Renoprotective Effect of Losartan Versus Enalapril in Children with Chronic Kidney Disease

Abstract:

Background: Proteinuria is a marker of severity of chronic kidney disease)CKD) and leads to progression to end stage renal disease which can be reduced by blocking renin angiotensin aldosterone system(RAAS) through angiotensin converting enzyme inhibitors(ACEis) (e.g .enalapril) and angiotensin receptor blockers (ARBs) (e.g. losartan)

Aim of the Work: To evaluate the renoprotective effect of losartan versus enalapril in children with CKD.

Patients and Methods: Sixty CKD children aged (5 to 17 years), were subdivided into three groups as the following: group I; 20 patients received enalapril, group II; 20 patients received losartan, group III; 20 patients didn't receive losartan nor enalapril. All patients were subjected to thorough history, clinical evaluation and laboratory investigations (blood urea, serum creatinine, GFR, 24hours urinary proteins, serum albumin, lipid profile and serum electrolytes) initially and after 6monthes of treatment.

Results: this prospective cohort study was conducted on 34males and 26 females CKD children. Steroid dependant nephrotic syndrome (SDNS) was the commonest cause (53.3%)followed by diabetic nephropathy (DN)(15%), lupus nephritis(LN) (12%) and only 1 case was frequent relapse NS (FRNS). protienuria improved with 76.7% reduction in losartan group versus 45.6%reduction in enalapril group after 6 months of treatment. GFR increased by(4.5%,8.6%) in losartan and enalapril groups respectively. Serum creatinine decreased by(11.6% and 8.3%) in losartan and enalapril groups respectively .

Conclusions: losartan and enalapril have a role in controlling proteinuria distinct from their antihypertensive effect .

Key word: Chronic kidney disease, glomerular filtration rate lower, steroid-resistant nephrotic syndrome and end-stage renal disease

Introduction:

Chronic kidney disease (CKD) is a serious public health problem, with national surveys showing a considerably higher prevalence than appreciated previously. In 2002, the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guide lines defined chronic kidney disease as a kidney damage or glomerular filtration rate lower(GFR) than 60 mL/min per 1.73 m² for 3 months or longer, and proposed a classification scheme based on GFR.(1)

The main etiologic factors of CKD in children are represented by congenital anomalies of the kidney and urinary tract (CAKUT), steroid-resistant nephrotic syndrome (SRNS), chronic glomerulonephritis (e.g. lupus nephritis, Alport syndrome) and renal cilliopathies, that account for approximately 49.1, 10.4, 8.1 and 5.3% of cases, respectively and for more than 70% of all pediatric CKD cases when considered together.(2)

Less common causes of CKD in children include thrombotic micro-angiopathies (especially atypical hemolytic uremic syndrome), nephrolithiasis/ nephrocalcinosis, Wilms tumor, infectious and interstitial diseases.(3)

The pathological changes associated with CKD include glomerulosclerosis and tubulointerstitial fibrosis which result in the loss of normal renal architecture, microvascular capillary rarefaction, hypoxia and tubular atrophy. These changes lead to loss of renal filtrative capacity and ultimately to end-stage renal disease (ESRD).(4)

There is a crucial role of proteinuria in accelerating kidney disease progression to ESRD through multiple pathways, including induction of tubular chemokine expression and complement activation. These events, in turn, lead to inflammatory cell infiltration in the interstitium and sustained fibrogenesis. The extent of proteinuria is widely recognized as a marker of the severity of chronic kidney

disease and as a predictor of future decline in glomerular filtration rate. More importantly, a reduction in proteinuria invariably translates into a protection from renal function decline in patients with CKD.[5]

As lowering of albuminuria is an important short-term goal of treatment, as albuminuria is regarded as a surrogate for renoprotection. [6]

The renin-angiotensin-aldosterone system (RAAS) is a hormonal system that plays an important role in blood pressure (BP) regulation through its effects on vascular tone and sodium homeostasis. Activation of the classical RAAS pathway maintains BP through promoting sodium and water retention, as well as direct vasoconstriction of systemic blood vessels, vasodilatation of afferent arteriole and vasoconstriction of efferent arteriole. In various disease states, RAAS also plays a role in inflammation, oxidative stress, and fibrosis through angiotensin II-mediated events that induce expression of cytokines and chemokines that recruit leukocytes to tissues, enhance smooth muscle cell hypertrophy, and promote vascular remodeling[7]

Angiotensin receptor blocker (ARB), angiotensin converting enzyme inhibitor (ACEi) both block (RAAS) at different levels with antiprotienuric effect distinct from their effects on BP and delay progression to stage 5 CKD.[8]

Aim of the Work

The aim of this study was to evaluate and compare the reno-protective effect of losartan and enalapril (antiprotienuric and slowing kidney disease progression) in children with chronic kidney disease

Patients and methods

Study design

A prospective cohort study that was carried out at Nephrology and Endocrinology Units, Pediatric Department, Tanta University Hospitals. Between April 2019 and May 2020 on sixty CKD patients, Ethical committee approval was 33121/05/19**.**

Patients were subdivided into three groups as the following:

Group I: 20 children with CKD received Enalapril (0.2 mg /kg/day).[9]

Group II : 20 children with CKD received Losartan (1mg/kg/day). [10]

Group III : 20 children with CKD didn't receive Enalapril nor Losartan.

