalpando C, Meigs JB, Ferrannini E. Hypertension and diabetes mellitus: coprediction and time trajectories. Hypertension. 2018 Mar;71(3):422-8.
25. Geldsetzer P, Manne-Goehler J, Theilmann M, Davies JI, Awasthi A, Vollmer S, Jaacks LM, Bärnighausen T, Atun R. Diabetes and hypertension in India: a nationally representative study of 1.3 million adults. JAMA internal medicine. 2018 Mar 1;178(3):363-72.
26. United Nations Population Division. The World Population Prospects: 2015 Revision. New York, NY: United Nations; 2015.
27. Zhou B, Bentham J, Di Cesare M, Bixby H, Danaei G, Cowan MJ, Paciorek CJ, Singh G, Hajifathalian K, Bennett JE, Taddei C. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19· 1 million participants. The Lancet. 2017 Jan 7;389(10064):37-55.
28. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity, kidney dysfunction and hypertension: mechanistic links. Nature reviews nephrology. 2019 Jun;15(6):367-85.
29. Koenen M, Hill MA, Cohen P, Sowers JR. Obesity, adipose tissue and vascular dysfunction. Circulation research. 2021 Apr 2;128(7):951-68.
30. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. Hypertension. 2006 Feb 1;47(2):296-308.
31. Tynjälä A, Forsblom C, Harjutsalo V, Groop PH, Gordin D. Arterial stiffness predicts mortality in individuals with type 1 diabetes. Diabetes Care. 2020 Sep 1;43(9):2266-71.
32. Tramunt B, Smati S, Grandgeorge N, Lenfant F, Arnal JF, Montagner A, Gourdy P. Sex differences in metabolic regulation and diabetes susceptibility. Diabetologia. 2020 Mar;63:453-61.
33. Pandya D, Nagrajappa AK, Ravi KS. Assessment and correlation of urea and creatinine levels in saliva and serum of patients with chronic kidney disease, diabetes and hypertension–a research study. Journal of clinical and diagnostic research: JCDR. 2016 Oct;10(10):ZC58.
34. Trojachanec J, Pavlovska K, Gjorgjievska K, Kolovchevski N, Shikole E, Labachevski B, Nikodinovski A, Kikerkov I, Zafirov D. Nephroprotectiv Effects Of Candesartan On Diabetic Nephropathy In Rats. Jms= Journal of Morphological Sciences. 2023
35. Fandinata SS, Darmawan R, Utami PR, Ulfa NM. Monitoring Kidney Function Through the Use of Candesartan, Telmisartan or Valsartan Antihypertensive Therapy towards Patients CKD. Media Kesehatan Masyarakat Indonesia. 2022 Mar 31;18(1):1-9.
36. Tamura Y, Kosuga M, Yamashita M, Tomioka S, Sasaki M, Hikita T, Nakajima H, Kojima K, Uchida S. Renoprotective effects of angiotensin II receptor blocker, candesartan cilexetil, in patients with stage 4–5 chronic kidney disease. Clinical and experimental nephrology. 2008 Aug;12:256-63.
37. Rossing K, Christensen PK, Hansen BV, Carstensen B, Parving HH. Optimal dose of candesartan for renoprotection in type 2 diabetic patients with nephropathy: a double-blind randomized cross-over study. Diabetes care. 2003 Jan 1;26(1):150-5.
38. Quinn GZ, Abedini A, Liu H, Ma Z, Cucchiara A, Havasi A, Hill J, Palmer MB, Susztak K. Renal histologic analysis provides complementary information to kidney function measurement for patients with early diabetic or hypertensive disease. Journal of the American Society of Nephrology. 2021 Nov 1;32(11):2863-76.
39. Puspita FM, Yunir E, Agustina PS, Sauriasari R. Effect of angiotensin receptor blocker and angiotensin converting enzyme inhibitor on kidney function and blood potassium level in Indonesian type 2 diabetes mellitus with hypertension: a three-month cohort study. Diabetes, Metabolic Syndrome and Obesity. 2021 Sep 7:3841-9.
40. Kobori H, Mori H, Masaki T, Nishiyama A. Angiotensin II blockade and renal protection. Current pharmaceutical design. 2013 May 1;19(17):3033-42.
41. Althanoon ZA, Thanoon IA. Comparative Effects of Amlodipine and Candesartan on Blood Pressure and Metabolic Profile in Non-Diabetic Hypertensive Patients. Pharmacognosy Journal. 2022;14(1).
42. Gonius A, Adisaputra A, Farahdina F, Rifdah S, Indrasari A, Tjempakasari A. Efficacy and Safety of Candesartan 16 mg versus 64 mg Candesartan in Renal Disease Patients with Proteinuria: A Systematic Review and Meta-analysis. Open Access Maced J Med Sci. 2021 Nov 24; 9 (F): 608-612.
43. Viazzi F, Russo E, Mirijello A, Fioretto P, Giorda C, Ceriello A, Copetti M, Russo GT, Di Bartolo P, Manicardi V, Leoncini G. Long-term blood pressure variability, incidence of hypertension and changes in renal function in type 2 diabetes. Journal of hypertension. 2020 Nov 1;38(11):2279-86.
44. Kochi M, Kohagura K, Oshiro N, Zamami R, Nagahama K, Nakamura K, Ohya Y. Association of blood pressure and hyperuricemia with proteinuria and reduced renal function in the general population. Hypertension Research. 2023 Jul;46(7):1662-72.

45. Weinberg MS, Weinberg AJ, Cord R, Zappe DH. The effect of high-dose angiotensin II receptor blockade beyond maximal recommended doses in reducing urinary protein excretion. Journal of the Renin-Angiotensin-Aldosterone System. 2001 Mar;2(1_suppl):S196-8.