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Research Article
L-Arginine Potentiates Lisinopril Effects in a Model of Resistant Hyperuricemia and Hypertension in Rats through Decreasing Oxidant Stress and Downregulating Renal ACE Expression

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Abstract

Background and Objective: Many hyperuricemic patients are hypertensive and hyperuricemia can lead to cardiovascular, hepatic and renal damage through different mechanisms including endothelial dysfunction. Also, some nephropathy patients are resistant to treatment with Angiotensin Converting Enzyme Inhibitors (ACEIs). Lisinopril is an active ACEI that does not need hepatic activation and hence can be used in hyperuricemia-induced hepatorenal damage. The current work was conducted to study the effects of L-arginine supplementation with lisinopril in oxonic acid (OA)-induced hyperuricemia and hypertension in rats which simulates the clinical situation of ACEI-resistant cases. **Materials and Methods:** Sprague Dawley male rats were distributed into four groups (n = 8) which received the following for 8 weeks: OA (750 mg/kg/day by gavage), OA+LA (OA+L-arginine 20 mg/mL drinking water), OA+LD (OA+Lisinopril 40 mg/kg/day by gavage) and OA+LA+LD. In the end, systolic blood pressure (SBP), plasma uric acid, urea, creatinine and NO levels and renal malondialdehyde, reduced glutathione and ACE mRNA were measured in addition to renal histological examination. **Results:** The OA-exposed rats showed elevations of SBP, plasma uric acid, urea and creatinine and renal malondialdehyde and ACE mRNA levels, as well as reductions of plasma NO and renal reduced glutathione, in addition to renal histopathological changes. The L-arginine and lisinopril significantly reversed these changes but none of them normalized them. In contrast, a combination of L-arginine and lisinopril completely improved these parameters with non-significant differences from the normal control. **Conclusion:** In OA-induced hyperuricemia and hypertension, L-arginine or lisinopril alone significantly improved; but did not normalize; BP, renal function tests and renal structural alterations probably through improving NO production and renal oxidant stress and downregulating ACE expression. In contrast, the combination of both normalized these parameters indicating that L-arginine supplementation could be a novel strategy to prevent renal disease progression in cases of hyperuricemia and hypertension that are resistant to treatment with ACEIs.

Key words: Hypertension, hyperuricemia, L-arginine, lisinopril, renal, angiotensin converting enzyme

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Hyperuricemia can lead to cardiovascular diseases and renal damage possibly through oxidant stress and endothelial dysfunction[1]. The L-arginine; a semi-essential amino acid; is the substrate for the Endothelial Nitric Oxide Synthase (eNOS) and the key precursor for nitric oxide (NO) in vascular endothelial and immune cells. Normally, the body forms its needs of L-arginine and also gets it from protein-rich foods. The L-arginine supplementation has been shown to decrease hypertension, incidence of nosocomial infections and duration of hospital stay for surgical patients[2]. In moderate doses, L-arginine is generally safe with some mild adverse effects such as gastrointestinal upset, headache and allergy. However, in chronic high doses, it can cause an increased risk of death following a heart attack, drug interactions, kidney damage and tumor growth[3]. In rats, hyperuricemia-induced hypertension and renal vascular disease were partially reversed by L-arginine supplementation through vasodilatation and improving the renal hemodynamic and vascular structural alterations[4]. In a model of organ toxicity in rats induced by dichlorvos; a pesticide; L-arginine significantly improved renal functions, reduced uric acid accumulation, restored redox balance and preserved hepatic and renal tissue histoarchitecture. These protective effects were attributed to its antioxidant potential, reduction of uric acid generation and obstruction of glutathione abnormal regulation[5].

