The comparison Losartan and medical combination of Losartan and pyridoxamine on reducing proteinuria in patients with diabetes type II

Seyyed Sadredin Rasi Hashemi[1], Kamaludin Golbazi[2], Amir Gorbani Haghjo[3], Majid Mobaseri[4], Javid Safa[5]

1- Assistant professor of Internal Medicine, Internal Medicine Department, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
2- Resident of Internal Medicine, Internal Medicine Department, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
3- Biochemical associate professor and clinical laboratories, biochemical group and clinical laboratories, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
4- Associate professor of Internal Medicine, Internal Medicine Department, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
5- Medical applied research center, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
*_Corresponding author: Kamaludin Golbazi (dr_an1077@gmail.com)

Abstract: Background and purpose: The diabetic nephropathy is one of final stage causes of renal disease. The angiotensin II locally increases because of hyperglycemia in kidney and causes renal lesions induction especially, glomerular lesions. Thus, in the present research, we try to treat patients suffering from diabetic nephropathy by Losartan, pyridoxamine, and study useful effects of these drugs on disease progression process. **Methodology:** In the present clinical experimental study, 44 patients with diabetic type II were selected without regard to sex sequentially and categorized in two groups randomly. First group (n = 22) were treated with Losartan by dose 25 mg every 12h for 2 months solely and tests controlled while start of drug and next two months. The second group (n = 22) were under treatment with conjoint Losartan (25mg/12h) and pyridoxamine (25mg) and tests controlled before and after 2 months treatment. **Results:** In case group, the average measured sodium before and after treatment were 146139.95±4.17 and 138.33±2.28, the mean triglyceride measured before and after treatment were 231.28±106.05 and 179.66±116.06, mean lipid – peroxide measured before and after treatment 3.39±1.57 and 1.79±0.84, the mean 24-h urine protein measured before and after treatment were 3157.38±2330.47 and 1587.52±1695m 91 and finally the mean uric acid measured before and after treatment were 8.46±2.13 and 6.69±2.28 respectively. In control group the mean sodium measured before and after treatment were 138.85±6 and 136.9±4.74, the mean triglyceride measured before and after treatment were 181.5±95.14 and 172.85±56.81, the mean lipid peroxide measured before and after treatment were 2.88±1,34 and 2.02±0.83, the mean uric protein 24h measured before and after treatment were 1087.18±1021.81 and 425.52±447.97 and finally the mean uric acid were 8.03±1.75 and 6.08±1.95 respectively. **Conclusion:** In the group treated by Losartan, there were meaningful difference between before and after treatment in the cases of cholesterol, blood sugar, uric acid, 24-h urine protein and lipid peroxide. In the group under treatment by combination of Losartan and pyridoxamine, there were meaningful difference between pre and pro treatment in the cases of triglycerides, blood suger, uric acid, 24-h urea protein and lipid peroxide. It is noticeable to say that there was more meaningful difference between pre and pro treatment in the group under treatment by combination of Losartan and pyridoxamine than group treated by Losartan. Thus, with attention to ontained results, it is recommended use of Losartan in combination with pyridoxamine.
[Rasi Hashemi SS, Golbazi K, Gorbani Haghjo A, Mobaseri M, Safa J. **The comparison Losartan and medical combination of Losartan and pyridoxamine on reducing proteinuria in patients with diabetes type II.** *J Am Sci* 2013;9(11s):53-61]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 10

Keywords: Dyssynchrony; Global longitudinal strain; Pacing; Speckle tracking echocardiography

1. Introduction

The incidence of renal chronic disease is on the increase. It is about 13% in some of developed countries (Coresh, 2002). This raised incidence of renal failure along with increased advanced renal failure need for dialysis, which results in higher treatment expenditures in keeping of these patients (Hebert, 2001; Foley, 2002). The diabetic nephropathy is one of main reasons of renal failure that occurs in terms of haemodynamic and metabolic disfunctions (Cooper, 2001). The activation of rennin-angiotensin system is one of involved factors in progression of renal failure which block of such system could inhibit progression of renal failure in the diabetic patients (Lewis, 2001; Brenner, 2001; Ravid, 1992). Now, the researchers pursue the methods in which could attenuate progression rate of renal failure in the diabetic patients, but these methods are based on finding pathophysiology of such problem that include chronic which causes to

end products in glycation process (Advanced glycation end products-AGES) that formed by metabolism of sugers and lipids which are resistant against proteolytic effects (Cooper, 2001; Thomas, 2009). It causes to expression of gen producing VEGF and $TGF-\beta$. These two materials lead to damage on glumerole and interstitial (Vlassara, 1997). Pyridoxamine as one of vitamins group B could decrease AGES effect (Kang, 2002) which has extensive effects on AGES production than other drugs such as aminoguanidine. This matter even could play a major role in regulating production of some protein promoters AGES such as Amadori combinations (Voziyan, 2007; Chetyrkin, 2002) and regulating peroxidation of lipids and non-producing and removing detrimental end – products in peroxidation process (Onorato, 2000). In the animal models, pyridoxamine could be effective in protection of kidneys in diabetic type I and II (Degenhardt, 2007; Alderson, 2000; Alderson, 2007).

