Effects of Losartan versus Enalapril on Serum Uric Acid Levels in Hypertensive Patients with Metabolic Syndrome[#]

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Abstract

To investigate the effects of losartan and enalapril on serum uric acid in hypertensive patients with metabolic syndrome, one hundred and twenty six newly diagnosed mild hypertensive patients, having markers of metabolic syndrome included in the study. The patients were divided into two groups. Group 1 (60 patients) was given losartan **(**50 mg/ day) and group 2 (66 patients) enalapril (20 mg/ day) for a duration of 2 months. A control group of seventy apparently healthy individuals were included. Metabolic syndrome was diagnosed according to diagnostic criteria of metabolic syndrome related to the American National Cholesterol Education Program-Adult Treatment Panel III. Serum uric acid levels were measured before and after drug administration. The results revealed a significant higher levels of uric acid were found in the hypertensive patients as compared with control group and a significant drop of uric acid was noted after treatment with losartan but not with enalapril. In conclusions: this study demonstrates significantly higher serum uric acid concentrations in hypertensive patients having markers of metabolic syndrome. Losartan but not enalapril therapy produced a significant fall in the serum uric acid level. Losartan can be useful therapeutic agent to control blood pressure and to reduce serum uric acid level in hypertensive patients having markers of metabolic syndrome and hyperuricaemia.

Key words: Hypertension, metabolic syndrome, uric acid, losartan, enalapril.

الخلاصة

لتَحرّي تأثيراتِ عقاري اللوسارتان والإنالابريل على مستوى الحامضِ البولي في مصل الدم لدى مرضى ارتفاع ضغط الدمّ والمتلازمة الأيضيةِ، أجريت هذه الدراسة على ١٢٦ مريضا شخصوا حديثا إصابتهم بالضغط العالي من النوع الخفيف ولديهم علامات المتلازمة الأيضيةِ . قسمت مجموعة المرضى إلى مجموعتان حسب العلاج المعطى لهم. أعطيت المجموعة الأولى عقار اللوسارتان ٥٠ ملغ يوميا، والمجموعة الثانية عقار الإنالابريل ٢٠ ملغ يوميا، .أستغرقت فترة العلاج مدة شهرين. تم إختيار ٧٠ شخصا سليما من المتطوعين (يبدون أصحاء) طبيعي الضغط ليكونوا مجموعة الضبط. شخصت المتلازمة الأيضية حسب معايير البرنامج الوطني لتعليم الكولسترول الأمريكي. تم قياس مستوى الحامض البولي لكل من مجموعة المرضى(قبل وبعد العلاج) ومجموعة الضبط. أظهرت النَتائج ارتفاعا معنويا ملحوظا في مستوى الحامضِ البوليِ في مصل الدم لدى مرضى ارتفاع ضغط الدمَّ بالمقارنة مع مجموعة الضبط وانخفاضا معنويا في مستوى الحامضِ البوليِ بعد المعالجة بعقار اللوسارتان لكن لَيسَ مَع عقار الأنالابريل. في الاستنتاجات: أظهرت هذه الدراسةِ أن هناك ارتفاعا معنويا ملحوظاً في مستوى الحامضِ البوليِ في مصل الدم لدى مرضى إرتفاع ضغط الدمَّ والذين لديهم علاماتُ المتلازمةِ الأيضيةِ. أدى العلاج بعقار اللوسارتان لكن لَيسَ العلاجَ بعقار الأنالابريل إلى انخفاض معنوي ملحوظ في مستوى الحامضِ البوليِ في مصل الدم. يُمكنُ أَنْ يَكُونَ اللوسارتان علاجّاً مفيداً للسَيْطَرَة على ضغطِ الدمّ ولتَخفيض مستوى الحامضِ البولي في مصل الدم في مرضى إرتفاع ضغط الدمِّ والذين لديهم علاماتُ المتلازمةِ الأيضيةِ وفرط الحامض البولي في الدم.

