Research Article

Effect of lisinopril therapy on serum leptin, oxidative stress and C-reactive protein in hypertensive patients

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Abstract

The pathogenesis of essential hypertension through the interaction with elements of the rennin angiotensin aldosterone system is affected by oxidative stress and inflammation. The present study aimed to assess the effects of ACE-Inhibitor, lisinopril, on blood pressure, lipid profiles (total cholesterol, triglycerides, LDL and HDL), MDA, and TAS, hsCRP, and serum leptin levels n hypertensive patients. A case control study included 100 newly diagnosed mild to moderate hypertensive patients and another 100 apparently healthy aged and sex matched subjects as controls. The patients were treated with 10 mg lisinopril orally per day for three months' duration. Venous blood sample was taken to test levels of MDA, GSH and TAS, hsCRP, lipid profiles and leptin in the serum before and after lisinopril therapy for both patients and controls. Systolic and diastolic blood pressure were also assessed before and after lisinopril therapy for both patients and controls. In hypertensive patients treated with lisinopril, markers of oxidative stress (MDA, TAS and GSH), high sensitive C-reactive protein and leptin were all found to be decreased significantly after drug treatment ($p < 0.01$). Lisinopril affectively lowered systolic and diastolic BP values ($p < 0.01$). A significant decrease in lipid profile ($p < 0.01$) with a significant increase in HDL-C and TAS levels ($p < 0.01$) were found in lisinopril treated group in comparison with their values before treatment. Lisinopril may be used as a treatment for high blood pressure, as well as for the insulin resistance, hyperleptinemic, and low-grade inflammatory states that are associated with the disease.

Keywords

Introduction

Hypertension is a chronic clinical condition in which the blood pressure gradually increases (Merkhan et al. 2021). A systolic blood pressure of less than 140 mmHg and a diastolic blood pressure of less than 90 mmHg are indicative of controlled hypertension (Ames et al. 2019; Arif et al. 2019). Although it is typically asymptomatic, it can have a long-term detrimental effect on the renal, cardiopulmo-

nary, and neurovascular systems. Hypertension is classified into two types: essential hypertension and secondary hypertension (Balakumar et al. 2019). The two types of hypertension are essential hypertension and secondary hypertension. Essential hypertension is more prevalent than secondary hypertension, which affects 90–95% of people and is caused by a combination of genetic and environmental factors. Secondary hypertension affects between 5% and 10% of hypertensive patients and is caused

by a variety of observable and treatable factors, such as deteriorating kidney function (Chandra et al. 2014; Bottinor et al. 2019; Faulkner and Belin de Chantemèle 2019).

When combined with chronic sympathetic nervous system activation, particularly of the kidney, leptin has been shown to influence nitric oxide production and natriuresis, which has been linked to sodium retention, systemic vasoconstriction, and blood pressure elevation (Shankar and Xiao 2010; Serafi et al. 2016; Ahmad et al. 2021). As a consequence, direct correlation has been established between elevated leptin levels and the development of hypertension in obese people (Almukhtar et al. 2021; Younis et al. 2021). There have been few studies comparing leptin levels prior to and following antihypertensive therapy, as well as their tumor necrosis factor levels and the production of reactive oxygen species (Xie and Bollag 2016; Von Schnurbein et al. 2019).

The renin angiotensin aldosterone system (RAAS) and reactive oxygen species (ROS) have been extensively studied (Romero and Reckelhoff 1999). Angiotensin II, a vasoconstrictor mediator, generates reactive oxygen species (ROS) and is a strong inducer of oxidative stress(Mahmood et al. 2012).

