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Renin-Angiotensin System Inhibition Improves Lipid Profile in Patients with Chronic Kidney Disease

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Abstract: The aim of this study was to evaluate whether the blockade of renin-angiotensin system (RAS), achieved by angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), could affect the plasma lipid profile in chronic kidney disease (CKD) patients. Ninety-four hypertensive patients with CKD (stage 3-5) were enrolled. Forty-nine patients were treated with either ACEIs or ARBs daily for 6 months, and forty-five patients were treated with other antihypertensive agents (calcium channel blockers (amlodipine), b blockers, diuretics) as positive control group. Creatinine, estimated glomerular filtration rate (eGFR), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride (TG) levels measurements were performed before and after the six-month treatment. An improvement in serum lipids levels in hypertensive patients with CKD resulted from RAS blocked therapy and other antihypertensive agents. Both treatment groups significantly decreased total cholesterol (TC), by 7.77% in ACEIs/ARBs group ($p \leq 0.01$) and 6.42% in other antihypertensive group ($p \leq 0.05$). In CKD patients treated with ACEIs/ARBs, levels of TG (3.29%), and LDL-C (3.15%) dropped more than with other antihypertensive medications (2.12%, and 1.19% respectively). RAS blocked therapy significantly increased HDL-C levels in CKD patients by 5.94% ($p \leq 0.05$). The results indicate that RAS blockade therapy with ACEIs or ARB positively affects lipid profile, which may improve the cardiovascular risks caused by CKD.

Keywords: Chronic Kidney Disease, Serum Lipid Profile, Hypertension, ACEIs, ARBs.

تثبيط جملة الرينين-أنجيوتنسين يحسن الصيغة اللبيدية لدى مرضى الداء الكلوي المزمن

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المستخلص: هدفت الدراسة لتقييم دور حصر جملة الرينين-أنجيوتنسين renin-angiotensin system (RAS) بوساطة مثبطات الأنزيم المحول للأنجيوتنسين أو حصر مستقبلات الأنجيوتنسين على الصيغة اللبيدية البلازمية لمرضى الداء الكلوي المزمن. شملت الدراسة أربع وتسعون مريض ارتفاع ضغط دموي مترافق مع الداء الكلوي المزمن من مراجعي قسم الكلية والتحال الدموي في مشفى تشرين الجامعي في مدينة اللاذقية في سوريا خلال الفترة الممتدة من شهر أيلول 2019 ولغاية شهر آذار 2022. تمت معالجة تسع وأربعين مريض إما بـ Angiotensin Converting Enzyme Inhibitors (ACEI) أو Angiotensin Receptor Blockers (ARB) بجرعة يومية لمدة ستة أشهر، في حين عولج خمس وأربعون مريض بعوامل أخرى خافضة للضغط الدموي بجرعة يومية لمدة ستة أشهر. تم قياس مستويات كل من الكرياتينين، معدل الترشيح الكبيبي، البروتين الشحمي منخفض الكثافة، البروتين الشحمي مرتفع الكثافة، الكوليسترول الكلي والشحوم الثلاثية قبل المعالجة وبعدها بستة أشهر من المتابعة. لوحظ تحسن مستويات اللبيدات البلازمية لدى مرضى ارتفاع الضغط الدموي المترافق مع الداء الكلوي المزمن لدى كلا مجموعتي المرضى المعالجين بحاصرات جملة الـ renin-angiotensin system (RAS) والمعالجين بخافضات الضغط الأخرى. حققت كلا مجموعتي المعالجة انخفاضاً هاماً إحصائياً لمستويات الكوليسترول الكلي، بنسبة 7.77% في مجموعة ACEIs/ARBs ($p \leq 0.01$) ونسبة 6.42% لدى المجموعة المعالجة بخافضات الضغط الأخرى ($p \leq 0.05$). لوحظ انخفاض مستويات الشحوم الثلاثية (3.29%) ومستويات البروتين الشحمي منخفض الكثافة (3.15%) بشكل أكبر لدى مرضى الداء الكلوي المزمن المعالجين بـ ACEIs/ARBs مقارنة مع مستوياتهم لدى مرضى الداء الكلوي المزمن المعالجين بخافضات الضغط الأخرى (2.12% و1.19% على التوالي). حققت المعالجة بحاصرات جملة RAS زيادة هامة إحصائياً في مستويات البروتين الشحمي مرتفع الكثافة لدى مرضى الداء الكلوي المزمن بنسبة 5.94% ($p \leq 0.05$). تشير هذه النتائج إلى أن المعالجة بحاصرات جملة RAS بواسطة ACEIs أو ARBs تؤثر إيجابياً على الصيغة اللبيدية مما قد يساهم في تحسين المخاطر القلبية الوعائية الناتجة عن الداء الكلوي المزمن.