Introduction

Some investigators have suggested that uric acid plays a causal role in the development of cardiovascular disease [(1)] whereas others have concluded that uric acid merely reflects other concomitant risk factors, such as hypertension, insulin resistance, obesity, or lipid abnormality [(2)]. Elevated serum uric acid concentrations are also found in healthy offspring of parents with coronary heart disease, indicating a possible causal relationship [(3)]. Krishnan *et al* [(4)] demonstrating that hyperuricemia increases the risk of developing hypertension by approximately 80%, independent of baseline blood pressure measurements, renal function, serum lipid levels, body mass index, proteinuria, alcohol use, and age. Johnson *et al* [(5)] reported that elevated uric acid level was observed in 40% to 60% of hypertensive subjects; similarly, hypertension was observed in 50% to 65% of subjects with gout. Johnson *et al* [(6)] reported that hyperuricemia was observed in 25% of treated hypertensive subjects, 50% of those without treatment, and 75% to 100% of those with malignant hypertension or renal dysfunction.

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Serum uric acid (SUA) levels are often increased in subjects with MS. However, none of the proposed sets of diagnostic criteria include SUA levels in the definition of MS [7,8]. In 2001, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) published the most widely used set of diagnostic criteria. These criteria include elevated plasma triglyceride (TRG) levels (≥150 mg/dl[1.69 mmol/l]), decreased levels of high-density lipoprotein cholesterol (HDL-C) (<40 mg/dl[1.04 mmol/l] in men and <50 mg/dl[1.29 mmol/l] in women), elevated blood pressure (BP)(≥130/85 mm Hg), increased fasting plasma glucose levels (≥ 110 mg/dl [6.1 mmol/l]), and abdominal obesity (waist circumference >102 cm in men and >88 cm in women)[9]. It is possible that the increased cardiovascular disease risk associated with the MS is partially attributed to elevated circulating SUA concentration [7,8]. Large epidemiologic studies demonstrated that the prevalence of MS showed a graded increase according to SUA levels [10-12]. Moreover, SUA concentration was positively correlated with blood pressure (BP), body mass index, levels of fasting plasma glucose, triglycerides, high-sensitivity C-reactive protein, and inversely correlated with high density lipoprotein cholesterol levels (HDL-C) [8]. Many drugs have hypouricaemic properties, in addition to their main therapeutic effects. The oral weight loss agent sibutramine decreases serum uric acid in obese patients by 20% to 25% [13]. Similarly, in patients with type 2 diabetes and hyperuricemia, the insulin sensitizing agent troglitazone lowers serum uric acid by 20% to 25% [14]. Ramipril was found to increase the excretion of uric acid in a number of hypertensive patients [15]. The present study was conducted to investigate the effects of losartan compared with enalapril on uric acid levels in hypertensive patient having markers of metabolic syndrome.

Patients and Methods

One hundred and twenty six hypertensive patients having markers of metabolic syndrome participated in this study. They were divided into two groups according to the type of the drug taken. Group 1 was given losartan (Angizar 50mg, Micro Pharmaceutical Industries, Co. Ltd., India) in doses of 50mg daily. They are 28 males and 32 females, with a mean age of 56.68±6.32 years. Group 2 received enalapril (Enalapril 20mg, Asia Pharmaceutical Industries, Co. Ltd., Aleppo-Syria) in doses of 20 mg once daily. They are 30 males and 36 females with mean ages of 52.80±7.23 years. Another 70 healthy, non obese, normotensive individuals, age and gender matching with study patients, participated in the study as a control group. They were 34 males and 36 females, with mean age of 53.51±6.66 years. This open 2-month, controlled, comparative clinical trial was conducted on hypertensive patients having markers of metabolic syndrome who were seen at Ibn-Sina teaching hospital in Mosul, Iraq. The study protocol was approved by the Ethics Committees of the College of medicine and Mosul health administration. Non-diabetic patients with mild hypertension (Stage 1: Systolic 140 - 159 mmHg and Diastolic 90 - 99 mmHg) [16], who met the diagnostic criteria of metabolic syndrome according to the American National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) [9] were included in this study. Those with hepatic or renal diseases, pregnancy and lactation, hypertensive patients on antihypertensive therapy, hypersensitive patients on losartan or enalapril, gouty patients and inflammatory diseases such as rheumatoid arthritis were excluded. Markers of metabolic syndrome including, waist circumference, blood pressure, serum glucose concentration, triglycerides, and HDL-cholesterol were determined before and at the end of study period. The presence of 3 or more of such markers indicates metabolic syndrome state. Blood pressure was measured by standard mercury sphygmomanometer. Goal BP after treatment was less than 140/ 90 mmHg. Serum glucose concentration, total cholesterol, triglycerides, and HDL-cholesterol were measured by using special kits. LDL-cholesterol was calculated from Friedewald equation [17]. Serum uric acid concentration was measured at baseline and after 2 months therapy with losartan or enalapril by enzymatic method using a kit supplied by Biolabo laboratories (France).