Angiotensin II stimulates the expression and function of Nicotine Amide Adenine Dinucleotide Phosphate (NADPH) oxidase in vascular wall and coronary microvascular endothelial cells, as well as the production of superoxide (Dimitriadis et al. 2016; Dikalova et al. 2020). Additionally, angiotensin II's long-term effects may result in reduced expression of anti-oxidant defense mechanisms such as superoxide dismutase. Additionally, an increase in ROS interns may promote the expression of RAAS components necessary for angiotensin II formation (Abdulrazzaq et al. 2020; Faisal et al. 2020). The inhibitors of the angiotensin converting enzyme and the angiotensin II receptor were found to have significant antioxidant properties that outperformed vitamin E and other commonly used antioxidants (Al-Hamodi et al. 2014; Merkhan and Abdullah 2020).

The aim of this study was to determine the effect of lisinopril on serum leptin, lipid profile (TC, TG, LDL, and HDL), malondialdehyde (MDA), total antioxidant status (TAS), glutathione (GSH), and high sensitivity C-reactive protein (hsCRP) in newly diagnosed hypertensive patients.

Material and methods

A total of 200 subjects were recruited and completed the study. The patient group includes one hundred newly-diagnosed hypertensive patients collected with the assistance of the medical staff of the out-patient clinic at IBN-SINA teaching hospital. The remaining 100 subjects were the control group of apparently healthy volunteers ranging in age from 28 to 65 years with a mean of 37.86 ± 10.02 years. The study was an open, controlled, comparative clinical trial study conducted to evaluate the effect of lisinopril therapy on blood pressure, oxidative stress markers (MDA, GSH and TAS), lipid profile, inflammatory marker (hs-CRP) and serum leptin levels. Blood pressure was measured at before and after drug administration using a standard mercury

sphygmomanometer (Frese et al. 2011). The target blood pressure was less than 140/90 mmHg following treatment.

Antihypertensive efficacy was determined by comparing blood pressure levels before and after drug therapy and by determining the proportion of patients who achieved normal blood pressure following therapy. Before and after two months of therapy, approximately 10 ml of venous blood was drawn from patients using disposable plastic syringes. The sera were separated and stored at (-20 °C) until further analysis following centrifugation of the blood (27). They were recruited as controls to establish normal values for SBP, DBP, MDA, TAS, hs-CRP, lipid profile, and serum leptin. Serum MDA levels were determined using a thiobarbituric acid (TBA) assay, and TAS and GSH levels were determined using the Randox TAS Kit.

High sensitivity C-reactive protein, hs-CRP was quantified in human sera using an enzyme-linked immunosorbent assay (ELISA). A Biochek hs-CRP ELISA kit was used. The level of serum leptin was determined using the IBL leptin ELISA kit (Germany). The serum lipid profile was determined enzymatically using a kit supplied by BIOLABO (France). Body mass index (BMI) was calculated using the following equation: (Kg) / (m2). Standard chemical methods were used to determine the lipid profile (TG, TC, LDL-C and HDL-C). The study's mean and standard deviation were calculated statistically (SD). For statistical comparisons, ANOVA and paired t-tests were used. 0.05 was chosen as the level of statistical significance. Frequency tables were analyzed using the chi-square test, while mean and standard deviation tables were analyzed using the independent sample t-test. The Pearson correlation coefficient is used to determine the relationship between the markers under investigation

Results

The baseline characteristics of the data were shown in Table 1. Body mass index (BMI), systolic blood presser (SBP), diastolic blood pressure (DBP), malonadialaldehyde (MDA) and Total antioxidant status TAS), lipid profile

Table 1. Comparison between control and lisinopril group for the studied parameters.