In addition, pyridoxamine in higher dose causes to decreased albuminuria and expression of some genes in kidney such as RNA messenger 1 – laminin TGF (Tanimoto, 2002). On the other hand, the effect of angiotensin II inhibitors or blockers receptor angiotensin II could inhibit progression of diabetic nephropathy in patients suffering from diabetic type II, although these drugs could slow progression process of diabetic nephropathy but could not stop it (Burns, 2000; Leehey, 2000 Taal and Brenner, 2000; Parving, 2001). Thus, now the object of treatment is to decrease AGES production (Metz, 2000). The present study is conducted in order to promote treatment of patients with diabetic nephropathy by combination of both drugs, Losartan and pyridoxamine until could slow progression rate of diabetic nephropathy.

2. Material and Methods

The current research is of clinical experimental one. In this study, 44 patients with diabete type II referring to medicinal and teaching center of Emam Reza during 12 months (2390-91) without regard to sex were selected randomly, determined their antropometric characteristics such as height and weight, The sample volume by considering meaningfully level 0.05 and power 80 percent and expected difference between reviewed variable, was estimated. 10 percent of 40 samples (44 patients, 22 cases in case group and 22 cases in control group). Thus, 22 persons who have admission criteria and lack of exclusion criteria were studied as case group. The studied variables, before and after treatment in both groups i.e case and control groups, were measured and recorded.

The admission criteria include males and milch or non-pregnant females between 18-70 years old suffering diabete type II, blood pressure lower than 170.80 on sitting position, glycation haemoglobin level lower or equals to 12, patients with diabetic nephropathy with cratenine lower than 18 mg/dl and 24-h uric albumin higher than 300 or albumine/cratenine rate higher than 30, lack of nephropathy in the fields of other diseases such as urinary infections or congenital diseases or advanced cardiac failure and accepting informed consent form. The exclusion criteria include allergy background to vitamins group B, advanced cardic and cerebral diseases, cancer patients or under chemotherapy, background of diabetic ketoacidose, self-immunity diseases and significant peripheral nephropathy.

The affection term of diabetic, patients were designated and the consuming drugs type determined based on mg or unit/weight and consumption term. The side effects of diabetic in these patients such as degree and intensity of retinopathy were determined. Also, the functional situation of kidney was designated based on cratinine, Urea, sodium, potassium, triglyceride, cholesterol, serum uric acid level, urin albumine/cratinine and protein/cratinine rate.

The blood pressure, of patients was determined based on mmHg and the blood pressure infection term, family background of diabetes and blood pressure were questioned. The patients were divided in to two groups.

1) First group (n =22) were treated by Losartan by dose 25mg/12h for two months solely and tests controlled while beginning of drug and next 2 months.

2) Second group (n = 22) were treated by Losartan (25mg/12h) and pyridoxamine (25mg) and tests controlled before and after two months treatment. There is needed to be said that the study was conducted as bouble – blind test namely the patients were unaware about setting in case or control groups. In addition, nurses and laboratory staff were responsible for taking and testing obtained samples from patients were unaware about their taken regimen. All of cases and diagnose and treatment stages shared with patients and they were studied by self-consent. In the present research, no additional cost was taken from the patients. In addition, all of patients file data has been maintained secretly. The obtained data fro study were analyzed by description statistical methods (mean ±standard deviation), frequency, percent and mean difference test for independent groups for quantities variables and Q-square test for qualitative variants by statistical software SPSS TM 15.

In the present study, P-Value > 0.05 was considered meaningful statistically. This study with record number IRCT 2012121311743N1 was registered in Iran clinical experimental center with address http://www.irct.ir.

3. Results

From 44 reviewed patients, 22 patients were set in case group and 22 patients in control group. From these patients, three patients (1 patient in case group, 2 patients in control group) were excluded because of mortality in follow-up period.

Finally, the complete data of 21 patients in case group and 20 patients in control group were analyzed and compared.