The inclusion criteria:

• Children aged from 5-18 years with chronic kidney disease stage (1-4).

The exclusion criteria:

• Children with chronic kidney disease less than 5 years old
• Stage 5 CKD.
• Children with CKD on Antihypertensive drugs.
• Renal artery stenosis
• Angioedema
• Kidney transplant
• Drugs that interact with these medications

All patients in this study were subjected to the following initially and after 6 months of drug therapy:

1-History:

Including the personal history, cause of CKD [Hereditary nephrotic syndrome, hypertension, diabetes mellitus and autoimmune diseases].

2- Physical examination:

Vital measurement: Anthropometric measurement [Height, Weight, Body mass index (BMI)], Arterial Blood Pressure, and Edema.

3- Laboratory investigations:

• Serum Albumin
• Lipid profile (cholesterol, triglycerides)
• Serum creatinine (measured by enzymatic method)
• Blood urea
• Serum Electrolytes (Na, K)
• Glomerular filtration rate GFR

(Shwartz formula):

eGFR = k x height in cm / serum creatinine

Where the value of "k" is equal to 0.413.[11]

• 24 hour urine proteins
• Pelviabdominal ultrasound

Medications used:
• **Losartan**
• **Enalapril**

Losartan Pharmacokinetics
Description: Losartan is an angiotensin II receptor blocker (ARB).which is available as losartan potassium oral tablets which was used in our study as well as a combination of losartan potassium and hydrochlorothiazide.

Absorption : Following oral administration, it is well absorbed, with systemic bioavailability approximately 33% and about 14% is converted to the active metabolite with a mean peak concentrations at about one hour, and that of its active metabolite at about 3-4 hours.(12)

Protein binding: Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses(12)

Elimination : Single oral dose has 4% excreted in the urine as unchanged losartan, 6% in the urine as the active metabolite(12)

Pharmacodynamics: It reversibly and competitively prevents angiotensin II binding to the AT receptor in tissues like vascular smooth muscle and the adrenal gland by binding themselves to these receptors leading to vascular smooth muscle relaxation, lowering blood pressure.**(13)**

Indications

Hypertension in patients older than 5 years.(14)

• Reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy.(15)

Side effect: Losartan is well tolerated by most patients with reported rare adverse reactions as syncope, hypotension, fatigue, dizziness and hyperkalemia. (12)

Drug interaction

Diuretics : Patients on diuretics may develop hypotension after initiation of therapy with losartan and hyperkalemia especially with potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride).(16)

Lithium Salts: As with other drugs which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.(112)

Drugs Affecting Cytochrome P450 System:Rifampin (inducer of drug metabolism) decreases the concentrations of the active metabolite of losartan. Ketoconazole and erythromycin (two inhibitors of P450 3A4) did not affect the conversion of losartan to the active metabolite after intravenous administration and had no clinically significant effect after oral losartan. Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration(17)

Non-steroidal Anti-inflammatory Drugs (NSAIDs) including Cyclooxygenase-2 Inhibitors (indomethacin) and selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs.(17)

Pharmacokinetics disposition of enalapril

Description:

Enalapril is a prodrug belonging to the ACE inhibitor drug class that works on the renin-angiotensin-aldosterone system, which is responsible for the regulation of

blood pressure and fluid and electrolyte homeostasis.[18]

Absorption:

Being a prodrug, enalapril is rapidly biotransformed into its active metabolite, enalaprilat after absorption from the small intestine, uptake in hepatocytes which is responsible for its pharmacological action, its maximum serum concentrations (Cmax) of around 45–49 ng/ml occur approximately 1 h after oral ingestion of a 10 mg tablet.[18]

The active metabolite of enalapril competitively inhibits the ACE to prevent the production of angiotensin II that promotes vasoconstriction and renal reabsorption of sodium ions in the kidneys. .[18]

Protein binding:

The protein binding of enalaprilat in the circulation is reported to be a little less than 50%, and it penetrates into most tissues, including the vascular endothelium of the lungs where ACE exists at the endothelial cell surface, which is shed and hydrolyses circulating peptides.[18]

Elimination

It is predominantly renal; 43% of the dose is recovered in urine as enalaprilat and 18% is recovered as enalapril. This renal elimination is biphasic. The initial phase reflects glomerular filtration combined with tubular secretion, followed by a later phase that reflects the equilibrium of the drug from tissue distribution sites.[18]

Enalapril Pharmacodynamics

Although it was initially developed as an antihypertensive drug, enalapril is prescribed in patients with CKD with the aim of reducing proteinuria and thereby improving renal survival. Its positive effect on kidney survival can be explained by two important factors; ACE inhibitors in general decrease the pressure within the efferent arteriole and thereby the intraglomerular pressure. Furthermore, inhibition of cytokine production results in less glomerulosclerosis andless fibrosis. [19]

Statistical Analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 22.0 Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage (R).

Results

Table 1 shows statistically non-significant differences regarding age, sex, weight, height and BMI among studied patients. This study was conducted on sixty CKD children; 34(57%) were males and 26(43%) were females with age ranged from 5 to 17 years. Distribution of chronic kidney disease patients (CKD) according to disease stages among the studied groups. shows CKD stages among studied patients, CKD stage 1 represented 53.3%, CKD stage 2 represented 38.3%, CKD stage 3 represented 5% and CKD stage 4 represented 3.4%. CKD etiologies among studied patients, SDNS was the commonest etiology (53.3%) followed by DN (25.0%), LN (20.0%). and there was only one case of FRNS. The statistically non-significant differences regarding systolic and diastolic blood pressure among studied patients .

