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Original Research Article

A Study of Impact of Losartan on Serum Uric Acid Levels in Essential Hypertension

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Conflict of interest: Nil

Abstract:

Background: There is a strong correlation between hypertension and elevated levels of uric acid, contributing to the onset of cardiovascular disease. The impact of angiotensin II AT-1 receptor antagonists on uric acid metabolism, along with potential variations in this effect among them, is yet to be conclusively determined. This study was structured to assess and compare the effects of losartan on uric acid metabolism in individuals experiencing mild to moderate essential hypertension.

Methods: This cross-sectional interventional study focused on newly diagnosed stage 1 and stage 2 essential hypertension patients with elevated serum uric acid levels. Conducted at the Non-Communicable Disease outpatient department, clinical assessments, and baseline investigations, including serum uric acid, blood urea, serum creatinine, random blood sugar, and serum cholesterol, were performed upon enrollment. Demographic data were recorded, and blood pressure measurements were taken after 10 minutes of rest in a seated position.

Results: Losartan therapy appears to be effective in improving blood pressure control in patients with essential hypertension. We saw a reduction in the number of patients in higher stages (Stages 2 and 1) and an increase in those categorized as Prehypertension or even returning to the normal range. This suggests successful blood pressure lowering over the 6-month follow-up period. Losartan therapy has been shown to have a positive effect on reducing serum uric acid levels in patients with essential hypertension. The gradual decrease observed over 6 months suggests a sustained benefit of the medication in managing uric acid levels.

Conclusion: The current study concluded that losartan effectively lowered blood pressure over 6 months, showing a significant decrease in both systolic and diastolic values. Additionally, there was a statistically significant reduction in serum uric acid levels with losartan treatment. This reduction in uric acid is noteworthy, as it is independent of blood pressure reduction, emphasizing that losartan possesses uric acid-lowering effects beyond its significant impact on blood pressure.

Keywords: Losartan, Essential Hypertension, Serum Uric acid.

Introduction

Cardiovascular disease is a major global health concern and the foremost cause of mortality and disability. Elevated uric acid levels are a significant contributor to cardiovascular disease and are directly correlated with heightened blood pressure [1, 2]. Hypertension, a chronic disease, poses a significant global health challenge, affecting 10-15% of the adult population worldwide. Several risk factors contribute to hypertension, including diabetes (insulin resistance), cardiovascular diseases, autoimmune diseases, and hyperuricemia. Projections suggest that approximately 1.56 billion individuals will be hypertensive by the end of 2025 [3]. Globally, hypertension leads to approximately 9.4 million deaths annually [4]. The rising prevalence of hypertension is attributed to factors such as population growth, aging, and behavioral risk factors such as an unhealthy diet, excessive alcohol consumption, sedentary lifestyles, obesity, and exposure to persistent stress. Prolonged hypertension can manifest symptoms such as palpitations, dizziness, vomiting, convulsions, and confusion in severe cases [5, 6]. Without timely and effective blood pressure control, prolonged hypertension poses a threat to vital organs, such as the heart, brain, and kidneys, thereby impairing patient well-being, safety, and survival [7]. Hypertension has the potential to cause damage to the renal and cerebral vessels, leading to conditions such as renal disease and stroke4. The primary objective of treating hypertension is to reduce cardiovascular morbidity and

prevent damage to the end organs [8]. Hyperuricemia is an independent risk factor for hypertension. The intricate relationship between hypertension and elevated uric acid levels increases the risk of cardiovascular disease. According to available data, a 59.5 μmol/L increase in blood uric acid levels corresponds to a 25% higher likelihood of combined hypertension [9]. Hypertension can disrupt uric acid excretion, leading to its accumulation in the kidneys and triggering inflammatory reactions. This, in turn, can further elevate blood pressure, creating a detrimental cycle. Therefore, it is imperative to incorporate effective strategies aimed at reducing both blood pressure and uric acid levels when managing patients with hypertension and elevated uric acid levels. Such interventions significantly impact the clinical symptoms and liver function indicators in these patients [10, 11]. Currently, drug treatment is the predominant approach in clinically managing hypertension coupled with high uric acid levels. Losartan is a well-known antihypertensive medication that is frequently prescribed for this purpose. Losartan effectively lowered uric acid levels by inhibiting renin and counteracting its effects. Additionally, it inhibits vasoconstriction, contributing to blood pressure reduction [12, 13]. Losartan facilitates the swift reabsorption of uric acid within kidney tubules through the inhibition of urate transporter expression. Moreover, it possesses the ability to alkalize uric acid through the secretory function of renal tubules, aiding the effective control of blood uric acid levels [14].