About 74% of people with hyperuricemia are also hypertensive[6]. In cancer patients, comorbid hypertension significantly affects prognosis and inhibitors of the renin angiotensin system (RAS) are commonly used for its management. However, these agents showed suboptimal effects in severe hypertension in preclinical studies and clinical data in this regard are few[7]. Moreover, cancer patients may suffer from chemotherapy-related tumor lysis syndrome that results in hyperuricemia which may induce nephropathy[8]. Some nephropathy patients have a poor response to Angiotensin Converting Enzyme Inhibitors (ACEIs)[9]. Unfortunately, hyperuricemia also causes hepatic damage[10] and then prodrug ACEIs which need hepatic activation should be avoided. Lisinopril is an active ACEI that does not need hepatic activation and also in hypertensive patients, it significantly decreases the uric acid levels in blood and urine preventing the development of angiopathy and nephropathy[11]. Therefore, the current study was performed to evaluate the effects of L-arginine supplementation with lisinopril therapy in an experimental model of oxonic acid-induced hyperuricemia and hypertension which simulates the clinical situation of patients with ACEI-resistant hypertension and hyperuricemia.

MATERIALS AND METHODS

Study area: The study was performed in the research laboratories at King Abdulaziz University, Jeddah, Saudi Arabia from January, 2023 to 2024.

Induction of a model of hyperuricemia and hypertension and experimental design: Oxonic acid (an uricase inhibitor, OA) potassium salt, L-arginine (LA) and lisinopril dihydrate (LD) were obtained from Sigma Company (St. Louis, Missouri, USA). They were dissolved in distilled water with gentle warming needed for OA. The kits were purchased from MyBioSource, Inc. (California, USA).

The study was approved by the Review Committee, Faculty of Medicine, Rabigh and was done according to the guidelines for use of laboratory animals.

Sprague Dawley male rats obtained from the University animal house (230-250 g) were housed in a 22°C room with a 12 hrs light-dark cycle with food and water *ad libitum*. After a week of adaptation, besides a normal control group (given the vehicle), a total of 32 rats were given OA (750 mg/kg/day by gavage) to induce hyperuricemia and hypertension. The rats were randomly divided into 4 groups (n = 8) which received the following for 8 weeks: OA (OA alone), OA+LA (OA+L-arginine 20 mg/mL drinking water)[12], OA+LD (OA+Lisinopril 40 mg/kg/day by gavage)[13] and OA+LA+LD (OA+both agents). At the end of the 8 weeks, systolic blood pressure (SBP) was measured using the non-invasive tail cuff system (AD Instruments Inc., Colorado, USA) which depends on the periodic block of the tail blood flow[14]. Blood was collected to determine plasma uric acid, urea, creatinine and NO levels. Rats with uric acid levels of more than 2.5 mg/dL and blood pressure of more than 140 mmHg were considered hyperuricemic and hypertensive. Thereafter, the rats were killed under sodium pentobarbital anesthesia (50 mg/kg i.p.) and the kidney was excised for histopathological examination. Also, a part of the kidney was kept in liquid nitrogen for measurement of malondialdehyde (MDA), reduced Glutathione (GSH) and renal ACE gene expression in the renal homogenate.

Renal function tests and plasma NO level: Fasting plasma uric acid, urea, creatinine and NO levels were measured using the kits with the following catalog numbers: MBS3808193, MBS2600001, MBS3807987 and MBS8243214.

Measurement of renal MDA and GSH levels: A 10% renal homogenate was prepared as previously described and the supernatant was kept at -80°C[15]. The protein concentration was measured by the kit #MBS355526. The levels of MDA and GSH were measured by the ELISA kits #MBS738685 and #MBS265966 and were expressed/mg protein.

Analysis of renal ACE mRNA by real-time PCR: The total RNA was extracted from renal tissue using the Qiagen RNeasy kit and then transformed to cDNAs by SuperScript II reverse transcriptase (California, USA). Real time PCR was conducted using the SYBR green PCR kit (Qiagen). The beta-actin mRNA was used as the internal standard. The forward and reverse primers for ACE were 5'-GCCACATCCAGTATTTCATGCAGT-3' and 5'-AACTGGAACTGGATGATGAAGCTGA-3' and those for beta-actin were 5'-TGTTGTCCCTGTATGCCTCT-3' and the reverse primer was 3'-TAATGTCACGCACGATTTCC-5'[16].