Table 2 and figure 2 ,3 and 4 show renal function in studied patients, there were statistically non significant differences regarding the blood urea levels among studied patients with reduction among patients of enalapril group and losartan group (37.3% and 25.9%) respectively in comparison to non-treated group 25%.

There were statistically non-significant differences among studied patients as regards serum creatinine levels with reduction among patients of losartan group and enalapril group by (11.6% and 8.3%) respectively in comparison to non-treated group (5.7%).

There were statistically non-significant differences regarding GFR among studied patients, it was increased among enalapril group (8.6%) and losartan group (4.5%) more than non treated group (3.8%).

Table 3 and figure 5 show, statistically significant differences of 24hrs urinary protiens among studied patients ($p< 0.05$), there was reduction among patients of treated groups by (76.7%) ilosartan group and (45.6%) in enalapril group than non treated group (4%).

Table 4 and figure 6,7 and 8 show that there were statistically non-significant differences regarding the blood cholesterol levels among studied patients, their levels showed reduction among losartan group (13.4%) and enalapril group (8.5%) versus group with no ttt (2.8%).

There were statistically non-significant differences regarding TG levels among studied patients, their levels showed reduction among patients of losartan group (11.3%) than enalapril group (9.6%) and group with no ttt (8.4%).

There were statistically non-significant differences among studied patients regarding serum albumin levels, their levels increased among enalapril group and losartan group (10.5% and 8.9%) respectively versus group with no ttt (1%).

Table 5 and figure 9 and 10 show statistically non-significant differences regarding serum electrolytes (sodium and potassium) levels among studied patients before and after treatment .

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Table (1): Distribution of demographic data and body measurement parameters among patients.

Parameter		Group I (enalapril) N=20	Group II (losartan) N=20	Group III (No ttt) N =20	F. test	p-value
Age (year)	Range	5 – 15	5 – 16	5 – 17	2.463	0.094
	Mean ± S.D	8.93 ± 2.74	11.20 ± 3.45	9.88 ± 3.52		
Sex	Male (%)	12 (60%)	12 (60%)	10 (50%)	**X^2:** 0.543	0.762
	Female (%)	8 (40%)	8 (40%)	10 (50%)		
Weight (kg)	Range	19 – 67	18 – 65	18 – 57	5.389	0.007*
	Mean ± S.D	35.10 ± 11.97	44.80 ± 14.87	32.65 ± 9.77		
Height (cm)	Range	73 – 160	90 – 162	80 – 156	1.955	0.151
	Mean ± S.D	118.20 ± 21.14	129.50 ± 19.36	119.05 ± 19.84		
BMI (kg/m^2)	Range	17.6 – 45	18 – 32.4	17.2 – 31.3	2.664	0.078
	Mean ± S.D	25.76 ± 6.23	25.90 ± 3.51	22.96 ± 3.30		
		Group I (enalapril) N (%)	**Group II (losartan) N (%)**	**Group III (No ttt) N (%)**	**total**	
Stage of CKD	**Stage 1**	13 (65%)	12 (60%)	7 (35%)	32(53.3%)	
	Stage 2	6 (30%)	7 (35%)	10 (50%)	23(38.3%)	
	Stage 3	1 (5%)	0 (0%)	2 (10%)	3(5%)	
	Stage 4	0 (0%)	1 (5%)	1 (5%)	2(3.4)	
Chi-square	**X^2**	**0.543**				
	P-value	**0.762**				
Primary cause	**SDNS**	10 (50.0%)	9 (45.0%)	13 (65.0%)	32 (53.3%)	
	LN	5 (25.0%)	4 (20.0)	3 (15.0%)	12 (20.0%)	
	DN	5 (25.0%)	7 (35.0%)	3 (15.0%)	15 (25.0%)	
	FRNS	0 (.0%)	0 (.0%)	1 (5.0%)	1 (1.7%)	
Chi-square	**X^2**	**4.913**				
	P-value	**0.555**				
Systolic BP	Range	80 – 120	75 – 110	80 – 115	0.271	0.763
	Mean ± S. D	94.00 ± 10.95	92.25 ± 9.52	91.75 ± 9.90		
Diastolic BP	Range	50 – 70	50 – 85	50 – 80	0.236	0.790
	Mean ± S. D	60.00 ± 6.49	61.75 ± 8.63	61.50 ± 10.53		

Table (2): Comparison of blood urea, serum creatinine and GFR in studied groups both at base line and at follow up