Statistical methods

Standard statistical methods were used to determine the mean and standard deviation (SD). Paired student t-test was used to compare the results between before and after drug therapy. Unpaired t-test was used to compare the results of cases before and after losartan or enalapril therapy with control and to compare the results between losartan and enalapril treated groups.. The statistical results were considered significant at p=0.05 or less.

Results

Baseline measurement of waist circumference, Body mass index (BMI) , blood pressure, serum glucose concentrations and lipid profile of the patient's groups showed a significant elevation as compared with the control group, while HDL-cholesterol showed lowered values as compared with the controls (P<0.001) (Table.1). Baseline uric acid levels were 306.69±67.72 µmol/l for losartan group and 302.94±56.86 µmol/l for enalapril group which showed a significant elevation (P<0.001) as compared with the control (284.95±76.52 µmol/l) (Table.1 and Table.3) respectively. Comparison of uric acid levels before and after 2 months of therapy by each drug showed a significant reduction in losartan group (P<0.001) (Table .2) but not in enalapril group (p=0.123) (Table .4). Comparison of uric acid levels between losartan group and enalapril group showed a significant reduction in the losartan group (P<0.001) as compared with the enalapril group (Table .5).

Table 1: Comparison of data between control and losartan group (before and after therapy).

Parameters	Mean ± SD		
	Control (n=70)	Before (n=60)	After (n=60)
BMI (kg/m^2)	22.2 ± 1.8	33.46 ± 2.08***	30.95 ± 1.8***
Waist circum. (cm)	83.95 ± 6.2	106.79 ± 8.53***	104.08 ± 8.3***
SBP (mm Hg)	127.05 ± 6.93	143.60 ± 7.72***	136.82 ± 8.4***
DBP (mm Hg)	79.24 ± 4.91	92.18 ± 6.21***	83.92 ± 6.3***
FSG (mmol/L)	4.75 ± 0.9	6.6 ± 0.4***	5.12 ± 0.7***
Total-C (mmol/L)	4.45 ± 0.63	5.28 ± 0.74***	4.65 ± 0.8***
TG (mmol/L)	1.48 ± 0.6	1.67 ± 0.37	1.23 ± 0.5*
HDL-C (mmol/L)	1.60 ± 0.28	1.32 ± 0.32***	1.54 ± 0.4***
LDL-C (mmol/L)	2.20 ± 0.70	3.20 ± 0.67***	2.84 ± 0.8***
Uric acid (□mol/L)	284.95 ± 76.52	306.69 ± 67.72***	275.92 ± 61.63***

* Significant difference from control at p≤0.05, ** at p≤0.01 and *** at p≤0.001 using unpaired t-test.

Table 2 : Comparison of the effects of losartan before and after therapy .