الكلمات المفتاحية: الداء الكلوي المزمن، الصيغة اللبيدية البلازمية، ارتفاع الضغط الدموي، ACEIs، ARBs .

Introduction:

Chronic kidney disease (CKD) is one of the most common and serious public health issues nowadays, with an increasing incidence and prevalence [1]. Patients with chronic kidney disease (CKD), particularly those with end-stage renal disease (ESRD), have a higher risk of cardiovascular diseases (CVD) morbidity and mortality [2]. Early detection and management of CVD risk factors in CKD patients are the key components of treatment approaches aiming at reducing cardiovascular mortality and morbidity. Because lipids are thought to play an essential role in CVD development, total plasma triglycerides (TG) and cholesterol (TC), as well as low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) are traditionally examined as predictors of cardiovascular events [3].

Poor lipid profiles are typical in patients with CKD and hypertension, who are at significant risk for cardiovascular events. In contrast to earlier strategies, that only concentrated on reducing cardiovascular risks by hypertension control, the assessment and management of all circumstances that provide a risk for cardiovascular disease are now essential for a comprehensive approach. Therefore, the possible lipid profile effects of antihypertensive therapy should be assessed to determine whether they are favorable or unfavorable [4].

The most commonly used treatments for CKD that includes angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). In addition to reducing blood pressure (BP) and proteinuria, ACEIs and ARBs have other mechanisms of action [5]. Studies have demonstrated that ACEIs and ARBs improve essential hypertension, type 2 diabetes, and plasma lipid levels in non-renal individuals. However, little is currently known regarding how ACEIs and ARBs use affects plasma lipid profile in CKD patients. In this study, the probable positive effects of ACEIs and ARBs on plasma lipid levels in individuals with CKD were investigated.

Materials and Methods

Patients and study design

In this 24-week follow-up study, 106 CKD (stage 3-5) patients with essential hypertension who received ACEIs/ARBs or another antihypertensive drug treatment, at the Department of Nephrology and Hemodialysis of Tishreen Hospital in Lattakia, Syria, from September 2019 to March 2022, were chosen to participate. All participants provided their signed consent after receiving full information.

Of the 106 CKD patients, 12 passed away during the 24-week follow-up period. Among them, two patients received treatment with ACEIs/ARBs, while ten patients received treatment with another antihypertensive medication, (3.92 %, and 21.27 % respectively). In all, 94 patients with CKD and essential hypertension were included and followed up.

The patients (51 men and 43 women) were non-dyslipidemic, older than 18 years, with an average age of 53.75 ± 14.88 years, non-obese (BMI ≤ 30). The 94 patients included 47 patients with

diabetes mellitus. All cases (n=94) had compromised renal function, as measured by an eGFR< 60 ml/min/1.73m2 and serum creatinine > 1.2 mg/dl, and were controlled hypertensives (BP ≤ 140/90 mmHg) treated with ACEIs/ARBs or with another antihypertensive drug. None of the patients received dietary guidance; they all continued to eat as normal.

Patients under the age of 18, women who were pregnant, those who had a life-threatening illness such as cancer, thyroid dysfunction, heart disease, liver disease, or those who were receiving lipid-lowering treatment were excluded.

The following patient groups were created in accordance to treatment plan:

- Group I: Forty-nine (49) hypertensive patients with CKD were treated with ACEIs/ARBs, once daily for six months.
- Group II: Forty-five (45) hypertensive patients with CKD were treated with another antihypertensive agent once daily for six months (the majority of agents were calcium channel blockers, particularly amlodipine).

