Renoprotective Effect of Losartan VersusEnalapril 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:this prospective cohort study was conducted on 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 dependantnephrotic 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, children , enalapril ,losartan ,renoprotection

Introduction:

Chronic kidney disease (CKD) is a serious public health problem, defined 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)

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 filtrativecapacity and ultimately to end-stage renal disease (ESRD).(3)

There is a crucial role of proteinuria in accelerating kidney disease progression to ESRD through multiple pathways. The extent of proteinuria is widely recognized as a marker of the severity of CKD and as a predictor of future decline in GFR. More importantly, a reduction in proteinuria invariably translates into a protection from renal function decline in patients with CKD.(4)

Activation of the classical renin angiotensin aldosterone system (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(5)

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.[6]

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.Egypt Between April 2019 and May 2020 on sixty CKD patients

Patients were subdivided into three groups as the following:

Group I: 20 children with CKD received Enalapril (0.2 mg /kg/day).[7]

Group II : 20 children with CKD received Losartan (1mg/kg/day). [8]

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,bloodurea,serumelectrolytes (Na, K), GFR,24 hour urine proteins,pelviabdominal ultrasound

Medications used:

• **Losartan**

• **Enalapril**

The sequence of events that occur in Renin angiotensin aldosteronsystem(RAAS) activation begins with the secretion of renin through decreased luminal sodium chloride delivery to the macula densa under tight control by the juxtaglomerular apparatus (JGA). Also its release is stimulated by another mechanism through renal baroreceptors that is stimulated by the decrease in afferent arteriolerpressure . The next steps require cleavage of the glycoprotein angiotensinogen into several active angiotensin peptides that play a role in regulating BP and sodium balance, with Ang II being the major bioactive peptideRenin cleaves angiotensinogen to produce the Ang I, which has minimal effects on vascular tone, as it circulates through the pulmonary capillary bed it is cleaved to form the Ang II by angiotensin converting enzyme (ACE) which has additional enzymatic properties including inactivation of bradykinin and kallidin (two vasodilator peptides). So one significant difference between ACEIs and ARBs is the additional suppression of bradykinin degradation by ACEIs, which may lead to the bradykinin-mediated side effects as dry cough and angioedema that can be seen with ACEIs but not with ARBs (9).

Written informed consents were obtained from the parents or guardians of all subjects of the study. The study was approved by the Ethics committee of faculty of medicine, Tanta University Ethical committee approval was 33121/05/19.

The risks to participants and measures used to minimize the risk:

- No risks for the subjects who shared in this study. No side effect of these drugs occurred to the patients .
- we followed up our patients after obtaining blood sample according to

infection control measures for any complication but no complication had occurred just mild pain recovered soon without analgesic , we got rid of all samples safely according to infection control measures .

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).

1- Analysis of variance [ANOVA] tests (f): According to the computer program SPSS for Windows. ANOVA test was used for comparison between more than two means in quantitative data.

2- Chi-square the hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chi-square and likelihood-ratio chi-square. Fisher's exact test and Yates' corrected chi-square are computed for 2x2 tables.

Chi-square test:

For comparison between two groups as regards qualitative data.

$$X^2 = \sum \frac{(O-E)^2}{E}$$

Where:

Σ = Summation.

O = Observed value.

E = Expected value= $\frac{\text{vertical total X Horizontal total}}{\text{grand total}}$

P-value: was used as a critical value.

P-value <0.05 was considered to be significant.

P-value >0.05 was considered to be Non significant.

% of change = mean of initial –mean of 6 m. / mean of initial

3- A paired t-test is used when we are interested in the difference between two variables for the same subject. Often the two variables are separated by time. Since we are ultimately concerned with the difference between two measures in one sample, the paired t-test reduces to the one sample t-test.

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, 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. There were statistically non-significant differences regarding systolic and diastolic blood pressure among studied patients .

Table 2 and figure 1 ,2 and 3 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 4 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 5, show that there were statistically non-significant differences 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 6 and 7 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		
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 m²	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 betweenenalapril group and losartan group