However, several studies have indicated that various angiotensin receptor antagonists effectively reduce uric acid reuptake by inhibiting urate transporter expression, thereby promoting uric acid excretion [15]. While some studies have suggested that losartan may be more effective than other angiotensin receptor antagonists in reducing uric acid levels, the existing evidence is not robust enough to definitively establish this perspective. This study aimed to determine the efficacy of losartan treatment on serum uric acid levels in patients with essential hypertension who visited our hospital.

Material and Methods

This cross-sectional labeled interventional study was conducted for 6 months on hypertensive patients. The study was approved by the institutional ethical committee after duly following the protocol for human research based on the Helsinki Declaration. The nature of the study was explained to the participants in the vernacular language and those willing to participate voluntarily were only included.

Inclusion Criteria

1. Newly diagnosed stage I or stage 2 essential hypertension as per JNC 8 criteria. [16]
2. Males and Females
3. Aged from 30 – 60 years
4. Serum uric acid levels are more than 6mg/dl in females and 6.5mg/dl in males.
5. Those available for follow-up appointments later

Exclusion Criteria

1. Secondary hypertension
2. Known Hypertensive patients on anti-hypertensive drugs
3. Patients with hepatic disease
4. History of gout and renal stones
5. Patients with myocardial infarction, and heart failure within the last 3 Months
6. Patients receiving any drugs that affect serum uric acid (Ex. aspirin, and allopurinol)
7. Pregnancy and lactation
8. History of allergic reactions to study drug
9. History of neurological disorder
10. Not as per inclusion criteria

Newly diagnosed patients with stage 1 and stage 2 essential hypertension, along with elevated serum uric acid levels, meeting the inclusion criteria, were recruited for the study at the outpatient department of Non-Communicable Diseases. Upon enrollment, a clinical assessment and baseline investigations, including serum uric acid, blood urea, serum creatinine, random blood sugar, and serum cholesterol, were conducted. Demographic data of the patients were recorded. Blood pressure measurements were carried out for all patients in a seated position, following 10 minutes of rest. A properly sized blood pressure cuff, covering at least 80% of the upper arm's circumference, was utilized. The cuff was wrapped around the upper arm, with its lower edge positioned one inch above the ante cubital fossa. The stethoscope's bell was gently pressed over the brachial artery just below the cuff's edge. Readings were recorded by simultaneously observing the sphygmomanometer, which rapidly inflated the cuff to 180 mmHg, followed by a controlled release of air at a moderate rate (2 mm/sec).

Serum uric acid concentration was assessed using the enzymatic oxidase method for all recently diagnosed hypertensive patients. To determine serum uric acid concentration, 1 ml of venous blood was drawn under aseptic precautions. Renal function tests (serum creatinine, blood urea), random blood sugar, and lipid profiles (total cholesterol) were conducted in random blood samples using an automated analyzer. Patients were prescribed T. Losartan 50mg once daily for 4 weeks, with further advice to continue T. Losartan 50mg once daily every morning. Monitoring for adverse drug reactions was carried out through patient interviews, physical examinations, and necessary laboratory investigations during follow-

up visits. Blood pressure and serum uric acid were measured at baseline, one-month, three months, and six months intervals.