Parameter	Mean±SD		
	Control (n = 100)	Before treatment (n = 100)	P-value
Weight (Kg)	74.60 ± 11.5	85.65 ± 8.79	<0.001
BMI (Kg/m2)	27.20 ± 2.8	30.46 ± 1.38	<0.001
SBP (mmHg)	127.05 ± 6.93	143.60 ± 7.72	<0.001
DBP (mmHg)	79.24 ± 4.91	92.18 ± 6.21	<0.001
TC (mmol/l)	5.45 ± 1.63	4.40 ± 1.93	<0.001
TG (mmol/l)	1.48 ± 1.55	2.63 ± 1.6	<0.001
HDL (mmol/l)	2.60 ± 1.28	1.90 ± 1.30	<0.001
LDL (mmol/l)	1.48 ± 1.60	2.26 ± 1.65	<0.001
hsCRP mg/L	5.60 ± 0.17	12.12 ± 9.81	<0.001
MDA (nmol/ml)	4.26 ± 0.78	10.05 ± 3.16	<0.001
TAS (mmol/l)	1.55 ± 0.22	1.53 ± 0.26	<0.001
GSH (µg/ml)	3.46 ± 1.37	2.37 ± 0.84	<0.001
Leptin (ng/ml)	12.34 ± 0.22	17.08 ± 8.16	<0.001

Using the unpaired t-test, there is a significant difference at $p \leq 0.001$.
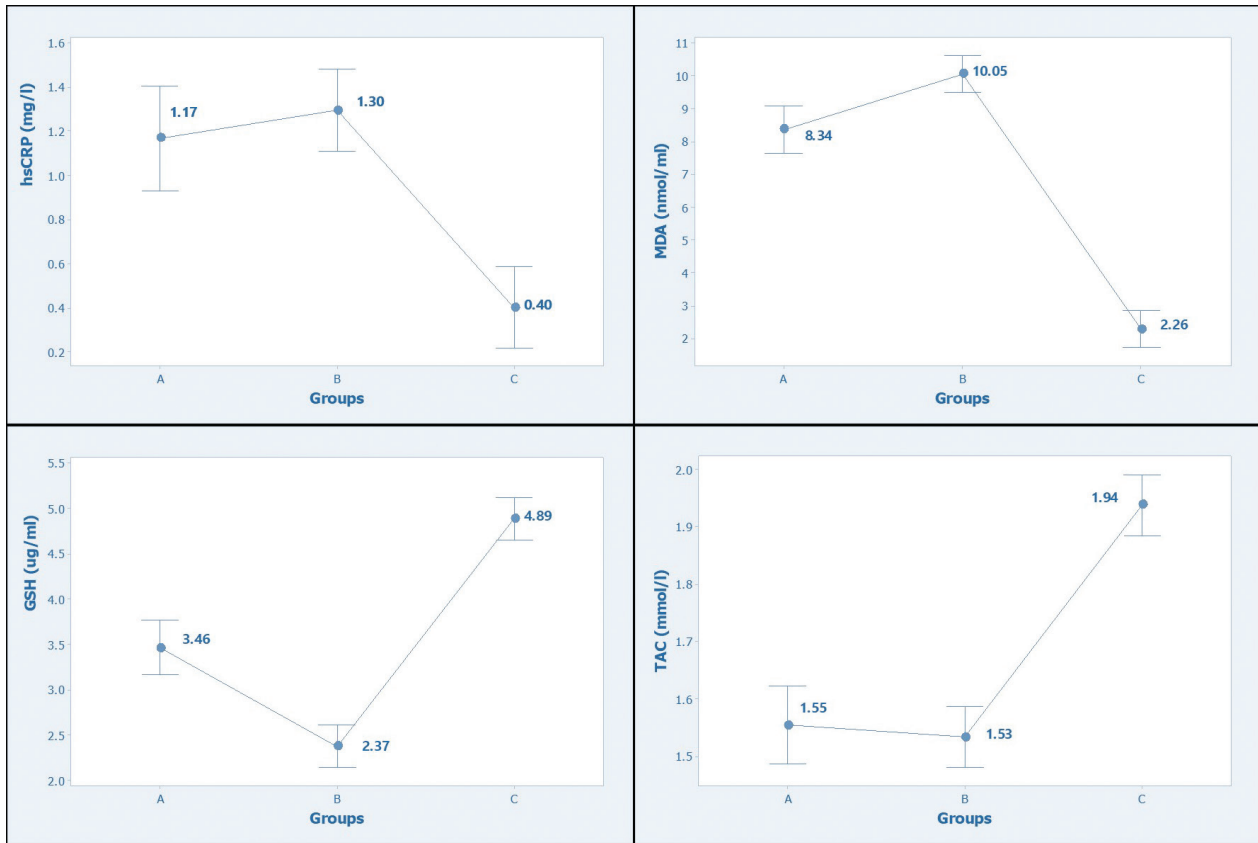
Figure 1. The difference in mean of measured parameters (MDA, hsCRP, TAC, and GSH) among the study sampled groups.