P2 compare between enalapril group and group with no ttt

P3compare between losartan group and group with no ttt

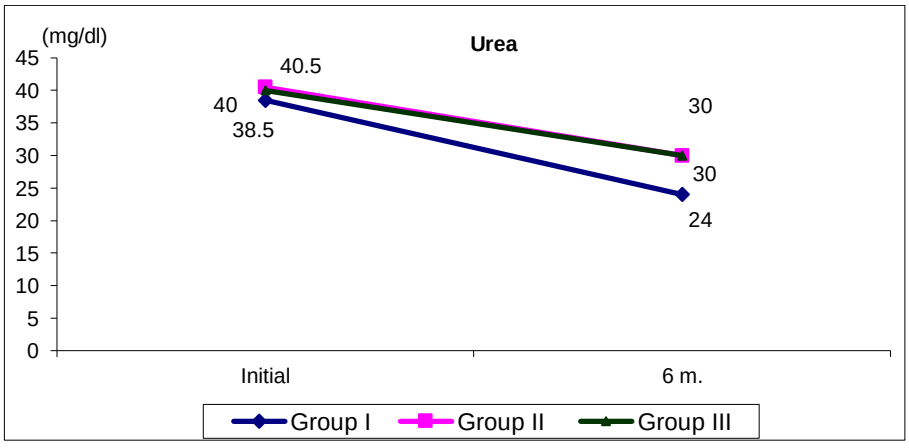

Figure (1):Blood Urea level follow up in the studied groups

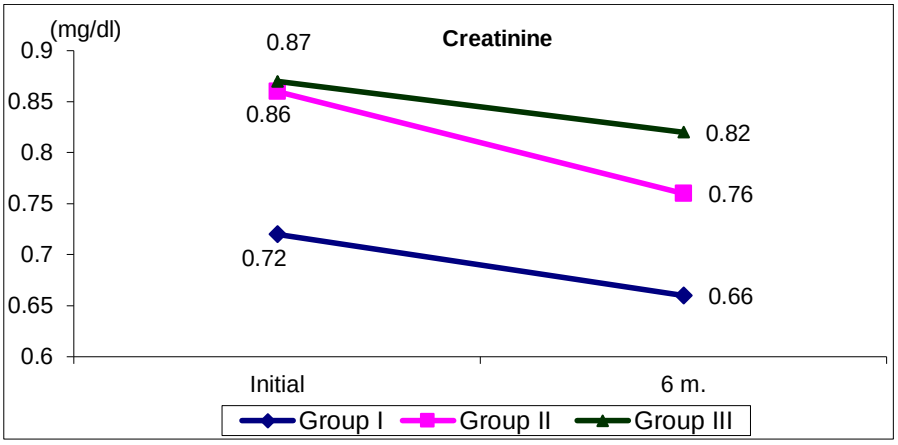

Figure (2): Serum creatinine follow up in the studied groups

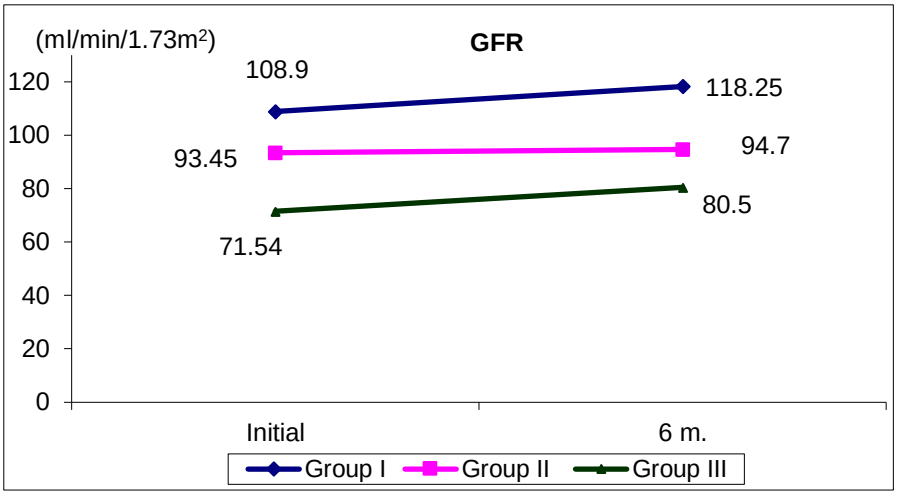

Figure (3): Glomeruler filtration rate follow up in the studied groups

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*			

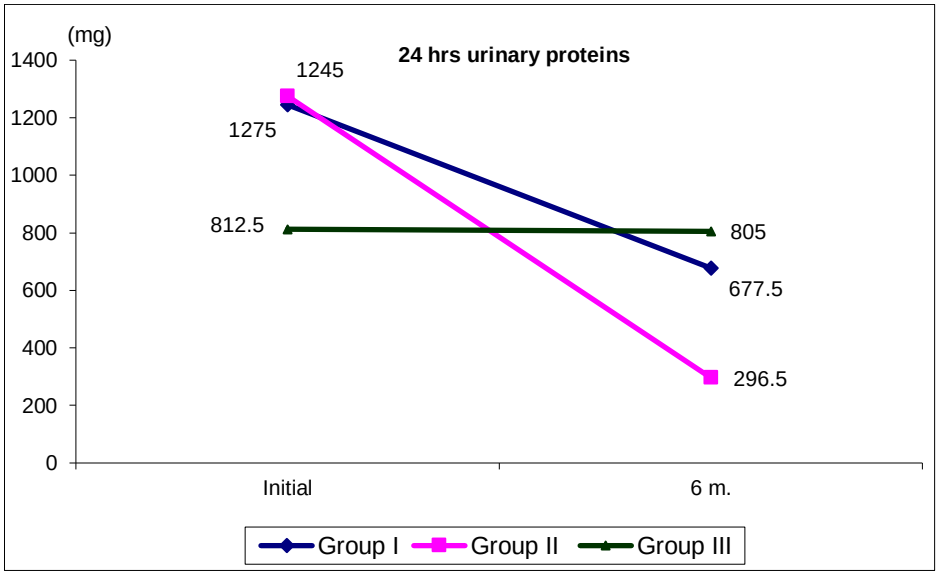

Figure (4): 24 hrs urinary proteins follow up in the studied groups

Table (4): Comparison of 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.		
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			