		Group I (enalapril)		Group II (losartan)		Group III (No ttt)		F. test	p. value
		Initial	6 m.	Initial	6 m.	Initial	6 m.		
Urea (mg/dl)	Range	14 – 92	19 – 71.6	23 – 65	20 – 95	23 – 45	20 – 52		
	IQR	25 – 63	21.25 – 34.5	28 – 45	25.75 – 38	26.5 – 40.75	22.75 – 43.75		
	Median	38.5	24	40.5	30	40	30		
	% of change	37.7↓		25.9↓		25↓			
	T test	1.869		0.929		0.053			
	P value	0.069		0.359		0.958			
	IQR	-0.825 – 23.75		-2 – 15.75		-14.75 – 5		1.928	0.297
	Median	5		8		3.8			
		p1: 0.589		p2: 0.115		p3: 0.237			
Creatinine (mg/dl)	Range	0.3 – 1.6	0.3 – 1.8	0.4 – 2.4	0.4 – 0.9	0.4 – 1.7	0.7 – 1		
	Mean ± S. D	0.72 ± 0.33	0.66 ± 0.32	0.86 ± 0.41	0.76 ± 0.14	0.87 ± 0.24	0.82 ± 0.11		
	% of change	8.3↓		11.6↓		5.7↓			
	T test	0.689		1.036		0.591			
	P value	0.459		0.307		0.554			
	Mean difference	-0.4 – 0.7		-0.2 – 1.5		-0.1 – 0.7		0.248	0.781
		0.06 ± 0.20		0.10 ± 0.34		0.12 ± 0.19			
		p1: 0.622		p2: 0.498		p3: 0.853			
GFR (ml/min/1.73 m^2	Range	41.2 – 220	48.8 – 220	28.8 – 172.2	75.6 – 145.8	28.1 – 190.8	47.8 – 190.8		
	IQR	77.6 – 139.5	81.775 – 141.25	84.9 – 117.875	86.125 – 122.5	64.875 – 97.55	71.125 – 106.7		
	Median	108.9	118.25	93.45	97.7	77.54	80.5		
	% of change	8.6↑		4.5↑		3.8↑			
	T test	0.697		0.607		0.716			
	P value	0.490		0.548		0.478			
	IQR	-23.975 – 0		-17.225 – 0		-15.35 – 0		0.377	0.687
	Median	-3.2		- 0.45		-8.2			
		p1: 0.391		p2: 0.724		p3: 0.613			