All patients had their study parameters measured twice, at the beginning of the study and again six months later. All blood samples were taken in the morning after at least 10-hour fast in order to conduct biochemical tests. Fasting plasma glucose (FBG), TC, TG, HDL-C, and LDL cholesterol levels were assessed using commercially available kits and the automated biochemical analyzer (Mindray BS-380). Glomerular filtration rate (GFR) was calculated according to the simplified version of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Weight (in kg) and height (in cm) were measured, and body mass index (BMI) was calculated as body weight/ height2 (kg/m2).

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) version 25.0 for Windows. All results were expressed as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. We used Student's t-test to compare means. Differences were considered significant at $P \leq 0.05$.

Results:

Demographic characteristics and biochemical results of study population:

Table (1) shows the demographic characteristics and biochemical results of study population at the beginning of the study, where all patients were suffering from CKD with hypertension.

The two groups were comparable in term of age, the mean age of ACEIs/ARBs group was (58.12±13.14) years, and the mean age of the other antihypertensive group (calcium channel blockers (amlodipine), b blockers, diuretics) was (49±15.17) years without significant differences. We found that (65.3%) of the ACEIs/ARBs group and (33.3%) of the other antihypertensive group had diabetes mellitus.

There was (32.65%) of the ACEIs/ARBs group on hemodialysis versus (66.67%) of other antihypertensive group.

All patients were non-dyslipidemic and their mean lipid levels were as following: TC <200 mg/dl (151.86 ± 42.44, 143.76 ± 34.32), TG <150 mg/dl (143.35 ± 77.50, 134.02 ± 66.45), LDL<130 mg/dl (98.62 ± 42.25, 83.44 ± 33.50) and HDL > 40 mg/dl (45.91 ± 13.24, 45.23 ± 12.86) for ACEIs/ARBs and other antihypertensive group respectively.

By monitoring blood pressure in all individuals during 24-week follow-up, we found that all patients had controlled hypertension in both ACEIs/ARBs and other antihypertensive group where the mean of systolic pressure was less than 140 mm Hg (136.82 ± 12.05, 138.71 ± 12.59) and the mean of diastolic pressure was less than 9 mm Hg (83.51 ± 9.26, 79.27 ± 9.05) correspondingly.

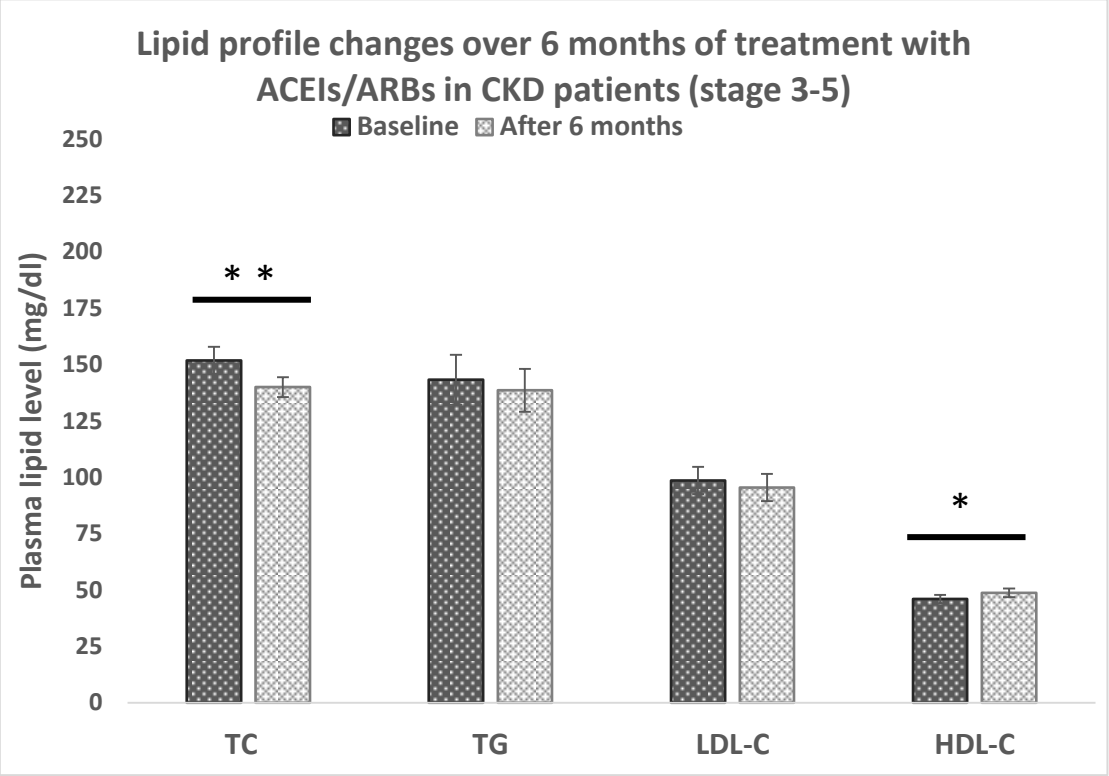
Table 1: Baseline demographic characteristics and biochemical results of the study population.