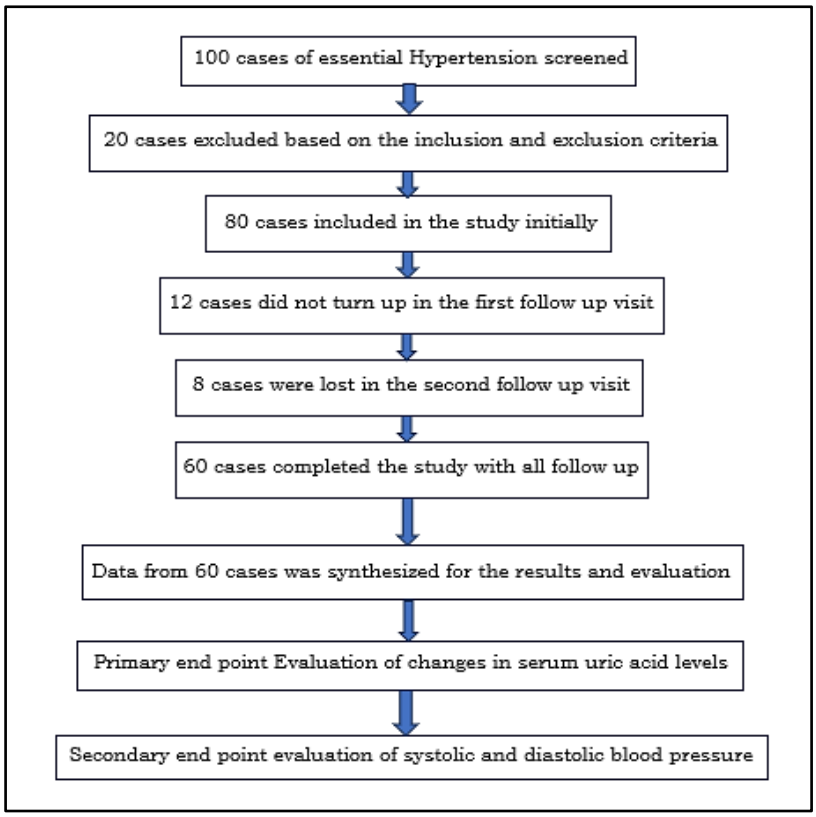

Figure 1: **Showing the blueprint of the study**

Efficacy Parameters: Primary End Point: Evaluation of changes in serum uric acid levels within the treatment group at 1-month, 3-month, and 6-month intervals.

Secondary End Point: Examination of changes in systolic and diastolic blood pressure within the treatment group at 1-month intervals.

Statistical Analysis: The data were entered into Microsoft Excel sheet software and analyzed using the SPSS-21 software version with coded representations. Categorical variables are presented as percentages, while continuous variables are expressed as percentages, mean, and standard deviation. The categorical variables were evaluated utilizing the paired t-test. A p-value less than 0.05 was deemed statistically significant.

Results

A total of 60 cases of essential hypertension were included in the study. In this study there were 36(60%) males and 24(40%) females. The total ratio of males to females is approximately 3:2. The mean age of the cohort in the study was 47.5 ± 4.5 years. 63.33% of the cases belonged to the age group 41 – 50 years. 20% of cases belonged to age group 51 – 60 years. Details of group-wise and sex-wise distribution have been given in Figure 2.

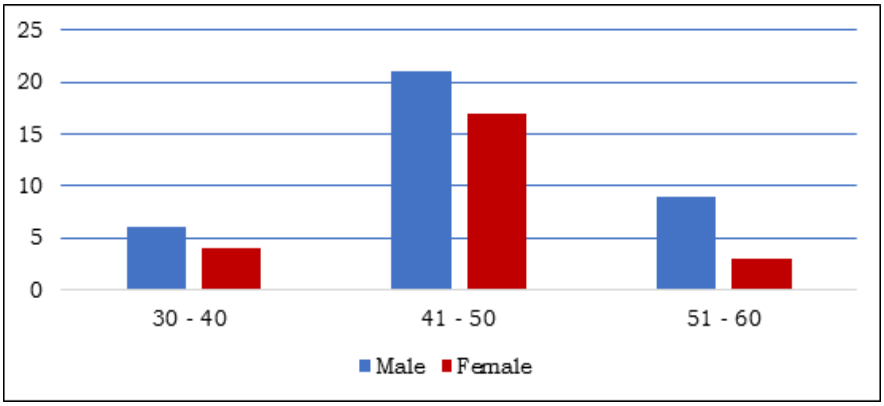

Figure 2: Age and sex-wise distribution of cases included in the study

The mean BMI of the cohort was 25.51 ± 2.15 Kg/m^2. Table 1 provides important information about the severity of hypertension within the 60 cases included in the study. Stage of Hypertension: Stage I: 35% (21 individuals) of the cases were diagnosed with Stage I hypertension, defined as systolic blood pressure (SBP) between 130-139 mmHg and diastolic blood pressure (DBP) between 85-89 mmHg. Stage II: 65% (39 individuals) fell into Stage II hypertension, with SBP ranging from 140-159 mmHg and DBP reaching 90-99 mmHg. Stage III: No cases were identified as Stage III, characterized by SBP exceeding 160 mmHg or DBP surpassing 100 mmHg. Systolic: The average SBP recorded was 146.21 mmHg with a standard deviation of 8.51 mmHg. Diastolic: The average DBP was 92.31 mmHg with a standard deviation of 4.57 mmHg.