The measured level in blood samples of patients in both groups i.e. case and control ones were shown as before and after treatment and statistical comparison based on results of pre and pro-treatment in table 1. The measured level for two major variables of 24-h urine protein and lipid peroxide were shown in table 2 in both case and control groups before and after treatment and statistical comparison between both groups based on results of before and after treatment in table 1. The measured levels in blood shown in table 2 in order to compare results in combinational treatment as before and after treatment and statistical comparison between both levels. Also, measured levels were shown in table 2 for two main variables of 24-h urine protein and lipid peroxide in order to compare results in combinational treatment as before and after treatment and statistical comparison between both levels.

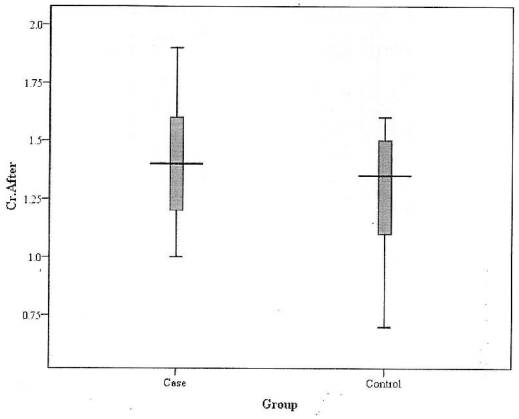

Diagram 1. The measured cratinine values distribution after treatment in both case and control groups

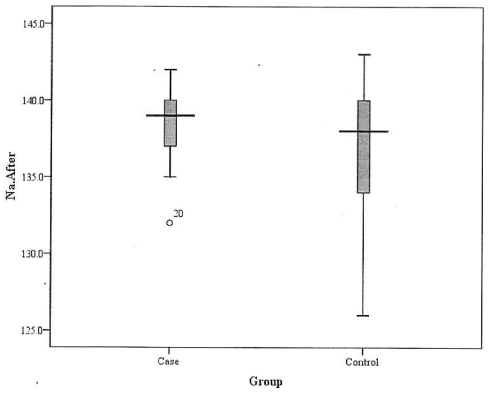

Diagram 2. The measured sodium values distribution after treatment in both case and control groups

4. Discussions and conclusion

The renal function loss in diabetic patients is because of nephronic lesions and consequently lack of nephrons. It could be reffered that, nephrons are formed before and alittle after birth and following it no longer there is nephrogensis. Thus, by glomerular lesions, the filteration ability of kidney declines and nephron numbers would be decreased (Kriz, 1992). The diabetic nephropathy begins by primary hypertrophy of glomerule and then leads to sclerosis and other lesions. It is notable to say that, glomerular lesions exist before occurrence of diabetic clinical signs.About 40% of patients who reach end-stage renal disease (ESRP) were because of diabetic nephropathy.

In this stage, the patient should to take dialysis or renal graft (Molitch, 2007). In the terms of diabetic nephropathy physiopathology, theories such as angiotensin II, Advanced glycation and products theory (AGES), oxidative stress, redoctase aldol or first bridge path, protein kinase C and some other theories has been posed (Sheetz and King, 2007).

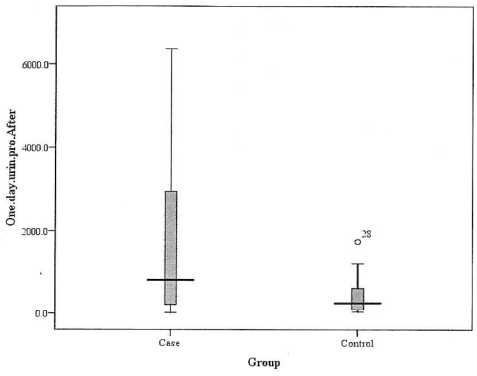

Diagram 3. The measured 24-h urine protein values distribution after treatment in both case and control groups

Table 1. The measured values in blood samples of patients in both case and control groups at before and after treatment

		Case	Control	P-value*
Urea	before treatment	51.04±24.96	53.5±33.77	0.94
	after treatment	52.92±23.06	53.65±19.81	0.17
P-value¥		0.73	0.98	-
Creatinine	before treatment	1.38±0.23	1.37±0.31	0.22
	after treatment	1.4±0.27	1.2±0.28	0.78
P-value¥		0.71	0.27	-
Sodium (Na)	before treatment	139.95±4.17	138.85±6	0.052
	after treatment	138.33±2.28	136.9±4.74	0.01
P-value¥		0.055	0.22	-
Potassium (K)	before treatment	4.53±0.45	4.67±0.73	0.047
	after treatment	4.36±0.3	4.47±0.44	0.23
P-value¥		0.06	0.29	-
Cholesterol	before treatment	188.9±57.03	222.45±87.01	0.009
	after treatment	163.28±62.1	170.75±50.48	0.30
P-value¥		0.07	0.03	-
Triglyceride	before treatment	231.28±106.05	181.5±95.14	0.42
	after treatment	179.66±116.06	172.854±56.81	0.01
P-value¥		0.005	0.71	-
Blood sugar	before treatment	238.81±99.91	205.15±67.12	0.15
	after treatment	147.71±59.72	169.35±52.09	0.62
P-value¥		0.001	0.04	
Uric Acid	before treatment	8.46±2.13	8.03±1.75	0.60
	after treatment	6.69±2.28	6.08±1.95	0.25
P-value¥		<0.0001	<0.0001	-