Table 2. Comparison of studied parameters before and after lisinopril therapy.

Parameter	Mean±SD		
	Before treatment (n = 100)	After treatment (n = 100)	P value
Weight (Kg)	85.65 ± 8.79	81.46 ± 7.61	<0.001
BMI (Kg/m2)	30.46 ± 1.38	30.95 ± 1.8	<0.001
SBP (mmHg)	143.60 ± 7.72	128.90 ± 7.14	<0.001
DBP (mmHg)	92.18 ± 6.21	80.45 ± 5.84	<0.001
TC (mmol/l)	4.40 ± 1.93	3.35 ± 1.00	<0.001
TG (mmol/l)	2.63 ± 1.6	1.48 ± 1.03	<0.001
HDL (mmol/l)	1.90 ± 1.30	2.46 ± 1.43	<0.001
LDL (mmol/l)	2.26 ± 1.65	1.89 ± 1.52	<0.001
hsCRP mg/L	12.12 ± 9.81	7.2 ± 8.9	<0.001
MDA (nmol/ml)	10.05 ± 3.16	8.34 ± 2.32	<0.001
TAS (mmol/l)	1.53 ± 0.26	1.94 ± 0.17	<0.001
GSH (µg/ml)	2.37 ± 0.84	4.89 ± 0.77	<0.001
Leptin (ng/ml)	17.08 ± 8.16	14.97 ± 8.93	<0.001

Significant difference at p < 0.001 using unpaired t-test.

(Total cholesterol TC, Triglycerides TG, Low density lipoprotein cholesterol LDL, High91 density lipoprotein HDL),high sensitivity C-reactive protein (hsCRP) and leptin levels were significantly increased in patients with hypertension compared to the healthy subjects group (p < 0.01),while high density lipoprotein cholesterol (HDL) and the antioxidant glutathione GSH levels were significantly lower (p < 0.01) in these patients as shown in Table 1. On the other hand comparison of baseline and after treatment with the antihypertensive drug lisinopril , the levels of BMI, SBP, DBP, MDA, lipid profile, hs-CRP and leptin levels in hypertensive patients were significantly decrease and HDL, TAS and GSH levels were significant-

Table 3. Correlation matrix between different parameters in the studied group.

Parameter	Correl coeff*	Leptin	Age	WT	hsCRP	MDA	TAS	GSH
WT	R	0.241	0.813	–	–	–	–	–
	P	0.140	0.132	–	–	–	–	–
hsCRP	R	0.546	0.238	0.253	–	–	–	–
	P	0.000	0.140	0.116	–	–	–	–
MDA	R	0.721	0.692	0.064	0.442	–	–	–
	P	0.000	0.073	0.694	0.004	–	–	–
TAS	R	-0.642	0.287	0.064	0.442	0.287	–	–
	P	0.000	0.073	0.694	0.004	0.073	–	–
GSH	R	-0.734	-0.734	-0.013	-0.162	-0.107	-0.303	–
	P	0.000	0.274	0.938	0.318	0.510	0.058	–
TC	R	0.526	-0.093	-0.140	0.152	-0.073	-0.055	0.120
	P	0.004	0.569	0.389	0.350	0.654	0.736	0.124
HDL	R	-0.561	0.080	0.051	0.354	0.117	0.390	-0.190
	P	0.004	0.623	0.755	0.025	0.473	0.013	0.239
LDL	R	0.745	-0.053	-0.094	0.119	-0.076	-0.111	-0.222
	P	0.004	0.746	0.564	0.465	0.641	0.496	0.168
TG	R	0.579	-0.374	-0.399	-0.202	-0.126	-0.070	0.001
	P	0.004	0.017	0.011	0.211	0.440	0.669	0.996