Renal histopathological examination: The kidney slices were fixed in 10% phosphate-buffered formalin and embedded in paraffin. Sections (3-5 µm) were stained with Hematoxylin and Eosin (H&E) and examined for evaluating structural changes, cellular degeneration and vascular congestion. The lesion was evaluated as mild, moderate or severe[13].

Statistical analysis: Data were expressed as Means±SEM. The SPSS software (version 22, USA) was used. Multiple comparisons were made using a One-way Analysis of Variance (ANOVA) followed by the Tukey's test. The $p<0.05$ were considered significant.

Ethical consideration: The study was approved by the Research Ethics Committee, Faculty of Medicine, Rabigh Campus and was carried out by the guidelines for the use of laboratory animals.

RESULTS

Effects on blood pressure and renal function tests: The rats receiving OA showed hypertension and elevations of plasma uric acid, urea and creatinine. The L-arginine and lisinopril significantly reduced SBP, urea and creatinine levels with non-significant differences in-between, but none of them normalized these levels in contrast to the combination therapy which significantly decreased these measures compared to each drug alone with non-significant differences from the normal control group. For uric acid, all treatments significantly reduced the OA-induced elevation. The reduction was greater with lisinopril than with L-arginine with a significant difference in-between and the combination treatment normalized the uric acid level with significant differences from each drug alone and a non-significant difference from the normal control group (Table 1).

Effects on plasma NO level: The OA-exposed rats showed decreased plasma NO levels. The L-arginine and lisinopril significantly increased NO levels with a larger significant effect with L-arginine, but none of them normalized it in contrast to the combination therapy which significantly increased NO level compared to each drug alone with a non-significant difference from the normal control group (Fig. 1a).

Effects on renal MDA and GSH levels: The OA-exposed rats showed elevated renal MDA and decreased renal GSH levels. The L-arginine and lisinopril significantly reversed these changes with larger significant effects with L-arginine, but none of them normalized these parameters in contrast to the combination therapy which significantly normalized them compared to each drug alone with non-significant differences from the normal control group (Fig. 1b-c).

Effects on renal ACE mRNA: The OA-exposed rats showed upregulated renal ACE mRNA levels. The L-arginine and lisinopril significantly downregulated it with a larger significant reduction with lisinopril, but none of them normalized it in contrast to the combination therapy which significantly downregulated it compared to each drug alone with a non-significant difference from the normal control group (Fig. 1d).

Table 1: Effects of L-arginine plus lisinopril on SBP and renal function tests in hyperuricemic hypertensive rats

Parameter	NC	OA	OA+LA	OA+LD	OA+LA+LD
SBP (mmHg)	106.12±2.12	173.50±2.65	149.88±4.82**,***	154.13±6.21*,***	115.13±1.25***
Uric acid (mg/dL)	1.29±0.06	4.02±0.15	2.86±0.11$^{\#\#\#}$	2.10±0.18$^{\#\#,\#\#\#}$	1.36±0.03$^{\#\#,\#\#\#}$
Urea (mg/dL)	10.85±0.53	22.13±1.10	15.80±0.49$^{\wedge\wedge\wedge}$	16.41±0.57$^{\wedge\wedge\wedge}$	12.09±0.56$^{\wedge\wedge,\wedge\wedge\wedge}$
Serum creatinine (mg/dL)	0.52±0.03	1.43±0.07	0.98±0.02§§§	0.87±0.04§§§	0.66±0.01§§,§§§