*_ P-value (between group) ¥_ P-value (within group)

Table 2. The measured values for two main variables 24-h urine protein and lipid peroxide of patients in case and control groups before and after treatment

		Case	Control	P-value*
24-h urine protein	before treatment	3157.38±2330.47	1087.18±1021.81	<0.0001
	after treatment	1587.52±1695.91	425.52±447.97	<0.0001
P-value¥		<0.0001	< 0.004	-
Lipid peroxide	before treatment	3.39±1.57	2.88±1.34	0.43
	after treatment	1.79±0.84	2.02±0.83	0.86
P-value¥		0.0001	0.006	-

*_ P-value (between group) ¥_ P-value (within group)

The angiotensin II theory shows that, hyperglacemia causes to increased renal rennin angiotensin system activity. This system is systemic apart from rennin angiotensin system (In diabetic kidney of rat and human, the production place of ACE is in gloerules and renal vessels and far from proximal bent tube and mesangal cell has specific rennin-angiotensin system and by increasing glucose, produces higher angiotensin II (Leehey, 2000; Huang, 2000; Carey and Siragy, 2000).

The increased angiotensin II intra-kidney causes to renal lesions especially one by effect on self-respectors located on renal different cells, induction and formation of various chemocain.

Losartan potassium is a non-peptide molecule with closed formula $C_{22}H_{22}CIKN_6O$ (Physicians' Desk Reference Companion Guide, 2007). It is a selected drug for patients with high blood pressure. Angiotensin II has receptors: one type of angiotensin II, is receptor type 1 or AT_1 which angiotensin II by connection to this receptor in renal cells actuates mechanisms which cause to cell multiplication, increased matrix production and fibrosis progression, Losartan blocks this receptor by connection to receptor which AT_1.

Other receptor of angiotensin II is type II or AT_2, which by connection to angiotensin II to such receptor conducts actions such as vascular dilation, antimitosis effects, decreased sodium resorption and activation of kinin system (Ramahi, 2001). Losartan and it's active metabolites have higher tendency to connection with AT_1 receptors than AT_2 ones (about 4-5 times) (Thurman and Schrier, 2000).

By blocking AT_1 receptor, the plasma angiotensin II increased and instead holded by AT_2 receptors.

In fact, part of useful effects of Losartan and it's metabolites is blocking AT_1 receptor and other part is, stimulation of AT_2 receptor by AGII and useful actions resultant of such connection.

With regard to increased renal angiotensin II apart from systemic angiotensin II in diabetes and

harmfulness of it in diabetic nephropathy and also in most conducted research with angiotensin II – producing blocker drugs or angiotensins II – receptor blocker drugs, the aim of research was to review albumin excretion level from kidney and cratinine clearance (renal function evaluation) or in some cases, hystopathologic qualitative study. There isn't adequate data on renal lesion level in diabetic nephropathy. The aim of research is to evaluate in quantitive study (steriologic) the effect of Losartan on number and volume of renal glomerules for first time, i.e by decreased albumin excretion and reduced proteinaria from diabetic kidney, to what extent Losartan could block renal structural lesions in diabetic patients.

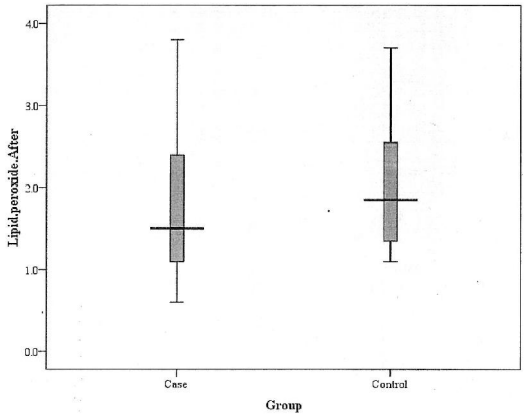

Diagram 4. The measured lipid peroxide values distribution after treatment in both case and control groups