Characteristic	ACEIs/ARBs group	Other antihypertensive group
	N=49	N=45
Male, number (%)	25 (51.02)	26 (57.7)
Age, years	58.12±13.14	49±15.17
BMI (kg/m^2)	24.38±3.28	22.38±3.78
Diabetes mellitus, number (%)	32 (65.3)	15 (33.3)
Hemodialysis, number (%)	16 (32.65)	30 (66.67)
Total cholesterol, mg/dl	151.86±42.44	143.76±34.32
LDL cholesterol, mg/dl	98.62±42.25	83.44±33.50
HDL cholesterol, mg/dl	45.91±13.24	45.23±12.86
Triglycerides, mg/dl	143.35±77.50	134.02±66.45
24-hour ambulatory BP, mm Hg for 24-week follow-up		
Systolic	136.82±12.05	138.71±12.59
Diastolic	83.51±9.26	79.27±9.05
Data are presented as total (%), mean±SD. BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein.		

Lipid profile changes over 6 months of treatment with ACEIs/ARBs in CKD patients

Figure (1) shows the effect of ACEIs/ARBs treatment on lipid profile in study population after six-month follow-up. For more illustration, the mean level of TC was 151.86 ± 42.44 mg/dl before treatment with ACEIs/ARBs (once dose/day) and significantly decreased to 140.06 ± 30.86 mg/dl at the end of the sixth month ($p \leq 0.01$). Additionally, the mean level of HDL-C significantly increased from 46.05±13.19 mg/dl to 48.79 ± 13.47 mg/dl after 6 months of treatment with ACEIs/ARBs ($p \leq 0.05$). However, the mean level of triglycerides was 143.35 ± 77.50 mg/dl at baseline, then dropped unremarkably to 138.63 ± 66.98 mg/dl after 6 months of treatment. The mean of LDL-C was also insignificantly lowered from 98.62 ± 42.25 mg/dl at baseline to 95.51 ± 41.86 mg/dl at the end of the sixth-month treatment with ACEIs/ARBs.

Figure 1: Lipid profile changes over 6 months of treatment with ACEIs/ARBs in CKD patients (stage 3-5).