Data are expressed as Mean±SEM, NC: Normal control, OA: Oxonic acid, 750 mg/kg/day by gavage, OA+LA: OA+L-arginine 20 mg/mL drinking water, OA+LD: OA+Lisinopril 40 mg/kg/day by gavage), SBP: Systolic blood pressure; *p<0.05: OA+LD vs OA (= 0.01), **p<0.01: OA+LA vs OA (= 0.001), ***p<0.001: OA+LA, OA+LD vs NC and OA+LA+LD vs OA, OA+LA, OA+LD. Uric acid; ##p<0.01: OA+LA+LD vs OA+LD and OA+LD vs OA+LA (= 0.001, 0.001), ###p<0.001: OA+LA, OA+LD vs NC and OA+LA, OA+LD, OA+LA+LD vs OA and OA+LA+LD vs OA+LA. Urea; ^^p<0.01: OA+LA+LD vs OA+LA and OA+LD (= 0.005 and 0.001), ^^^p<0.001: OA+LA, OA+LD vs NC and OA+LA, OA+LD, OA+LA+LD vs OA. Creatinine; §§p<0.01: OA+LA+LD vs OA+LD (= 0.004), §§§p<0.001: OA+LA, OA+LD vs NC and OA+LA, OA+LD, OA+LA+LD vs OA and OA+LA+LD vs OA+LA