The blocker drugs for angiotensin type I (AT_1) receptors such as Losartan valsartan and telmisartan have higher tendency to block angiotensin receptors than ACE blockers. These drugs are used to treat higher blood pressure and control ……. failure of heart (Liu 2000; Chrysant and Chrysant, 2002; Ji, 2009; Nakao, 2000). Angiotensin II dupl cates renal cells and their hypertrophy especiall mesangal cell inside glomerule by connection to receptor AT_1 (Palmer, 2007) and by stimulating growth factors production in especial TGF-B activate extra cellular matrix production and deactivate matrix degeneration enzymes and causes to glomerular sclerosis (Thurman and Schrier, 2000; Fakhouri, 2001). Additionally angiotensin II induces PDGF production (growth factor derived from platelet) which leads to extra cellular matrix deposition and renal fibrtosis (Carey and Siragy, 2000). Angiotensin II induces new fibroblasts from enveloped cells of proximal bent tube (Palmer, 2007). The results of prior research showed that Losartan causes to reduced protein excretion and declined glomerular filtration rate (Remuzzi, 1990; Kohzuki, 1999). Some sclerosis in diabetic animals (Zhoung, 2001; Mauer, 2007; Sasaki, 2007). The various studies showed that, Losartan has protective effects in some of tissues. The various mechanisms have been posed for such protective effect on different tissues. Chrysant and his colleagues showed that blockers of angiotensin receptors have protective effects after cardiac and cerebral strokes and inhibit following lesions of strokes. Also they proposed that Losartan could have anti-accumulation effects of platelet, anti-diabetic, anti-platelets of vascular wall, reducing blood uric acid and atrium anti-fibrilation (Chrysant and Chrysant, 2002).

The results of the present research correspond with our results.

In our study, in control group who were treated by Losartan, there was meaningful decrease in blood uric acid in comparing with state before commencement of Losartan so that uric acid values were 8.03±1.75 and 6.08±1.95 ($P<0.0001$) before and after treatment by Losartan respectively. Iino and his colleagues observed that in patients with chronic renal failure and blood pressure, Losartan has protective effects on kidney (Iino, 2007).

Kohzuk and his colleagues showed that Losartan following occurrence of chronic renal failure and high blood pressure. In rat, could block proteinuria and glomerulosclorosis meaningfully (Kohzuki, 2001). In other study, Ji and his colleagues showed that rennin angiotensin-system ingibitors such as Losartan could decrease glomerulosclerosis, proteinuria, albuminura and hypercholesterolemia resultant of unilateral ablation of kidney (Ji, 2009). Yang & his colleagues showed that Losartan inhibits collagen deposition in renal parenchyma and proteinuria in rats with diabetic nephropathy. In our study, also, in reviewing urine protein in-group treated by Losartan, the values were 1087.18±1021.81 and 425.52±447.97 before and after treatment respectively which shows meaningful decrease statisticaly. In case group whom were treated by combination of lasartan and pyridoxamine also, there was meaningful difference between 24-h urine protein before and after treatment (before treatment 3157.38±2330.47 and after treatment 1587.52±1695.91) but statistically there was more statistical difference between before and after treatment in case group than control group ($P<0.0001$). Heller, Tokutama & their colleagues showed that Losartan could decrease damages resultant of ischemia and oxidative stress ans inhibit tubular cells proliferation and penetration of macrophages in to renal parenchyma and decline creatinine and blood urea levels (Heller, 1992; Tokuyama, 2002). In our study, also, the measured

cratinine level declined in control group treated by Losartan after treatment than before it (before treatment 1.37±0.31 and after treatment 1.2±0.28) but it wasn't meaningful statistically (p = 0.27). In case group treated by combination of Losartan and pyridoxamine, there was not significant change in cratinine level before and after treatment (P=0.71). Pyridoxamine is a vitamer in family of vitamine B6 that includes pyridoxal and pyridoxine. Biologically pyridoxamine is active vitamin B6, pyridoxal-5-phosphate that converts through retrieval pathof vitamin B6 (Roje, 2002). Vitamin B6 acts in various metabolic processes as enzyme cofactor. In study of Tanimoto on animal models, they observed that, treatment by pyridozamine with varies doses, could have different but useful effects on AGEs production through any three metabolism paths of suger, protein and lipid, and could decline urine albumine excretion which occurs in dose 400mg for any key (Tanimoto, 2002). In our study, in group under treatment with combination of Losartan and pyridoxamine, there was meaningful difference between before and after treatment in the cases of triglyceride, blood suger, uric acid, 24-h urine protein and lipid peroxase ($p<0.05$). Alderson & his colleagues (2003) reffered that pyridoxamine could refine metabolic dysfunctions such as dislipid and also inhibit from progression of nephropathy (Alderson, 2000).