IQR: interquartile range

GFR: glomerular filtration rate

P1compare between enalapril group and losartan group

P2 compare between enalapril group and group with no ttt

P3compare between losartan group and group with no ttt

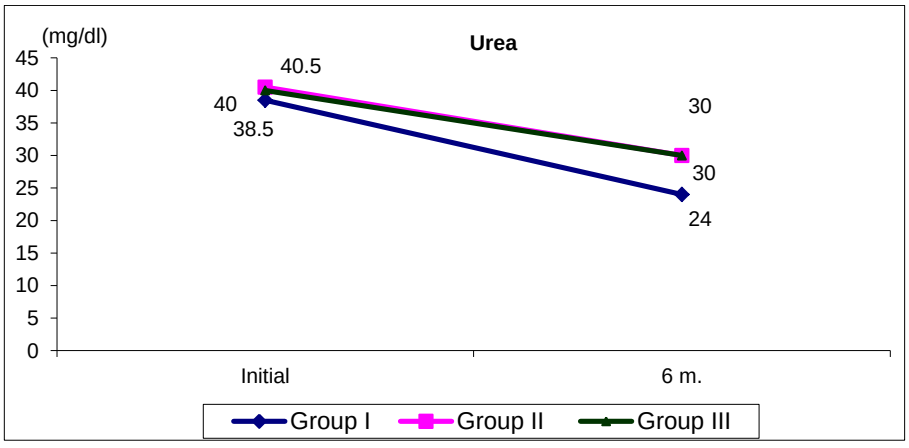

Figure (1): Blood Urea level follow up in the studied groups

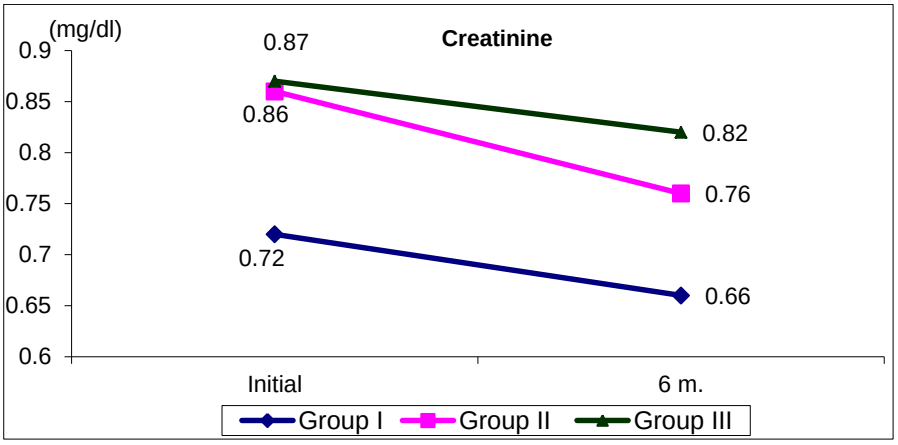

Figure (2): Serum creatinine follow up in the studied groups

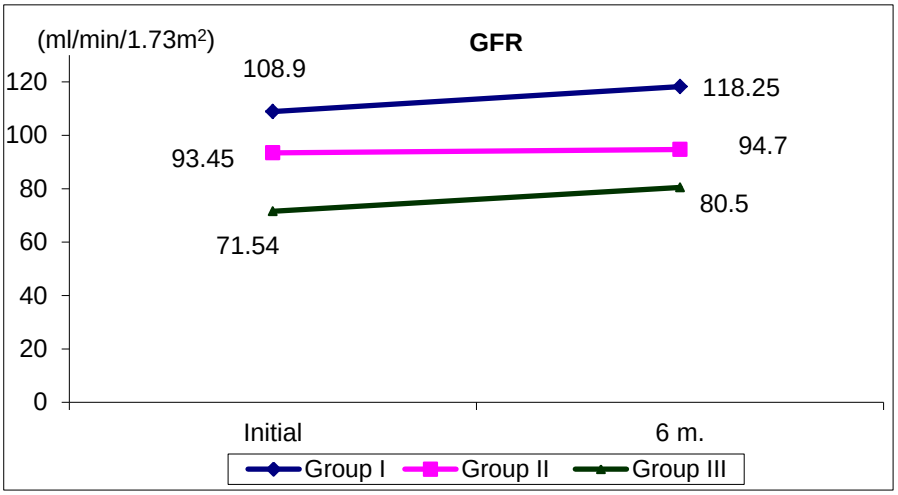

Figure (3): Glomeruler filtration rate follow up in the studied groups

Table (3): Comparison of 24 hours proteinuria in studied groups both at base line and at follow up

		Group I (enalapril)		Group II (losartan)		Group III (No ttt)		F. test	p. value
		Initial	6 m.	Initial	6 m.	Initial	6 m.		
24 hrs urinary proteins(mg)	Range	360 – 1820	160 – 1300	455 – 3250	102 – 1000	300 – 950	192 – 1380		
	IQR	805 – 1407.5	532.5 – 937.5	895 – 1390	202 – 447.5	397.5 – 892.5	555 – 975.25		
	Median	1245	677.5	1275	296.5	812.5	780		
	% of change	45.6↓		76.7↓		4↓			
	T test	3.362		6.530		1.157			
	P value	0.002*		0.001*		0.254			
	IQR	186.25 – 507.5		476.75 – 1082.25		-327.5 – 223.75		21.741	0.001*
	Median	685		882.2		-72			
		p1: 0.002*		p2: 0.002*		p3: 0.001*			

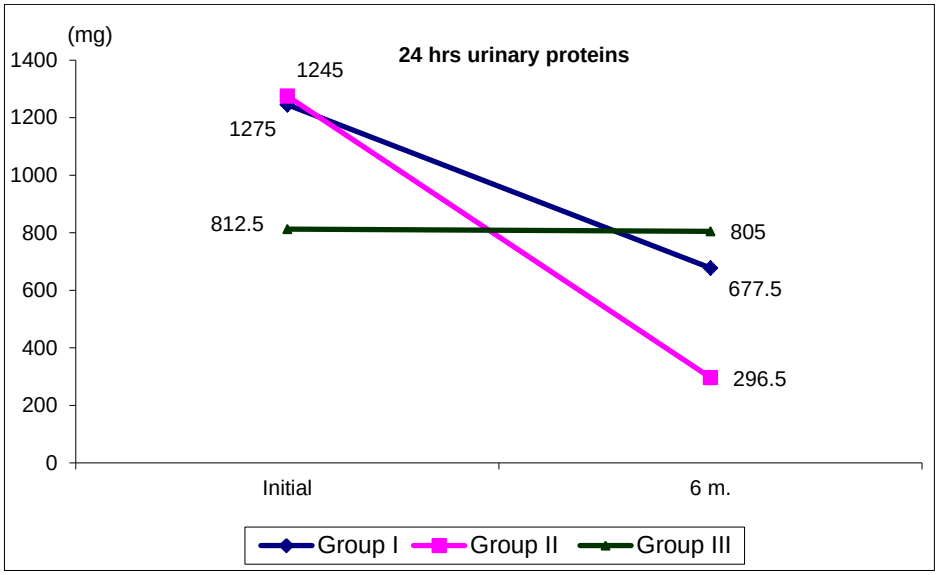

Figure (4): 24 hrs urinary proteins follow up in the studied groups

Table (4): Comparison of blood cholesterol, triglycerides (TG) and serum albumin levels among the studied groups both at base line and at follow up.

		Group I (enalapril)		Group II (losartan)		Group III (No ttt)		F. test	p. value
		Initial	6 m.	Initial	6 m.	Initial	6 m.		
Cholesterol (mg/dl)	Range	180 – 554	145 – 556	127 – 648	117 – 530	175 – 365	145 – 364		
	IQR	215.25 – 367.75	193.5 – 408	214.25 – 427	203.5 – 293	265 – 320.75	263.5 – 340		
	Median	291	266	335	290	300	291.5		
	% of change	8.5↓		13.4↓		2.8↓			
	T test	0.107		0.990		0.148			
	P value	0.915		0.328		0.883			
	IQR	-9.25 – 19.25		-11.75 – 59		-17.5 – 19.25		2.987	0.058
	Median	9		17		-0.5			
		p1: 0.058		p2: 0.743		p3: 0.051			
TG (mg/dl)	Range	68 – 315	50 – 340	85 – 490	83 – 471	86 – 182	70 – 181		
	IQR	86.75 – 212.25	84.25 – 197.85	142.5 – 313.5	141.75 – 312.5	100.75 – 174.75	91 – 168.25		
	Median	132.5	120	212.5	188.5	167.5	153.5		
	% of change	9.6↓		11.3↓		8.4↓			
	T test	0.178		0.561		0.883			
	P value	0.860		0.578		0.383			
	IQR	-0.825 – 23.75		-2 – 15.75		-14.75 – 5		0.992	0.377
	Median	5		8		-1.5			
		p1: 0.170		p2: 0.619		p3: 0.377			
Serum albumin (g/dl)	Range	2 – 3.9	2.3 – 3.8	2.1 – 4.7	2.4 – 3.5	2.6 – 3.5	2.5 – 3.5		
	Mean ± S.D	2.87 ± 0.55	3.17 ± 0.41	2.90 ± 0.64	3.16 ± 0.33	2.90 ± 0.21	2.93 ± 0.27		
	% of change	10.5↑		8.9↑		1↑			
	T test	1.949		1.618		0.196			
	P value	0.059		0.114		0.846			
	Mean difference	-1.1 – 0.5		-1 – 2.2		-0.6 – 0.4		1.850	0167
		-0.30 ± 0.46		-0.26 ± 0.71		-0.02 ± 0.25			
		p1: 0.804		p2: 0.081		p3: 0.132			