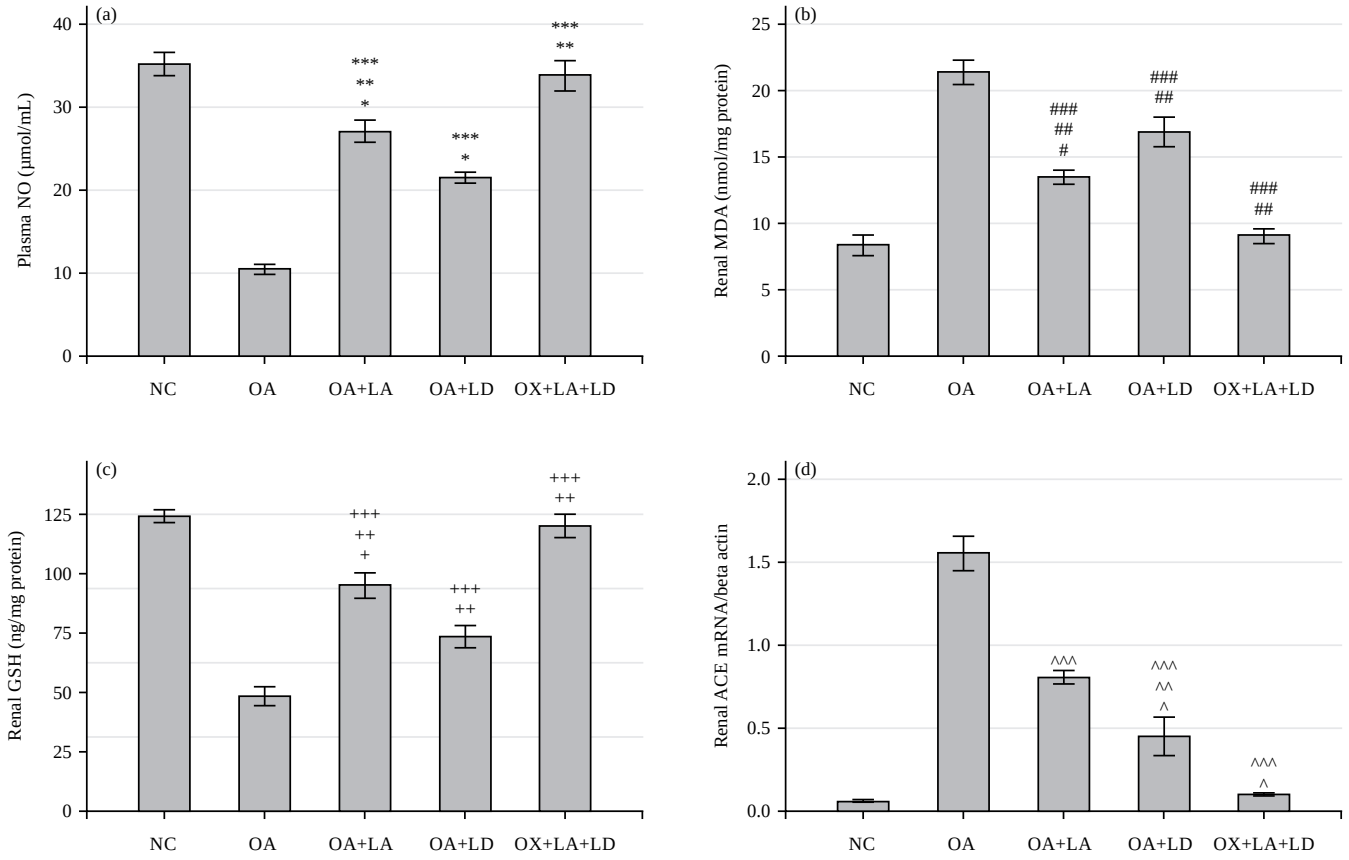

Fig. 1(a-d): Effects of L-arginine plus lisinopril on (a) Plasma NO, (b) Renal MDA, (c) Renal SGH and (d) Renal ACE mRNA in hyperuricemic hypertensive rats

Data are expressed as Mean±SEM. NC: Normal Control, OA: Oxonic acid (750 mg/kg/day by gavage), OA+LA (OA+L-arginine 20 mg/mL drinking water, OA+LD (OA+Lisinopril 40 mg/kg/day by gavage), OA+LA+LD (OA+both). (a) NO; *p<0.05: OA+LA vs OA+LD (= 0.026), **p<0.01: OA+LA vs NC and OA+LA+LD vs OA+LA (= 0.001 and 0.006), ***p<0.001: OA+LA, OA+LD, OA+LA+LD vs OA and OA+LD vs NC and OA+LA+LD vs OA+LD. (b) GSH; $^{+}$p<0.05: OA+LA vs OA+LD (= 0.012), $^{++}$p<0.01: OA+LD vs OA and OA+LA+LD vs OA+LA (= 0.003 and 0.003), $^{+++}$p<0.001: OA+LA, OA+LA+LD vs OA and OA+LA, OA+LD vs NC and OA+LA+LD vs OA+LD. (c) MDA; $^{\#}$p<0.05: OA+LA vs OA+LD (= 0.042), $^{\#\#}$p<0.01: OA+LA vs NC and OA+LD vs OA and OA+LA+LD vs OA+LA (= 0.001, 0.003 and 0.004), $^{\#\#\#}$p<0.001: OA+LA, OA+LA+LD vs OA and OA+LD vs NC and OA+LA+LD vs OA+LD and (d) ACE mRNA; $^{\wedge}$p<0.05: OA+LA vs OA+LD and OA+LA+LD vs OA+LD (= 0.011 and 0.015), $^{\wedge\wedge}$p<0.01: OA+LD vs NC (= 0.005), $^{\wedge\wedge\wedge}$p<0.001: OA+LA, OA+LD, OA+LA+LD vs OA and OA+LA vs NC and OA+LA+LD vs OA+LA