Table 1: Baseline blood pressure characteristics recorded in 60 cases of the study

	Frequency	Percentage
Stage of Hypertension		
Stage 1	21	35.00
Stage 2	39	65.00
Stage 3	00	00.00
Mean Systolic Blood pressure in mmHg	146.21 ± 8.51	
Mean Diastolic Blood pressure in mmHg	92.31 ± 4.57	

Table 2 provides information about various biochemical parameters measured in 60 patients with essential hypertension at the beginning of a study. The mean uric acid levels were 7.51 mg/dl although some individuals might have elevated levels, the average doesn't suggest widespread hyperuricemia. The mean creatinine levels were 0.93 and 0.93 mg/dl. This suggests normal kidney function in most patients. The mean triglyceride level was 210.15 mg/dl is slightly above the optimal range (<150 mg/dl) but still within the acceptable range (<200 mg/dl). However, some individuals had elevated levels (hypertriglyceridemia), which can be a risk factor for cardiovascular disease. The mean cholesterol levels were 184.33 mg/dl which indicated that most of the patients had borderline high or high cholesterol levels (hypercholesterolemia).

Table 2: Values of parameters recorded in 60 essential hypertension patients at the beginning of the study

Parameters	Mean	±SD
Uric acid (mg/dl)	7.51	1.12
Creatinine (mg/dl)	0.93	0.27
Triglycerides (mg/dl)	210.15	25.67
Cholesterol (mg/dl)	184.33	10.37

Table 3 shows the changes in hypertension stage distribution among patients after 1, 3, and 6 months of Losartan therapy, compared to their baseline condition. Pre-Hypertension: At baseline, no patients were categorized as "Pre-Hypertension." However, after 1 and 3 months, 10 and 30 patients, respectively, moved into this category. This suggests a decrease in blood pressure for some patients, bringing them closer to the normal range. Stage 1 and 2: The number of patients in both Stages 1 and 2 decreased across the follow-up period. At baseline, there were 21 cases in stage 1 and 39 cases in stage 2, but these numbers reduced to 23 and 7 cases, respectively, after 6 months. This indicates successful blood pressure control for a significant portion of patients, moving them to lower stages of hypertension. Stage 3: None of the patients were in Stage 3 at baseline or during the follow-up period. This suggests either the study had no participants with severe hypertension initially or Losartan therapy effectively prevented progression to Stage 3 in those with earlier stages.

Table 3: Changes in distribution among HT patients at 1, 3, and 6 months after Losartan therapy compared with baseline

Stage of Hypertension	Baseline	1 month	3 months	6 months	P values
Pre HT	00	00	10	30	0.001
Stage 1	21	32	35	23	0.012
Stage 2	39	28	15	7	0.034
Stage 3	00	00	00	00	0000

Figure 3 demonstrates a statistically significant reduction in systolic blood pressure from baseline to one month, a reduction at the end of the 3rd month, and a reduction at the end of the 6th month from baseline, as evidenced by a p-value less than 0.001.