Parameters	Mean ± SD		
	Before (n=60)	After (n=60)	p-value
BMI (kg/m^2)	33.46 ± 2.08	30.95 ± 1.8***	<0.001
Waist circum. (cm)	106.79 ± 8.53	104.08 ± 8.3***	<0.001
SBP (mm Hg)	143.60 ± 7.72	136.82 ± 8.4***	<0.001
DBP (mm Hg)	92.18 ± 6.21	83.92 ± 6.3***	<0.001
FSG (mmol/L)	6.6 ± 0.4	5.12 ± 0.7***	<0.001
Total-C (mmol/L)	5.28 ± 0.74	4.65 ± 0.8	0.135(NS)
TG (mmol/L)	1.67 ± 0.37	1.23 ± 0.5	0.240(NS)
HDL-C (mmol/L)	1.32 ± 0.32	1.54 ± 0.4***	<0.001
LDL-C (mmol/L)	3.20 ± 0.67	2.84 ± 0.8	0.098(NS)
Uric acid (□mol/L)	306.69 ± 67.72	275.92 ± 61.63***	<0.001

***Significant difference at p≤0.001 using paired t-test. NS= Not significant.

Table 3:Comparison of data between control and enalapril group (before and after therapy).

Parameters	Mean ± SD		
	Control (n=70)	Before (n=66)	After (n=66)
BMI (kg/m^2)	22.2 ± 1.8	32.79 ± 1.9***	30.6 ± 2.18***
Waist circum. (cm)	83.95 ± 6.2	103.44 ± 8.87***	100.8 ± 8.53***
SBP (mm Hg)	127.05 ± 6.93	145.78 ± 5.39***	136.95 ± 7.58***
DBP (mm Hg)	79.24 ± 4.91	91.44 ± 6.15***	86.07 ± 5.0***
FSG (mmol/L)	4.75 ± 0.9	6.55 ± 0.38***	5.35 ± 0.66***
Total-C (mmol/L)	4.45 ± 0.63	5. 40 ± 0.93***	5.42 ± 0.76***
TG (mmol/L)	1.48 ± 0.6	1.36 ± 0.60	1.2 ± 0.51*
HDL-C (mmol/L)	1.60 ± 0.28	1.40 ± 0.3***	1.57 ± 0.32***
LDL-C (mmol/L)	2.20 ± 0.70	3.26 ± 0.72***	3.27 ± 0.99***
Uric acid (□mol/L)	284.95 ± 76.52	302.94 ± 56.86***	289.99 ± 50.28***

* Significant difference from control at p≤0.05, ** at p≤0.01 and *** at p≤0.001 using unpaired t-test

Table 4 : Comparison of the effects of enalapril before and after therapy .

Parameters	Mean ± SD		
	Before (n=60)	After (n=60)	p-value
BMI (kg/m^2)	32.79 ± 1.9	30.6 ± 2.18***	<0.001
Waist circum. (cm)	103.44 ± 8.87	100.8 ± 8.53***	<0.001
SBP (mm Hg)	145.78 ± 5.39	136.95 ± 7.58***	<0.001
DBP (mm Hg)	91.44 ± 6.15	86.07 ± 5.0***	<0.001
FSG (mmol/L)	6.55 ± 0.38	5.35 ± 0.66***	<0.001
Total-C (mmol/L)	5. 40 ± 0.93	5.42 ± 0.76	0.205(NS)
TG (mmol/L)	1.36 ± 0.60	1.2 ± 0.51	0.193(NS)
HDL-C (mmol/L)	1.40 ± 0.3	1.57 ± 0.32	0.178(NS)
LDL-C (mmol/L)	3.26 ± 0.72	3.27 ± 0.99	0.716(NS)
Uric acid (□mol/L)	302.94 ± 56.86	289.99 ± 50.28	0.132(NS)

***Significant difference at p≤0.001 using paired t-test. NS= Not significant.

Table 5: Comparison of data after losartan and enalapril therapy.