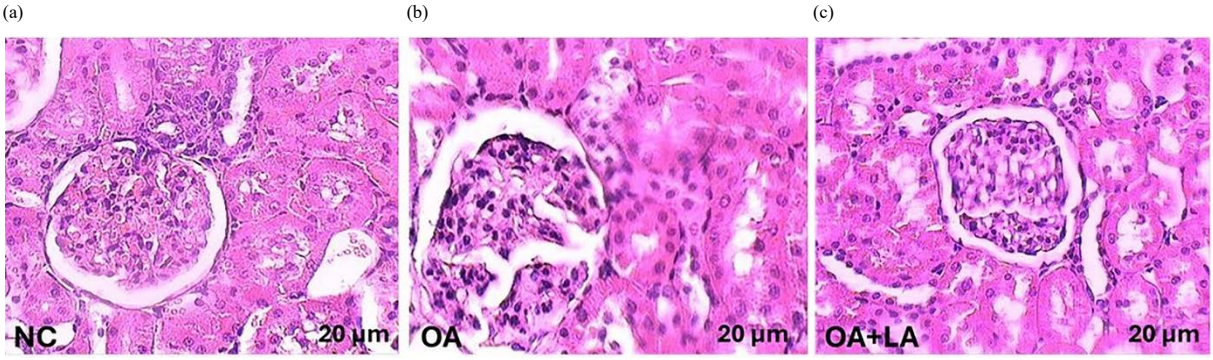

Fig. 2(a-e): Continue

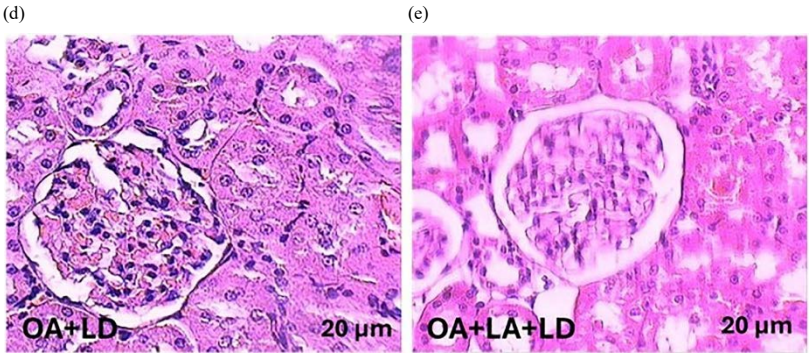

Fig. 2(a-e): Effects of L-arginine and lisinopril on renal structure in rats with hyperuricemia and hypertension (HE, ×20), (a) NC, (b) OA, (c-d) OA+LA & OA+LD and (e) OA+LA+LD

(a) Normal control group showing normal renal tissue and preserved renal architecture, (b) Oxonic acid-exposed group showing disrupted renal tissue, cellular degeneration and widening of the capsular space, (c-d) OA+L-arginine and OA+Lisinopril groups showing moderate improvement and (e) OA+both showing marked improvement with nearly normal picture

Effects on renal structure: The OA caused renal cellular degeneration and necrosis as well as vascular congestion and renal fibrosis. The L-arginine and lisinopril moderately preserved the renal histoarchitecture and minimized vascular congestion, while combined L-arginine and lisinopril showed mild cellular degeneration with no vascular congestion (Fig. 2).

DISCUSSION

Hyperuricemia plays a key role in the progression of cardiovascular and renal morbidities which may be mediated by activating the RAS, inhibiting the renal NOS expression and decreasing the NO level. The endothelial cells can upregulate ACE activity increasing angiotensin II and superoxide anions which cause vasoconstriction, hypertension, renal structural and vascular changes followed by renal dysfunction and renal fibrosis. Treatment of hyperuricemia may delay or prevent the onset of chronic kidney disease[17]. In the current study, the OA-exposed rats showed elevations of SBP, plasma uric acid, urea and creatinine and renal MDA and ACE mRNA levels, as well as reductions of plasma NO and renal GSH, in addition to renal histopathological changes. The L-arginine and lisinopril significantly reversed these changes to varying degrees but none of them normalized any parameter in contrast to the combination treatment which significantly reversed all measures compared to each drug alone with non-significant differences from the normal control.

The current results agreed with previous studies which showed that rats on a 2.0% oxonic acid diet for 9 weeks showed high plasma uric acid, creatinine and urea levels[18]. The uric acid elevation was reported to inhibit NO production in bovine aortic endothelial cells inducing endothelial dysfunction, hypertension and vascular disease[4]. Moreover, the rats receiving oxonic acid in the diet developed hyperuricemia which induced hypertension and renal injury via a crystal-independent mechanism, with stimulation of the RAS and inhibition of neuronal NO synthase[19]. Controlling hyperuricemia is crucial to prevent its complications including acute renal failure and allopurinol was reported to improve oxonic acid-induced hyperuricemia, hypertension and renal alterations[20]. However, due to allopurinol's slow onset of action and inadequate effectiveness in high risk patients[21], a new recombinant conjugated variant of urate oxidase is recently tried[22]. Unfortunately, ACE inhibitors can cause hyperuricemia, especially with chronic high doses. Therefore, losartan; but not the other angiotensin receptor blockers; and/or calcium channel blockers should be used in hypertensive patients with gout. However, with the increasing number of resistant hypertensive patients who need three or more antihypertensive medications, this approach will not always be possible[6]. Following the current results, it was reported that 6-8 weeks of therapy of lisinopril significantly decreased the uric acid levels in the blood and urine of hypertensive patients preventing the development of angiopathy and nephropathy[11].