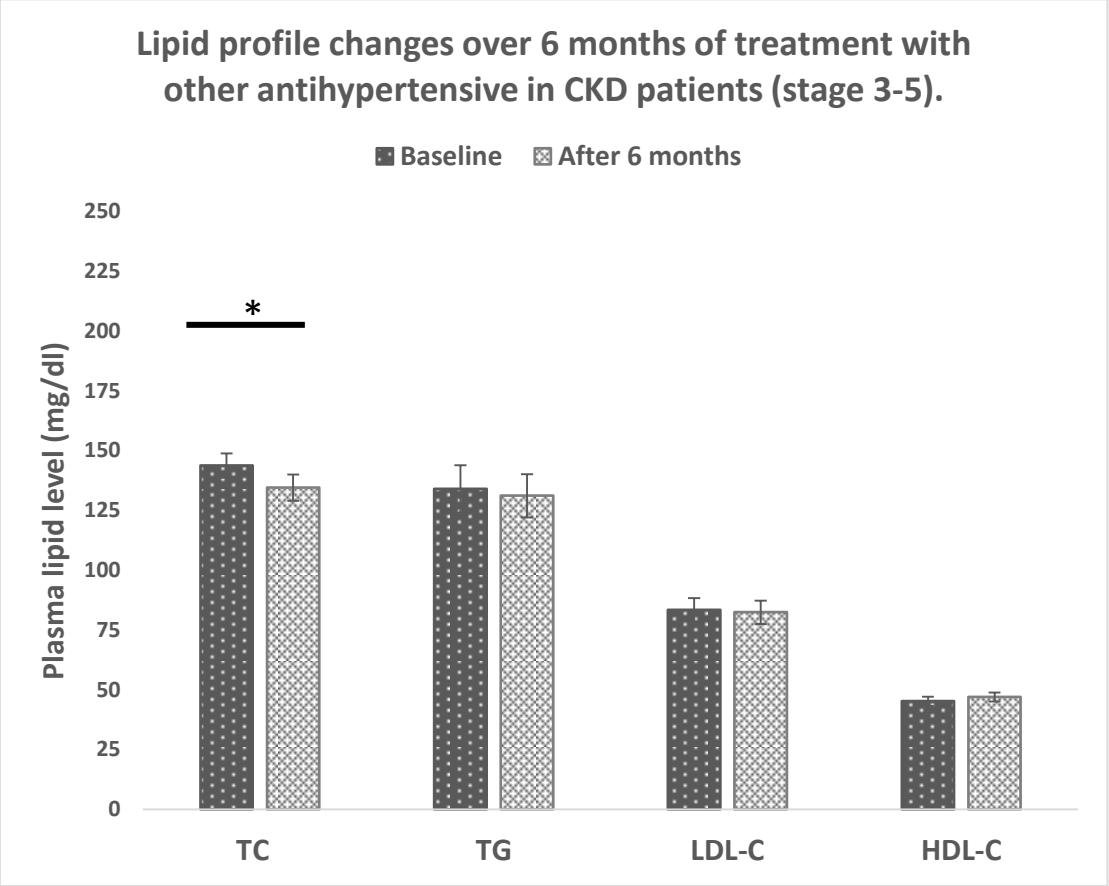


*: p≤0.05, **: p≤0.01

Lipid profile changes over 6 months of treatment with other antihypertensive in CKD patients

Figure (2) shows the effect of other antihypertensive treatments on lipid profile among the study population after six-month follow-up. To clarify, the mean level of total cholesterol was 143.76 ± 34.32 mg/dl before treatment and significantly decreased to 134.53 ± 37.03 mg/dl at the end of the study (p≤0.05). However, the mean level of triglycerides was 134.02 ± 66.45 mg/dl and decreased insignificantly to 131.18 ± 60.65 mg/dl at the end of the treatment course. Additionally, there was no statistically significant change in the mean LDL-C level between baseline and six months of treatment (83.44 ± 33.50 mg/dl, 82.45 ± 32.63 mg/dl). In a similar manner, HDL-C level increased negligibly from 45.23 ± 12.86 mg/dl before therapy to 47.06 ± 12.45 mg/dl after six months of treatment with other antihypertensive.

Figure 2: Lipid profile changes over 6 months of treatment with other antihypertensive in CKD patients (stage 3-5)



Comparison between ACEIs/ARBs and other antihypertensive effects on lipid profile after six-month follow-up treatment

The results presented in table (2) show the differences between the percentages of change in lipid profile levels between patients treated with ACEIs/ARBs or other antihypertensive agents. Throughout the course of the treatment, there were no statistically significant variations in the levels of serum total cholesterol or triglycerides between the two groups. Total cholesterol and triglyceride levels decreased in both groups, although the angiotensin-inhibitor therapy group's benefit was more noticeable. Similarly, the percentages of changes in HDL-C levels were not significantly different at the end of the study. This shows that the antihypertensive medications employed improved serum levels of LDL-C and HDL-C although the effect was stronger in the group treated with ACEIs/ARBs (Table 4).

Table 2: Comparison between the effects of ACEIs/ARBs and other antihypertensive on lipid profile at baseline and at the end of six-month follow-up period.