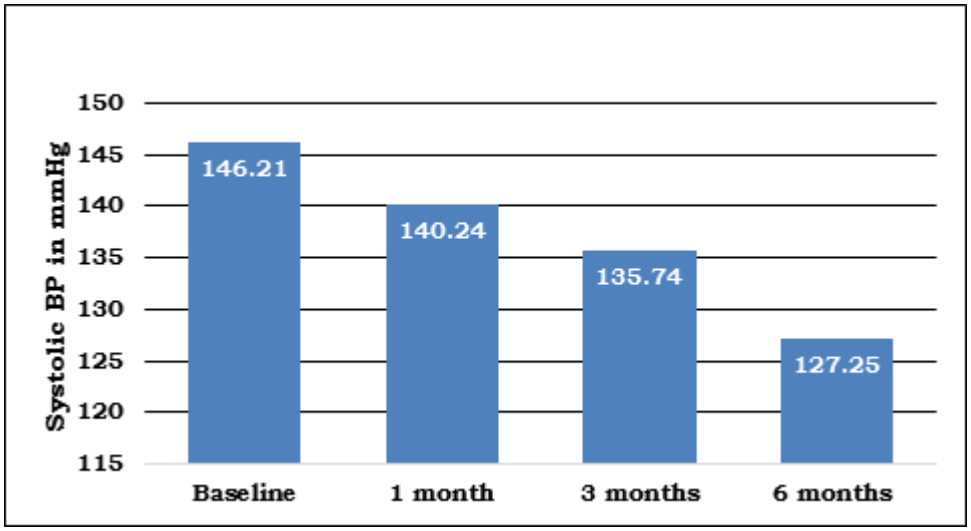

Figure 3: Showing the mean systolic BP changes occurring in the cohort at various intervals of therapy.

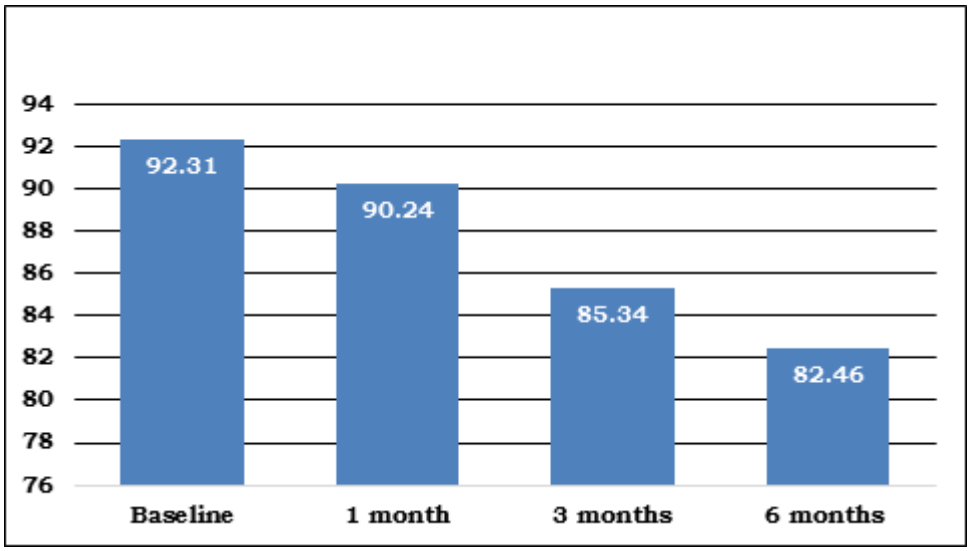

Figure 4: Showing the mean systolic BP changes occurring in the cohort at various intervals of therapy.

Figure 3 illustrates a statistically significant decrease in diastolic blood pressure from baseline to 1 month, as well as reductions at the end of the 3rd month and the end of the 6th month, with a P value less than 0.001.

Table 4: Shows the average baseline serum uric acid level was 7.51 mg/dL. While this falls within the normal range (3.4-7.0 mg/dL for men and 2.7-5.7 mg/dL for women), it could indicate slightly elevated levels in some individuals.

Mean Uric acid levels (mg/dL)	Mean levels in mg/dL	Mean decrease in mg/dL
Baseline	7.51	0
1 month	7.1	-0.41
3 months	6.63	-0.88
6 months	6.01	-1.5

Change over time: After 1 month of Losartan therapy, the average uric acid level decreased by 0.41 mg/dL (to 7.1 mg/dL). 3 months: At 3 months, the mean level further decreased by 0.88 mg/dL (to 6.63 mg/dL). 6 months: The largest decrease occurred by 6 months, with the average uric acid level dropping by 1.5 mg/dL (to 6.01 mg/dL). The p values were found to be 0.012 therefore significant. Losartan therapy appears to have a positive effect on reducing serum uric acid levels in patients with essential hypertension. The gradual decrease observed over 6 months suggests a sustained benefit of the medication in managing uric acid levels.

Adverse reactions: Among the 60 patients who successfully concluded the study, mild adverse effects were observed in 4 patients. Importantly, none of the patients necessitated a dosage reduction or discontinuation of losartan. Furthermore, no

participants were withdrawn from the study due to adverse drug reactions throughout the study period.