In patients with essential hypertension, the circulating ACE gene expression and ACE protein expression significantly increased[23]. Treatment with L-arginine and lisinopril in the present work downregulated the renal ACE expression and this agrees with previous studies which showed that downregulation of the upregulated renal ACE in the diabetic rats by ACEIs could be a reno-protective mechanism of these agents[24]. Moreover, in sodium fluoride-induced hypertensive rats, L-arginine and lisinopril significantly ameliorated hypertension, increased NO level and renal antioxidant enzymes and reduced urea, creatinine, MDA and renal ACE

expression. Therefore, L-arginine could be a potential therapy against hypertension and renal damage[25]. The antioxidant effects of L-arginine and lisinopril shown in the current study also agree with previous studies which reported that L-arginine supplementation in exercised rats decreased plasma creatine kinase, lactate and uric acid levels and hence it alleviated the exercise-induced oxidative and inflammatory damage on the heart[26] and on the skeletal muscles, kidney and liver[27]. In addition, it was recently reported that lisinopril could decrease renal oxidative damage in the L-NAME induced hypertensive rats and could protect against oxidative stress and fibrosis in AC16 human cardiomyocytes[28]. In rats, chronic L-arginine reduced SBP, increased urinary NO_2^-/NO_3^- and improved the renal vascular and structural alterations through the antiproliferative effect of NO[29]. In rats with passive Heymann nephritis, L-arginine and lisinopril increased urinary cGMP levels (an indirect measure of NO level) and a combination of both nearly normalized its level and ameliorated glomerulosclerosis and tubular damage. Consequently, co-administration of L-arginine to ACE inhibitors (such as lisinopril) could be a new approach for patients with severe nephropathy, who are not fully responsive to ACE inhibition, that can help in preventing renal disease progression[13].

Based upon the aforementioned data, in OA-induced hyperuricemia and hypertension, L-arginine or lisinopril alone ameliorated; but did not normalize; BP, renal function tests and renal structural alterations probably through enhancing NO production, reducing renal oxidant stress and downregulating ACE expression. In comparison, the combination of both agents normalized these parameters indicating that L-arginine supplementation could be a new approach to halt renal disease progression in cases of hyperuricemia and hypertension that are resistant to treatment with ACEIs. Therefore, the use of this combination in such cases is recommended. However, the short duration of the current study and using single doses of the drugs are considered limitations. Performing a longer duration study for evaluating the effects of multiple doses of both L-arginine and lisinopril is recommended.

CONCLUSION

In a model of oxonic acid-induced hyperuricemia and hypertension, treatment with each of L-arginine or lisinopril significantly improved; but did not normalize; blood pressure, renal function tests and renal structural alterations probably through increasing the NO production, improving the renal oxidant stress and downregulating the ACE expression. In contrast, treatment with a combination of both normalized all these parameters indicating that L-arginine supplementation, in moderate doses, could be a novel strategy that could halt renal disease progression in cases of hyperuricemia and hypertension who are not completely responsive to ACE inhibition.

SIGNIFICANCE STATEMENT

Hyperuricemia can cause cardiovascular, hepatic and renal damage. Lisinopril is an Angiotensin Converting Enzyme Inhibitor (ACEI) that does not need hepatic activation. In oxonic acid-induced hyperuricemia and hypertension in rats, which simulates ACEI-resistant clinical cases, L-arginine or lisinopril significantly improved; but did not normalize; BP, renal function tests and renal structural alterations probably through improving NO production and renal oxidant stress and downregulating ACE expression. In contrast, a combination of both normalized all parameters indicating that L-arginine supplementation could be a novel strategy for cases of hyperuricemia and hypertension who are not completely responsive to ACEIs to prevent renal disease progression.

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