Parameter	Time	ACEIs/ARBs group	% Δ	Other antihypertensive group	% Δ	P. value*
TC (mg/dl)	Baseline	151.86	↓ 7.77	143.76	↓ 6.42	0.832
	After 6 months	140.06		134.53		
TG (mg/dl)	Baseline	143.35	↓ 3.29	134.02	↓ 2.12	0.986
	After 6 months	138.63		131.1		

Parameter	Time	ACEIs/ARBs group	% Δ	Other antihypertensive group	% Δ	P. value*
LDL-C (mg/dl)	Baseline	98.62	↓3.15	83.44	↓1.19	0.883
	After 6 months	95.51		82.45		
HDL-C (mg/dl)	Baseline	46.06	↑5.94	45.45	↑3.55	0.390
	After 6 months	48.79		47.06		

*P. values (P<0.05) were calculated for % Δ by independent-samples t-test.

Discussion:

The current study demonstrates the role of RAS inhibition in improvement lipid profile in CKD patients. Abnormal lipid profile was considered as a traditional risk factor of cardiovascular events especially atherosclerosis [6]. It has been proven to be the main cause of morbidity and mortality in CKD patients [2].

This study showed that RAS inhibitors (ACEIs and ARBs) had favorable effects on lipid profile in CKD patients after six-month treatment. Although the patients in our study were non-dyslipidemic, there were significant effects on total cholesterol and HDL-C level.

Evidence of relationship between lipid profile and RAS activation in cardiovascular disorders is growing. Angiotensin II, a mediator of RAS, has emerged as a multifunctional cytokine with growth factor, pro-fibrogenic and pro-inflammatory properties. Angiotensin II also plays a role in lipid metabolism [7]. **Ma et al**.[8]reported that angiotensin II induced lipid accumulation in human renal mesangial cells (HMCs). **Borghi et al.**[9]reported that angiotensin II affected the cholesterol level in macrophages and foam cells.

The interaction between RAS and LDL-C can also be bidirectional. Native or oxidized LDL, an atherogenic lipoprotein, increases the expression of the angiotensin-converting enzyme (ACE) and angiotensin II receptor type 1 (AT1) in human endothelial cells via LDL receptors and scavenger receptors. Angiotensin II, in its turn promotes LDL oxidation, macrophage and smooth muscle cell absorption of LDL[10]. **Daugherty et al.**[11]demonstrated that hypercholesterolemia per se exerts a stimulatory effect on the different components of RAS at tissue level. **Pizoń et al.**[12]showed a positive association between plasma renin activity and LDL-C in well-phenotyped and untreated low-renin primary hypertension (LREH) patients. **Jacobsen et al.**[13]suggested a beneficial effect of RAS blockade on plasma TC and LDL-cholesterol levels in type I diabetic patients with diabetic nephropathy. Taking into consideration the literature cited above, there are enough theoretical evidence to suspect that inhibiting the angiotensin system could have a positive impact on the plasma lipid levels of CKD patients.

It is very likely that the selection of the group of CKD patients in our study, i.e. normal lipid levels in CKD subjects, could have influenced the obtained results, where the effect was modest. Furthermore, we did not distinguish between the treatment with ACEIs and ARBs as RAS inhibitors. Therefore, it may be challenging to determine which medication in our study had the most positive effects on lipid levels in

CKD patients. **Derosa et al**.[14]suggested that compared to eprosartan in a double-blind, placebo-controlled study, telmisartan significantly decreased plasma TC, LDL-cholesterol, and TG. **Kyvelou et al**.[15]showed that only valsartan and losartan, from six different ARBs, improved TG, although losartan also improved TC, LDL, TC/HDL, and apoprotein B (ApoB). Notably, the study only looked at people with hypertension and excluded anyone who had renal disease.

In the current study, angiotensin-II inhibition had a minimal impact on TG and LDL levels in the hypertensive individuals who also had CKD. This goes against several earlier studies, which claimed that RAS inhibition could affect TG and LDL. The majority of these trials, however, were conducted on specialized populations such diabetic patients, those with reduced glucose tolerance, and people with nephrotic syndrome [16, 17]. On the other hand, many trials had used high doses or combination therapy of ACEIs and ARBs to achieve that impact on lipid profile[18, 19]. In our study, we did not evaluate the effect of specific dose of ACEIs or ARBs. Moreover, the lengths of our treatment periods were 24 weeks, we cannot be sure if full treatment effects have developed. However, studies in renal [13, 20] and nonrenal [14, 21] hypertensive patients have suggested an antilipidemic and antihypertensive effect of ARBs or ACEIs to be present after less than 48 week of treatment.