In study by Zheng and his colleagues who reviewed conjoint effect of AGEs- producers and angiotensin – reseptor blockers, in one group, there were rats that have diabetes for 16 weeks and in other one, their diabetic nephropathy has been established (Zheng, 2002). The concluded that, rats treated by combination of analaprile and pyridoxamine, the mortality and renal failure occurrence in them is lower than any of drugs solely (Alderson, 2007). In our study, the case group were treated by combination of Losartan and pyridoxamine and control group with Losartan (solely). The obtained data showed that combination of Losartan and pyridoxamine has better results than Losartan solely. The researchers in a review by Alderson NL (2004) in the interval of 29 weeks in patients with diabetic nephropathy showed that, combination of analaprile and pyridoxamine and antioxidants such as vitamin E could inhibit of progression of nephropathy resultant of toxic production as lipids and sugers (AGE/ALE) (Alderson, 2007). In our study, there was not meaningful difference between case and control groups in cases of urea, cratinine, sodium, triglyceride, blood sugar, uric acid and lipid peroxiase and there was similar level between both groups. In reviewing these cases following treatment, there was difference between both groups in the cases of sodium ($p=0.01$) and triglyceride ($p=0.01$).

Conclusion

In reviewing both case and control groups, there was meaningful difference between. Both groups in the cases of sodium and triglyceride after commencement of two different.

In reviewing of two different regimen, the following results, were obtained. In-group under treatment by Losartan, there was meaningful difference between before and after treatment in cases of cholesterol, blood suger, uric acid, 24-h urine protein and lipid peroxidase. In-group under treatment with combination of Losartan and pyridoxamine, there was meaningful difference between before and after treatment in cases of triglyceride, blood suger, uric acid, 24-h urine protein and lipid peroxidase.

It is noticeable to say that there is more difference between before and after treatment in-group under treatment with combination of Losartan and pyridoxamined that group under treatment with Losartan.

Thus, based on obtained results, it is recommended use of Losartan in combination with pyridoxamine.

Corresponding Author:
Dr. Kamaludin Golbazi
Internal Medicine Department, Emam Reza Hospital, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
Email: dr_an1077@gmail.com

References

1- Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al(2002). Prevalence of chronic kidney disease in the United States. JAMA;792(12):7002-72.
2- Hebert LA, Wilmer WA, Falkenhain ME, Ladson-Wofford SE, Nahman NS, Jr(2001)., Rovin BH. Renoprotection: one or many therapies? Kidney Int;99(7):1711-72.
3- Foley RN, Collins AJ(2002). End-stage renal disease in the United States: an update from the United States Renal Data System. J Am Soc Nephrol;12(10):7277-2.
4- Cooper ME(2001). Interaction of metabolic and haemodynamic factors in mediating experimental diabetic nephropathy. Diabetologia;77(11):1992-27.
5- Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al(2001). Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 7 diabetes. N Engl J Med;079(17):291-20.