TG: triglycerides

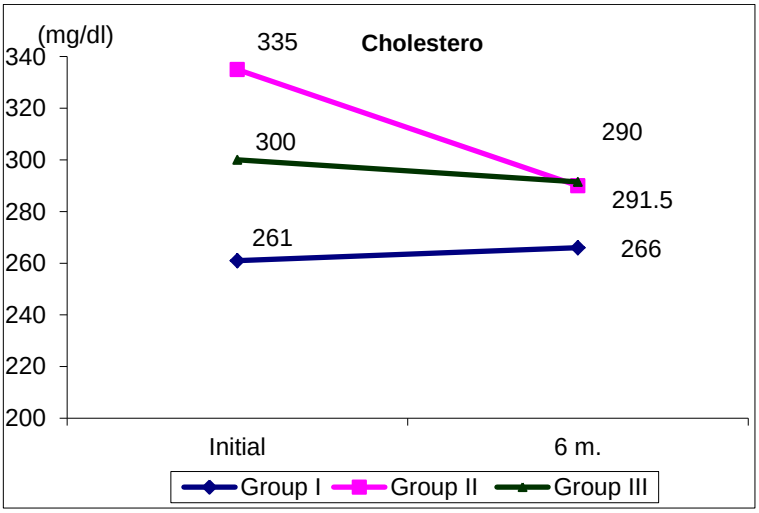

Figure (5): Demonstration of blood cholesterol level in the three groups baseline and six months later

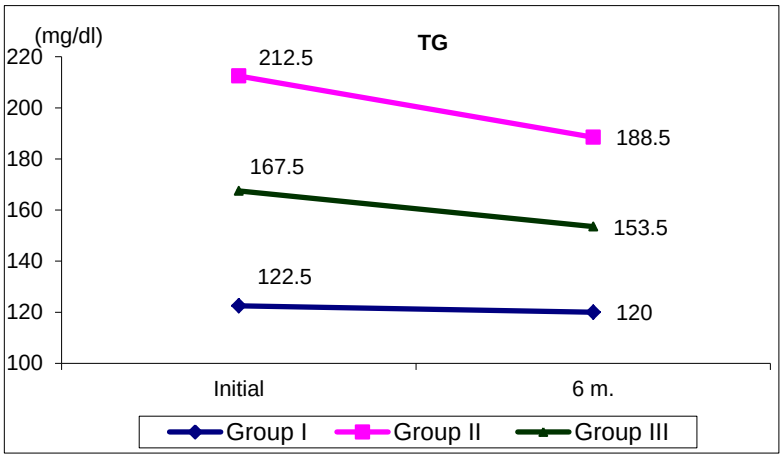

Figure (6): Demonstration of triglycerides (TG) level in the studied groups baseline and six months later

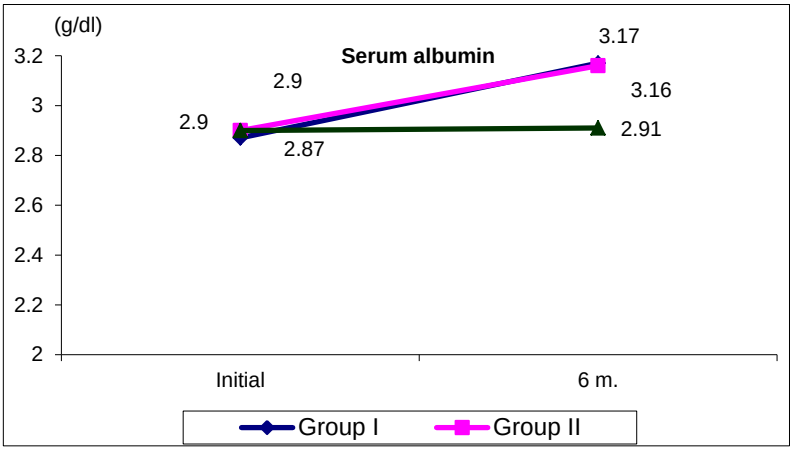

Figure (7): Demonstration of serum albumin level in the three groups baseline and six months later

Table (5): Comparison of serum electrolytes levels among patients of the studied groups both at baseline and at follow up