* Pearson correlation method (r) was used.

ly increased in comparison with pretreatment values as shown in Table 2. Concerning for correlations study, the results found that there was a positive correlation between leptin and hsCRP, MDA, TC, TG and LDL while there was a negative correlation between leptin and TAS, GSH and HDL as shown in Table 3. A significant positive correlation was found between systolic and diastolic blood pressure and leptin in all studied groups (p < 0.01). Table 4. The difference in mean MDA, hsCRP, TAC and GSH levels among the study sampled groups were shown in Figure 1.

Table 4. Correlations between blood pressure and leptin in all studied groups.

Parameter	Systolic blood pressure		Diastolic blood pressure	
	r	p-value	r	p-value
Leptin(ng/ml)	0.8	0.01	0.7	0.01

Discussion

Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve endothelial function and oxidative stress, as well as inflammatory factors (Abdollahi et al. 2012). This study showed a significantly decreased in TAS and GSH levels, a significantly higher serum leptin, hs-CRP and MDA between patients with hypertension before treatment in comparison with controls. After 3 months therapy with lisinopril, a significant increase in TAS, GSH and HDL levels, and a significant reduction in serum leptin, MDA and hs-CRP were found in such patients in comparison to pretreatment values. These results were in agreement with results of studies which reported that patients with essential hypertension observe a significantly lower antioxidant markers as compared with healthy subjects and that TAS values increased during therapy with antihypertensive drug (Merkhan et al. 2020). The conclusion drawn from the presence of oxidative stress, diminished Total antioxidant status and elevated superoxide dismutases with a decreased levels of glutathione as well as the finding of hypertension, which was substantiated, was that inflammation (as evidenced by an increase in MDA and decrease in SOD) and the increase in hsCRP indicated that hypertension is usually associated with an inflammatory response (Erejuwa et al. 2011; Hage 2014).

Recent research has established that oxidative stress plays a significant role in the development of hypertension (Merkhan et al. 2021). Oxidative stress has gained prominence as a critical mechanism underlying the development of hypertension. Reactive oxygen species (ROS) play a critical role in maintaining the vascular wall's homeostasis; thus, they may be a component of the mechanism underlying hypertension (Sies and Jones 2020; Abdullah et al. 2021). Thus, in experimental and human hypertension, increased reactive oxygen species (ROS) production, decreased nitric oxide (NO) levels, and decreased antioxidant bioavailability were observed (Ray et al. 2012). When stimulated by hormones such as angiotensin II (AT-II), endothelin-1 (ET-1), and urotensin II, vascular superoxide dismutase is primarily derived from nicotinamide adenine dinucleotide diphosphate (NADPH) oxidase (Hend et al. 2021). It has also been proven that mechanical stimuli cause an increase in the formation of free radicals, which lead to an additional increase in the circulating R'(+O) S levels in those who have hypertension. Increased intracellular calcium concentrations has a deleterious effect on the formation of vasoconstriction, which in itself is thought to contribute to hypertension (Andreadou et al. 2020). The amount of the vascular elements and oxygen demand are adjusted by the presence of oxidative stress, each of which is made to maintain a precise balance by the interactions of the vasodilator and vasoconstrictor forces, both of which are determined by the quantity of red blood cells. These studies have piqued interest in medications that inhibit free radical formation or delivery to tissues and are now being investigated a new classes of antihypertensive agents (Andreadou et al. 2020).