6- Brenner BM, Cooper ME, de ZD, Keane WF, Mitch WE, Parving HH, et al(2001). Effects of Losartan on renal and cardiovascular outcomes in patients with type 7 diabetes and nephropathy. N Engl J Med;079(17):221-9.
7- Ravid M, Brosh D, Levi Z, Bar-Dayan Y, Ravid D, Rachmani R(1992). Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 7 diabetes mellitus. A randomized, controlled trial. Ann Intern Med;172(17 Pt 1):927-2.
8- Thomas MC, Baynes JW, Thorpe SR, Cooper ME(2009). The role of AGEs and AGE inhibitors in diabetic cardiovascular disease. Curr Drug Targets;2(7):790-27.
9- Vlassara H, Striker LJ, Teichberg S, Fuh H, Li YM, Steffes M(1997). Advanced glycation end products induce glomerular sclerosis and albuminuria in normal rats. Proc Natl Acad Sci USA;91(77):11207-2.
10- Kang Z, Li H, Li G, Yin D(2002). Reaction of pyridoxamine with malondialdehyde: mechanism of inhibition of formation of advanced lipoxidation end-products. Amino Acids;10(1):99-21.
11- Voziyan PA, Metz TO, Baynes JW, Hudson BG(2007). A post-Amadori inhibitor pyridoxamine also inhibits chemical modification of proteins by scavenging carbonyl intermediates of carbohydrate and lipid degradation. J Biol Chem;722(9):0092-700.
12- Chetyrkin SV, Zhang W, Hudson BG, Serianni AS, Voziyan PA(2002). Pyridoxamine protects proteins from functional damage by 0-deoxyglucosone: mechanism of action of pyridoxamine. Biochemistry;72(1):992-1002.
13- Onorato JM, Jenkins AJ, Thorpe SR, Baynes JW(2000). Pyridoxamine, an inhibitor of advanced glycation reactions, also inhibits advanced lipoxidation reactions. Mechanism of action of pyridoxamine. J Biol Chem; 729(72):71122-27.
14- Degenhardt TP, Alderson NL, Arrington DD, Beattie RJ, Basgen JM, Steffes MW, et al(2007). Pyridoxamine inhibits early renal disease and dyslipidemia in the streptozotocin-diabetic rat. Kidney Int;21(1):909-90.
15- Alderson NL, Chachich ME, Youssef NN, Beattie RJ, Nachtigal M, Thorpe SR, et al(2000). The AGE inhibitor pyridoxamine inhibits lipemia and development of renal and vascular disease in Zucker obese rats. Kidney Int;20(2):7170-00.
16- Alderson NL, Chachich ME, Frizzell N, Canning P, Metz TO, Januszewski AS, et al (2007). Effect of antioxidants and ACE inhibition on chemical modification of proteins and progression of nephropathy in the streptozotocin diabetic rat. Diabetologia; 72(2):1029-99.
17- Tanimoto M, Gohda T, Kaneko S, Hagiwara S, Murakoshi M, Aoki T, et al(2002). Effect of pyridoxamine (K-120), an inhibitor of advanced glycation end products, on type 7 diabetic nephropathy in KK-A(y)/Ta mice. Metabolism;92(7):120-2.
18- Burns KD(2000). Angiotensin II and its receptors in the diabetic kidney. Am J Kidney Dis;02(0):779-22.
19- Leehey DJ, Singh AK, Alavi N, Singh R(2000). Role of angiotensin II in diabetic nephropathy. Kidney Int Suppl;22:S90-S92.
20- Taal MW, Brenner BM(2000). Renoprotective benefits of RAS inhibition: from ACEI to angiotensin II antagonists. Kidney Int;92(9):1200-12.
21- Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P(2001). The effect of irbesartan on the development of diabetic nephropathy in patients with type 7diabetes. N Engl J Med;79(17):220-2.
22- Metz TO, Alderson NL, Thorpe SR, Baynes JW(2000). Pyridoxamine, an inhibitor of advanced glycation and lipoxidation reactions: a novel therapy for treatment of diabetic complications. Arch Biochem Biophys; 719(1):71-9.
23- Kriz W, Hosser H, Hahnel B, Gretz N, Provoost AP(1992). From segmental glomerulosclerosis to total nephron degeneration and interstitial fibrosis: a histopathological study in rat models and human glomerulopathies. Nephrol Dial Transplant;10(11):7221-92.
24- Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, et al(2007). Nephropathy in diabetes. Diabetes Care72(1):S29-S20.
25- Sheetz MJ, King GL(2007). Molecular understanding of hyperglycemia's adverse effects for diabetic complications. JAMA; 722(2):7929-22.
26- Leehey DJ, Singh AK, Alavi N, Singh R(2000). Role of angiotensin II in diabetic nephropathy. Kidney Int Suppl;22:S90-S92.
27- Huang XR, Chen WY, Truong LD, Lan HY(2000). Chymase is upregulated in diabetic nephropathy: implications for an alternative pathway of angiotensin II-mediated diabetic