The second finding of our study is that compared to other antihypertensive drugs (calcium channel blockers (amlodipine), b blockers, diuretics), RAS inhibitors achieved better improvement in serum lipid profiles after 6 months of treatment, although that improvement did not reach the significant importance. Different antihypertensive medications are known to affect lipid metabolism in different ways. Some of them have been seen to have cholesterol-lowering benefits, while others have negative effects on lipid metabolism. According to what is currently known, β-blockers and diuretics have detrimental effects on lipid metabolism [22], whereas calcium channel blockers, particularly amlodipine, decrease LDL oxidation and LDL entry into cells and thereby reduce atherosclerosis [4].

It is interesting that, in our study, CCBs, notably amlodipine, made up the bulk of the other hypertensive group of treatments, which can explain why they had a lowering effect on lipid levels in CKD patients. In keeping with this, **Saker and colleagues**[20] demonstrated that, after 6 months of treatment, TC, LDL-C, and TG levels significantly decreased in both treated groups when amlodipine (a calcium channel blocker) was used alone as well as in conjunction with enalapril (an angiotensin converting enzyme inhibitor). Additionally, both treatment groups showed a clear and significant increase in serum HDL-C levels.

Iyalomhe et al.[23]showed that in hypertensive Nigerian patients, amlodipine monotherapy dramatically reduced TC, TG, LDL, and improved HDL-C mean values while amlodipine and hydrochlorothiazide combination therapy significantly increased TC and TG as well as lowered HDL values. This discovery of amlodipine's greater therapeutic advantages may be related to its pleiotropic activities, which are independent of BP lowering and include anti-atherosclerotic, anti-oxidant, anti-inflammatory, and potentiation of nitric oxide activity. Amlodipine's physicochemical characteristic

(positive charge at physiological pH) results in potent electrostatic interactions with the head groups of membrane phospholipids and prevents cholesterol from widening membranes. Including antihypertensive medications (other CCBs, ACEIs) that lack these physicochemical properties do not exhibit this atheroprotective benefit.

The third finding of our study is that the percent of mortality in ACEIs/ARBs group was 3.92% versus 21.27% in another antihypertensive treatment group (calcium channel blockers (amlodipine), b blockers, diuretics) during six-month follow-up duration. ACEIs and ARBs are still superior to other antihypertensive drugs and have the highest benefits for the prevention of kidney events, cardiovascular outcomes, cardiovascular death and all-cause mortality in dialysis and non-dialysis dependent CKD patients [24-26]. Notably, the twelve patients who passed away from both treated groups were receiving maintenance hemodialysis (MHD). Maintenance hemodialysis (MHD) lowers HDL functions, such as the ability to take up cholesterol from lipid-loaded cells and the ability to reduce inflammation and oxidative stress [27].

The underlying mechanisms by which various ARBs and ACEIs affect lipid profiles in patients with hypertension, diabetes, and kidney disease still unclear. **Vanitha M. et al**.[21]showed that telmisartan was beneficial in managing lipid profiles in addition to blood pressure. Telmisartan, an angiotensin receptor blocker with a partial agonistic effect on PPAR- α, may be blame for such outcome. They speculated that this effect might be due to unique molecular structural properties of telmisartan, not shared by other ARBs. However, 50 individuals were included in their research, and all of them had moderate dyslipidemia and grade I essential hypertension. **Srivastava et al**.[19]speculated that losartan, independent of the antiproteinuric effect, improves dyslipidemia by reducing hepatic VLDL production or improving VLDL catabolism (or a combination of the two).

We should be aware of various restrictions on our study. First off, more individuals received ARBs treatment than ACEIs treatment during the course of the 24 weeks of the trial. Second, patients were not dyslipidemic, which could have prevented the effect from being clearly seen. Third, due to the limited sample size and brief therapy period (24 weeks), we were unable to determine which antihypertensive medication might be helpful in terms of lipid metabolism in those hypertensive patients with CKD. Finally yet importantly, we did not impose a synthetic diet on patients in order to maintain a constant daily intake of cholesterol and fat throughout the trial.

In conclusion, additional studies are required to examine the impact of RAS blocker drugs in the various stages of CKD, and more patients with more advanced CKD must be enrolled in clinical trials to improve our comprehension of how to improve outcomes for this high-risk population.

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