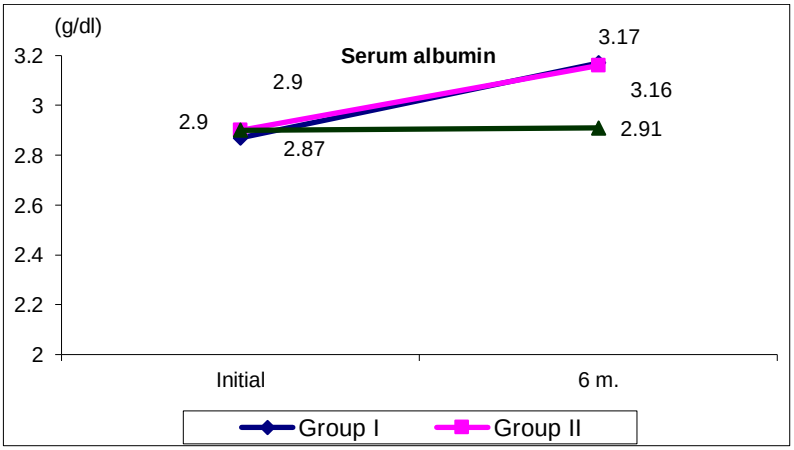

Figure (5): Demonstration of serum albumin level in the three groups baseline and six months later

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

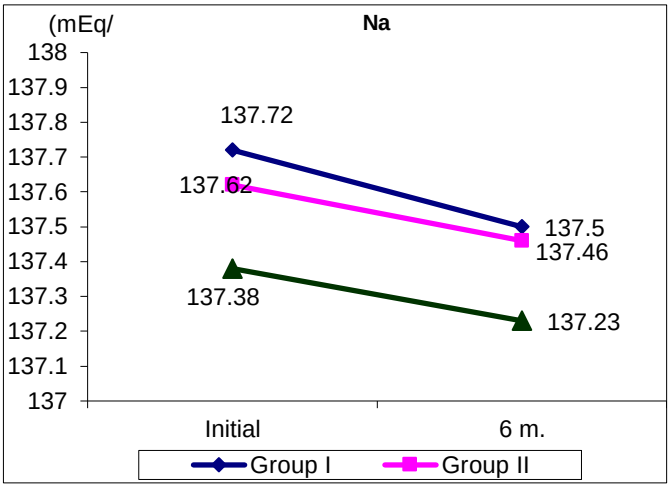

Figure (6): Serum sodium (Na) level in the three groups

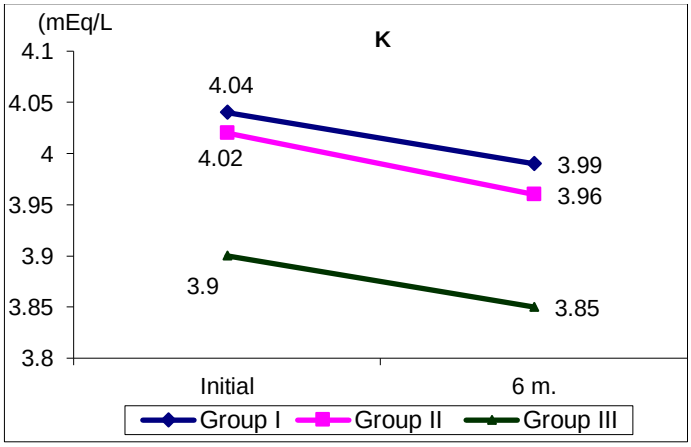

Figure (7): Serum potassium (K) levelin the three groups

DISCUSSION

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**[10]studywhich 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 **Ruggenentietal**[11]study which reported that serum creatinine decreased in patients who received combined enalapril and losartan. This result is also passingwith**Ripley et al**[12]study which reported that renoprotection with losartan or benzapril showed reduced risk for doubling serum creatinine. This finding is in disagreement with**Reynoldset al**[13] 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** [14] 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**Webbet al**[14] 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**[11]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**[15]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**Webbet al**[14] 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**[16]studywhich 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** [17] 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**[7] study which reported that losartan significantly reduce proteinuria as compared to amlodipine or placebo.

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**[11] 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**[18]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**[17] study which reported that serum potassium was not statistically different at follow up and also came in agreement with **Ruggenentiet al**[11] study which demonstrated that serum potassium levels was relatively stable during the follow-up.

This finding is in contrast with Web et al [14] 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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