		Group I (enalapril)		Group II (losartan)		Group III (No ttt)		F. test	p. value
		Initial	6 m.	Initial	6 m.	Initial	6 m.		
Na (mEq/L)	Range	133 – 143	135 – 143	127 – 143.7	130.6 – 141.7	135 – 142	136 – 141		
	Mean ± S. D	137.72 ± 2.44	137.50 ± 2.01	137.62 ± 3.63	137.46 ± 3.13	137.38 ± 2.15	137.23 ± 1.52		
	% of change	0.2		0.1		0.1			
	T test	0.318		0.149		0.255			
	P value	0.752		0.882		0.800			
	Mean difference	-3 – 4		-5.8 – 3.1		-2.1 – 3		0.008	0.992
		0.23 ± 2.11		0.16 ± 2.24		0.15 ± 1.72			
		p1: 0.920		p2: 0.908		p3: 0.988			
K (mEq/L)	Range	3.5 – 5.3	3.5 – 4.6	3.5 – 5.3	3.6 – 4.5	3.5 – 4.5	3.5 – 4.1		
	Mean ± S. D	4.04 ± 0.48	3.99 ± 0.27	4.02 ± 0.45	3.96 ± 0.24	3.90 ± 0.27	3.85 ± 0.16		
	% of change	1.2↓		1.5↓		1.3↓			
	T test	0.407		0.572		0.780			
	P value	0.687		0.570		0.440			
	Mean difference	-0.4 – 1.1		-1 – 1.3		-0.5 – 0.4		0.009	0.991
		0.05 ± 0.35		0.07 ± 0.44		0.06 ± 0.27			
		p1: 0.896		p2: 0.965		p3: 0.930			

Na: serum sodium K^+: serum potassium mEq/L: milli equivalent per liter

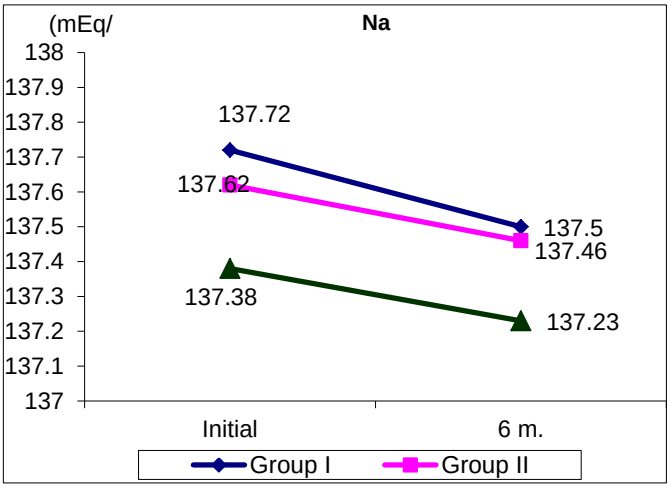

Figure (8): Serum sodium (Na) level in the three groups

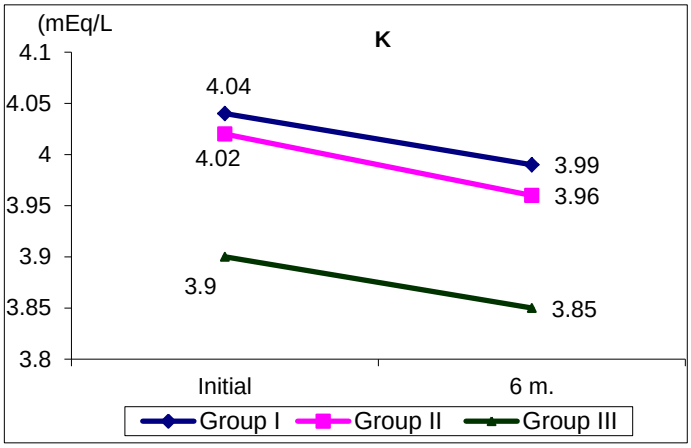

Figure (9): Serum potassium (K) level in the three groups

DISCUSSION

Chronic kidney diseases (CKD) is a serious public health problem that burden the community defined as glomerular filtration rate (GFR) lower than 60ml /min/1.73m^2 for 3monthes or longer and proposed a classification scheme based on GFR. They are more common in males than females. The most common etiologic factors in children are congenital anomalies of the kidney and urinary tract (CAKUT), steroid dependant nephrotic syndrome (SDNS), chronic glomerulonephritis (e.g. lupus nephritis) (LN) and diabetic nephropathy (DGN). proteinuria is a marker of severity of CKD and predict the future decline of GFR to end stage renal disease (ESRD), so reduction of proteinuria can prevent further decline of GFR and preserve the kidney function, this can occur by blocking renin angiotensin aldosterone system (RAAS) via angiotensin converting enzyme inhibitors(ACEIs) e.g. (Enalapril) and angiotensin receptor blockers (ARBs) e.g.(Losartan).Both ACEIs and ARBs block RAAS at different levels with anti proteinuric effect distinct from their effect on blood pressure and delay progression to ESRD.

This prospective cohort study was conducted on 60 CKD children (5 to 17 years), 57% were males 43% were females SDNS was the most common cause (53.3%) followed by DN 25% and LN 20% and only one case was FRNS and this is in agreement with **Ruggenenti et al**[6] study in which the renoprotective effect of losartan and enalapril were demonstrated in CKD children with different etiology e.g. (LN, SDNS and Alport syndrome). And with **van der Snade et al** [20] study in which the renoprotective effect of RAAS inhibitors was demonstrated in diabetic nephropathy patients.