renal and vascular disease. J Am Soc Nephrol;17(2):1202-72.
28- Carey RM, Siragy HM(2000). The intrarenal renin-angiotensin system and diabetic nephropathy. Trends Endocrinol Metab; 17(2):727-21.
29- Medical E. 2007 Physicians' Desk Reference Companion Guide, Keyed to PDR 92th Edition (Physicians' Desk Reference Guide to Drug Interactions, Side Effects, & Indications). 92 ed. Thomson Healthcare; 2007.
30- Ramahi TM(2001). Expanded role for ARBs in cardiovascular and renal disease? Recent observations have far-reaching implications. Postgrad Med;109(7):119-77.
31- Thurman JM, Schrier RW(2000). Comparative effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on blood pressure and the kidney. Am J Med;117(2):922-92.
32- Liu BC, Chen Q, Luo DD, Sun J, Phillips AO, Ruan XZ, et al(2000). Mechanisms of irbesartan in prevention of renal lesion in streptozotocin-induced diabetic rats. Acta Pharmacol Sin;77(1):22-20.
33- Chrysant SG, Chrysant GS(2002). The pleiotropic effects of angiotensin receptor blockers. J Clin Hypertens (Greenwich);2(7):721-2.
34- Ji Z, Huang C, Liang C, Chen B, Chen S, Sun W(2009). Protective effects of blocking renin-angiotensin system on the progression of renal injury in glomerulosclerosis. Cell Mol Immunol;7(7):190-7.
35- Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T(2000). Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. Lancet;021(9097):112-77.
36- Palmer BF(2007). Renal dysfunction complicating the treatment of hypertension. N Engl J Med;072(12):1792-21.
37- Fakhouri F, Placier S, Ardaillou R, Dussaule JC, Chatziantoniou C(2001). Angiotensin II activates collagen type I gene in the renal cortex and aorta of transgenic mice through interaction with endothelin and TGF-beta. J Am Soc Nephrol;17(17):7201-10.
38- Remuzzi A, Perico N, Amuchastegui CS, Malanchini B, Mazerska M, Battaglia C, et al(1990). Short- and long-term effect of angiotensin II receptor blockade in rats with experimental diabetes. J Am Soc Nephrol;7(1):70-9.
39- Kohzuki M, Yasujima M, Kanazawa M, Yoshida K, Fu LP, Obara K, et al(1999). Antihypertensive and renal-protective effects of Losartan in streptozotocin diabetic rats. J Hypertens;10(1):92-100.
40- Zhoung HJ, Zhang DM, Zhou M(2001). Effects of Losartan on renal ultrastructure in diabetic rats. Hunan Yi Ke Da Xue Xue Bao;72(0):700-7.
41- Mauer M, Zinman B, Gardiner R, Drummond KN, Suissa S, Donnelly SM, et al(2007). ACE-I and ARBs in early diabetic nephropathy. J Renin Angiotensin Aldosterone Syst;1(7):727-9.
42- Sasaki M, Uehara S, Ohta H, Taguchi K, Kemi M, Nishikibe M, et al(2007). Losartan ameliorates progression of glomerular structural changes in diabetic KKAy mice. Life Sci; 29(2):229-20.
43- Iino Y, Hayashi M, Kawamura T, Shiigai T, Tomino Y, Yamada K, et al(2007). Renoprotective effect of Losartan in comparison to amlodipine in patients with chronic kidney disease and hypertension--a report of the Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) study. Hypertens Res ;72(1):71-00.
44- Kohzuki M, Kamimoto M, Wu XM, Xu HL, Kawamura T, Mori N, et al(2001). Renal protective effects of chronic exercise and antihypertensive therapy in hypertensive rats with chronic renal failure. J Hypertens; 19(10):1222-27.
45- Yang L, Fan J, Mi X, Liu X, Xu G(2000). Protective effect of angiotensin II receptor blockage on rats with experimental diabetes nephropathy in early stage. Sichuan Da Xue Xue Bao Yi Xue Ban;07(7):012-9.
46- Heller J, Kramer HJ, Cervenka L, Hellerova S(1992). Losartan protects the rat kidney from ischemic injury. Kidney Int Suppl;99:S110-S117.
47- Tokuyama H, Kelly DJ, Zhang Y, Gow RM, Gilbert RE(2002). Macrophage infiltration and cellular proliferation in the non-ischemic kidney and heart following prolonged unilateral renal ischemia. Nephron Physiol;102(0):97-27.
48- Roje S(2002). Vitamin B biosynthesis in plants. Phytochemistry;22(17):1907-71.
49- Tanimoto M, Gohda T, Kaneko S, Hagiwara S, Murakoshi M, Aoki T, et al(2002). Effect of pyridoxamine (K-120), an inhibitor of

advanced glycation end products, on type 7 diabetic nephropathy in KK-A(y)/Ta mice. Metabolism;92(7):120-2.

50- Alderson NL, Chachich ME, Youssef NN, Beattie RJ, Nachtigal M, Thorpe SR, et al(2000). The AGE inhibitor pyridoxamine inhibits lipemia and development of renal and vascular disease in Zucker obese rats. Kidney Int;20(2):7170-33.

51- Zheng F, Zeng YJ, Plati AR, Elliot SJ, Berho M, Potier M, et al(2002). Combined AGE inhibition and ACEi decreases the progression of established diabetic nephropathy in B2 db/db mice. Kidney Intug;20(0):902-17.

52- Alderson NL, Chachich ME, Frizzell N, Canning P, Metz TO, Januszewski AS, et al (2007). Effect of antioxidants and ACE inhibition on chemical modification of proteins and progression of nephropathy in the streptozotocin diabetic rat. Diabetologia;72(2):1029-99.

11/3/2013