This study also showed that the hs-CRP levels in patients with hypertension were significantly higher than those of healthy controls and that the administration of the antihypertensive drug, lisinopril, for 3 months was associated with a significant reduction in its level. Many studies reported that hsCRP is significantly elevated in patients with essential hypertension, normalizing over weeks on therapy, thereby correlating with clinical response (Almukhtar et al. 2020; Caetano-Silva et al. 2021). C-reactive protein (CRP) is a marker of systemic inflammation that has been linked to an increased risk of hypertension development. Although numerous studies demonstrate that elevated circulating CRP levels are associated with elevated blood pressure, these associations may be noncausal. Numerous clinical findings corroborate the existence of a link between interleukin-6, IL-6, and CRP (Volpe 2008).

Additional studies have provided data that contradicting previous reports about leptin levels in high blood pressure states have been performed (Herold et al. 2020). Elevated levels of leptin levels have been observed in some previous studies in patients with high blood pressure (Hage 2014). Research has also shown that plasma levels of leptin were lower with treatment of hypertension and higher in those patients who experience resolution of their hypertension (De Faria et al. 2013). as indicated by this study's findings, Lisinopril treatment resulted in significant reduction in serum MDA, hs-CRP, and leptin levels, as well as a substantial increase in TAS and GSH in patients with hypertension in agreement with these findings, our current studies, individuals found that patients suffering from hypertension could not produce enough antioxidants to combat the oxidative stress, but antioxidant treatment along with antihypertensive drugs appears to help with rapid relief. As compared to normotensive patients, the levels of MDA, hs-CRP, and leptin were reduced in those taking lisinopril, while those of TAS and GSH levels were elevated. This effect may be mediated by inhibition in improving T cell immune functions (Kamimura et al. 2018) which other studies have shown to be capable of preserving the cell membranes from oxidation as well as substantiating the claim that they can protect the lipid membrane from attack by ROS (Nowzari et al. 2018). One study discovered a link between adiponectin expression and body fat mass (Luo et al. 2005). They concluded that, while ACEIs are well known for their antioxidant properties, they may also affect adipocytokine levels (Katsiki et al. 2011) via non-antioxidant mechanisms such as inhibition of protein kinase C and regulation of cell growth and expression of the membrane glycoprotein CD36 (Fontana et al. 2014).

In addition, leptin may contribute to the regulation of blood pressure in hypertensive normal as well as in the obese patient (Furuhashi et al. 2003). Numerous clinical

studies have found increased plasma leptin levels in hypertensive patients (Nagamia et al. 2007). Moreover, leptin plays a role in end organ damage related to hypertension, including left ventricular hypertrophy, retinopathy, and nephropathy (Al-Thanoon and Mahmood 2012; Nedogoda et al. 2013). The role of leptin in blood pressure regulation and arterial hypertension is illustrated in various studies (Furuhashi et al. 2003; Althanoon et al. 2020). Correlation analysis the results of the present study found that there was a positive correlation between leptin and hsCRP,MDA,TC,TG and LDL,as shown in Table 3, and there was a negative correlation between leptin and TAS, GSH and HDL, a significant positive correlation was found between systolic and diastolic blood pressure and leptin in all studied groups (Table 4), these finding were in agreement with other studies as reported by Man et al. 2020; Ahmad et al. 2019. Interestingly, in the current study, hypertensive patients treated with lisinopril result in a significant improvement in leptin, hsCRP, MDA, TC, TG, and LDL-C levels, despite the fact that they did not change their diet in any way during the course of the study. To date, it has not been determined whether such an effect was a cause or a result of the observed changes in leptin levels and insulin resistance.

Conclusion

The findings of this study suggest that, while the ACEI lisinopril has effective blood pressure lowering effects, lisinopril may have an advantage in the treatment of hypertensive subjects because of its improvement of some obesity-related metabolic disorders, such as BMI, hyperleptinemia, and insulin resistance, as well as its lack of sympathetic activation. As a result, lisinopril may be used as a medication for patients with hypertension to lower their blood pressure while also improving their insulin resistance, hyperleptinemic status, and low-grade inflammatory condition.

Acknowledgements

Conflicts of interest

No potential conflicts exist. We had full access to all the information in the study and take full responsibility for the integrity of the information and the accuracy of the data analysis.

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