In our study CKD stage 1 represented 53.3%, CKD stage 2 represented 38.3%, CKD stage 3 represented 5% and CKD stage 4 represented 3.4%. But **Kitamura et al** [21] study reported the effect of losartan on CKD patients stage 3 and stage 4.

There were statistically non significant differences regarding the blood urea levels among patients of studied groups at follow up but there was reduction among Enalapril group and Losartan group (37.3% and 25.9%) respectively more than non-treated group (25%). This result is in coexistence with **van den Belt et al** [22] study which reported decrease blood urea levels and preservation of kidney function and lower risk for CKD progression after enalapril treatment.

There were statistically non-significant differences among patients of the studied groups as regards serum creatinine levels, there was reduction among patients of losartan group and enalapril group (11.6% and 8.3%) respectively in comparison to non-treated group 5.7%. this result is passing with **Ruggenenti et al**[6] study which reported that serum creatinine decreased in patients who received combined enalapril and losartan. This result is also passing with **Ripley et al** [23] study which reported that renoprotection with losartan or benzapril showed reduced risk for doubling serum creatinine. This finding is in disagreement with **Reynolds et al** [24] study which reported that fewer patients in the enalpril group experienced doubling of serum creatinine levels or progressed to dialysis when enalapril was combined with losartan, and also **Webb et al** [25] study which reported that serum creatinine levels increased in some patients of losartan group and also with enalapril group after 3 years of open lapel treatment of 109 cases this may be, due to more prolonged duration of therapy and large number of cases than our study.

There were statistically non-significant differences regarding GFR among studied patients both at baseline and at follow up, there were improvement among patients of enalapril group (8.6%) and losartan group (4.5%) more than group without treatment (3.8%). This result is in accordance with **Webb et al** [25] study which reported that after treatment the estimated Least Square mean change from baseline in eGFR improved with losartan group and with Enalapril group with no significant differences between both groups and with **Ruggenenti et al**[6] study which reported that eGFR increased in patients who achieve remession using combined enalapril and losartan therapy. This finding is in disagreement with **Clase et al** [26] study which reported that in analysis of Ontarget and Transcend trials, a GFR decline of 15% or more at 2 and 8 weeks was observed following benzapril initiation then improved after 8.5

months of follow up. This may be due to short duration of follow up as ACEIs and ARBS may decrease GFR initially.

Regarding 24hrs urinary proteins, statistically significant differences were found among studied patients, with 76.7% reduction in losartan group and 45.6 % reduction in enalapril group than which was only 4% reduction in non treated group .This result came in agreement with **Webb et al** [25] study which reported sustained reduction of proteinuria in losartan group and in enalapril group after 3 years of follow-up, and losartan was comparable in terms of efficacy and safety to enalapril. Also with **Wuhl et al** [27] study which reported that there is significant reduction from baseline proteinuria in both enalapril group and losartan group after 6 months of treatment. Also with **Ellis et al (28)** study which demonstrated that protein excretion decreased after a mean period of 1.9 months with maximal and sustained decrease in proteinuria occurred after a mean of 4.7 months after starting losartan and with **Web et al** [25] study which reported that losartan significantly reduce proteinuria as compared to amlodipine or placebo.

There were statistically non-significant differences regarding the blood cholesterol levels among studied groups both at baseline and at follow up, there were reduction among patients of losartan group (13.4%) and enalapril group (8.5%) than the group without treatment (2.8%) at follow up. This finding is in accordance with **Tershakovec et al** [28] study which reported that lowering albuminuria after losartan is associated with reduction of blood cholesterol levels due to decreased hepatic lipoprotein synthesis secondary to albuminuria and with **Srivastava et al** [29] study which reported reduction in blood cholesterol level with enalapril.

There were statistically non-significant differences regarding triglycerides levels among the studied groups both at baseline and at follow up, there were reduction among patients of losartan group (11.3%) than enalapril group (9.6%) than the group without treatment (8.4%) at follow up. This finding is in accordance with **Srivastava et al** [29] study which demonstrated that TG levels were decreased in patients treated with losartan and enalapril with improvement of lipid profile.

There were statistically non-significant differences among patients of the studied groups regarding serum albumin levels, there were improvements among patients of enalapril group and losartan group (10.5% and 8.9%) respectively versus group with no treatment (1%). This result came in agreement with **Ruggenenti et al** [6] study which demonstrated that the reduction in proteinuria was associated with increase in serum albumin levels at the last available follow-up visit after 3 years, as reduction of proteinuria translated to elevated serum albumin levels and with **Cortinovis et al** [30] study which reported that serum albumin levels increased in patients who achieve remission receiving either ACEIs or ARBs.

The current study revealed that there were statistically non-significant differences regarding the serum electrolytes (sodium and potassium) levels among studied patients . This finding is in agreement with **Elli et al** [28] study which reported that serum potassium was not statistically different at follow up and also came in agreement with **Ruggenenti et al** [6] study which demonstrated that serum potassium levels was relatively stable during the follow-up.

This finding is in contrast with Web et al [127] study which reported increase in serum potassium levels was frequently observed in patients of losartan group and enalapril group this may be due to doubling of dose of both losartan and enalapril than our study dose and prolonged time of study (3 years).

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