Discussion

In cases of essential hypertension, the coexistence of hyperuricemia is common. In addition to hypertension, hyperuricemia is associated with cardiovascular disease, renal failure, and stroke. Consequently, there is therapeutic merit in reducing serum uric acid levels as a part of hypertension management. Traditional uric acid-lowering agents, such as allopurinol, probenecid, and febuxostat, while effective in reducing serum urate levels, have shown limited impact on lowering blood pressure and reversing cardiovascular risk in hypertensive patients with hyperuricemia [17], and these agents are often poorly tolerated. Losartan, an angiotensin receptor blocker, has garnered interest in recent years. Previous research has indicated that losartan not only reduces serum uric acid but also exhibits a hypouricemic effect distinct from other angiotensin receptor blockers. Unlike its counterparts, the uricosuric effect of losartan is not mediated by angiotensin inhibition. Instead, its hypouricemic impact is attributed to the blockade of human URAT transporter 1, which reduces the net urate reabsorption in the proximal tubule of the kidney [18]. Notably, Losartan also significantly increased the urinary pH, a unique property absent in other uricosuric drugs, thereby mitigating the risk of urolithiasis associated with elevated uric acid excretion. The mean age of the participants in this study was 47.5 years, with 63% falling within the 50-60 age group. This trend is attributed to the age-related increase in uric acid levels, posing a pooled risk ratio of 1.13 for incident hypertension with each 1 mg/dl uric acid elevation. Men exhibited a higher prevalence of hypertension with hyperuricemia than women, possibly influenced by estrogen-promoting uric acid excretion in women. A similar study by Chen et al. [19] reported a higher incidence of hyperuricemia in middle-aged males than females.

Losartan, an established and well-tolerated antihypertensive medication, blocks angiotensin II at the type I receptor. In a study by Naritomi et al. [20] systolic blood pressure decreased significantly from 163.7 mmHg to 143.1 mmHg after 3 months of losartan treatment. In our study, a statistically significant reduction in the mean systolic blood pressure was observed from 146 to 127 mmHg after 6 months of losartan therapy. Similarly, losartan demonstrated efficacy in lowering the mean diastolic blood pressure from 92 to 82 mmHg, with statistical significance ($p < 0.01$). The LIFE study conducted by Ahlof et al. [21] in 9193 patients indicated a greater reduction in blood pressure (30.2/16.6 mmHg) in the losartan group than in the atenolol group (29.1/16.8 mmHg). Furthermore, the LIFE study highlighted that losartan was more effective than atenolol in preventing cardiovascular morbidity and mortality, with comparable blood pressure reduction and favorable tolerability.

As reported by Naritomi et al. [20] the mean serum uric acid decreased from 7.65 mg/dl to 6.3 mg/dl after 3 months of losartan treatment. In our study, losartan exhibited a significant reduction in mean serum uric acid from 7.51 mg/dl (baseline) to 6.01 mg/dl after 6 months of treatment, with statistical significance ($p < 0.01$). This suggests that losartan may be a favorable choice for hypertensive patients with hyperuricemia. In Brian L. Rayner et al's [22] study, the reduction in mean serum uric acid level after 6 months of losartan treatment was 0.5 mmol/l, and in Paul A. Smink et al's [23] study, it was 0.16 mg/dl. In our study, the reduction in mean serum uric acid levels was 0.48 mg/dl at 3 months and 1.2 mg/dl at 6 months. Paul et al. [23] also noted that the protective effect of losartan on serum uric acid may be hindered by chronic diuretic usage, as some diuretics can induce hyperuricemia. The adverse effects associated with losartan in this study were mild, including hypotension, dizziness, and headache. A study by Cushman et al. [24] reported similar side effects with infrequent first-dose hypotension and no documented adverse metabolic or laboratory abnormalities during losartan therapy. No patient experienced serious adverse effects, such as angioedema or cough, in our study. In a study by Circardi et al. [25], only a small percentage of patients who developed angioedema while on ACE inhibitors continued to experience this symptom when switched to losartan or another ARB. Therefore, Losartan demonstrated a favorable tolerability profile compared with ACE inhibitors.

Conclusion

The current with its limitations concludes that losartan effectively lowered blood pressure over 6 months, showing a significant decrease in both systolic and diastolic values. Additionally, there was a statistically significant reduction in serum uric acid levels with losartan treatment. This reduction in uric acid is noteworthy, as it is independent of blood pressure reduction, emphasizing that losartan possesses uric acid-lowering effects beyond its significant impact on blood pressure.

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