Parameters	Mean ± SD		
	Losartan (n=60)	Enalapril (n=66)	p-value
BMI (kg/m^2)	30.95 ± 1.8	30.6 ± 2.18	0.026 (NS)
Waist circum. (cm)	104.08 ± 8.3	100.8 ± 8.53	0.605(NS)
SBP (mm Hg)	136.82 ± 8.4	136.95 ± 7.58	0.134 (NS)
DBP (mm Hg)	83.92 ± 6.3	86.07 ± 5.0*	0.05
FSG (mmol/L)	5.12 ± 0.7	5.35 ± 0.66*	0.05
Total-C (mmol/L)	4.65 ± 0.8	5.42 ± 0.76	0.120(NS)
TG (mmol/L)	1.23 ± 0.5	1.2 ± 0.51	0.321(NS)
HDL-C (mmol/L)	1.54 ± 0.4	1.57 ± 0.32	0.062(NS)
LDL-C (mmol/L)	2.84 ± 0.8	3.27 ± 0.99	0.126(NS)
Uric acid (□mol/L)	275.92 ± 61.63	289.99 ± 50.28***	<0.001

* Significant difference at p≤0.05 and *** at p≤0.001. NS= Not significant.

Discussion

The present study demonstrates significantly higher uric acid levels in subjects with metabolic syndrome as compared with the control group. These results are in consistent with the results obtained from many articles which also demonstrate increased levels of uric acid in patients with metabolic syndrome [8, 12, 18]. Several mechanisms were attributed to the increase of UA levels in MS. One of these mechanisms is related to insulin resistance, which is accompanied by MS. Proximal tubular reabsorption of UA occurs by an active transport mechanism closely linked to or identical with the tubular reabsorption of sodium. Insulin can enhance renal tubular sodium reabsorption in humans. Furthermore, renal excretion of UA is reduced in situations with increased renal tubular reabsorption of sodium . This relationship suggests an altered tubular sodium handling and uric acid metabolism which is constituent with hyperinsulinemia. Insulin resistance being the possible pathophysiological link[19]. Another mechanism for the increased SUA levels in MS is that MS is associated with increased oxidative stress [20]. Because uric acid is considered to be an effective antioxidant. The elevated SUA levels encountered in individuals with MS may reflect a compensatory mechanism counteracting the increased oxidative stress associated with the MS [21].In the present study, only losartan causes a significant reduction of serum uric acid concentrations in patients with metabolic syndrome after 2 months of therapy. These results indicate that losartan have uricosuric effects. Many studies have demonstrated that the uricosuric effect of losartan was due to the parent compound and not to the active metabolite EXP 3174 and that this effect is independent of angiotensin II receptor blockade and is due to unique biochemical properties of losartan [22-24]. The hypouricemic effect of losartan may be due to that losartan target the urate anion exchange and diminish urate reabsorption in the proximal convoluted tubule; as a result, the urate excretion fraction is increased by 13%-30% and increases renal uric acid excretion [25]. This aspect of losartan therapy might have therapeutic advantages by reducing the risk of elevated uric acid in patient with MS, since elevated serum uric acid levels in patient with MS is regarded as a risk factor for the development of CV diseases [26] and may ameliorate hyperuricemia induced by other drugs. It was reported that the risk of death due to ischemic heart disease increased by 77% (men), and by 30% (women) when serum uric acid levels where in the highest quartile (>416 µmol/l) compared with the lowest quartile (<321 µmol/l) [27]. Data obtained from the present study showed that enalapril produce non significant effects on uric acid concentration in patients with metabolic syndrome. Data from the literature demonstrates different results. No effect was reported by Tikkanen *et al.*, [28], rise in SUA levels reported by De Rosa *et al* [29], and and others demonstrates SUA lowering effect [8, 30].

In conclusion: This study demonstrates significantly higher serum uric acid levels in hypertensive patients having markers of metabolic syndrome. losartan therapy but not enalapril therapy produced a significant fall in serum uric acid levels. Losartan can be a useful therapeutic agent to reduce serum uric acid level in hypertensive patients having markers of metabolic syndrome and hyperuricaemia.

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