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Research Article

NON-DIABETIC HYPERTENSIVE PATIENTS TREATED WITH LOSARTAN AND ATENOLOL: EFFECT ON INSULIN SENSITIVITY

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ABSTRACT
The research examined the changes in glucometabolic parameters after treating nondiabetic hypertensive patients with losartan and atenolol. Using a prospective, open-label, parallel-group study, patients without diabetes and mild to moderate hypertension were randomly assigned to receive either losartan (titrated from 50 to 100 mg/day, n = 40) or atenolol (titrated from 25 to 100 mg/day, n = 40) for 24 weeks. The following were measured at baseline, 12 weeks and 24 weeks: FPG, FPI, HOMA-IR, lipid parameters and average systolic and diastolic blood pressure. At the end of the study, losartan caused a substantial drop ($P < 0.05$) in FPG, FPI and HOMA-IR compared to atenolol and the beginning of the study. Similarly, atenolol was associated with an increased value of HOMA-IR compared to when ADRP was given. This study suggests that insulin sensitivity is increased with losartan, whereas atenolol reduces this sensitivity. That is why losartan is more effective than atenolol when it comes to glucose-insulin metabolism.

Keywords :- Losartan, Atenolol, Insulin, Hypertensive Patients.

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INTRODUCTION
Lowering blood pressure in people with high blood pressure is linked to reduced death from cardiovascular disorders, independently of which medication is being taken [1]. When treating hypertension, medicines such as ACEIs, ARBs, BBs, thiazide diuretics and CCBs are used as antihypertensive drugs [2]. Although these medicines all decrease cardiovascular deaths, they vary in the side effects they bring. A number of antihypertensive drug groups have the potential to affect blood sugar, insulin and lipid levels negatively.Hypertension causes a rise in insulin resistance and difficulties handling blood sugar which may result in DM for many hypertensive people [3]. Diabetes and hypertension together greatly increase a person's chances of having heart disease [4]. Because of these differences, blood pressure drugs used for hypertension in people without diabetes should also work to prevent diabetes [5].

Several experiments have suggested that angiotensin receptor blockers, especially telmisartan, help people with diabetes use insulin better. Most ARBs, particularly losartan, are tetrazole-based, but telmisartan features only one carboxylic acid group and is lipid-soluble. It is thought that its similarity to thiazolidinediones leads to beneficial changes in glucose-insulin metabolism by stimulating the peroxisome proliferator-activated receptor gamma.[6]Still, there is doubt about whether all ARBs produce this result. In particular, a metabolite of losartan, known as EXP-3174, displays some activity as an agonist at the PPAR-γ receptor [7].

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It has not been clear whether losartan helps or worsens resistance to insulin. A couple of recent studies highlight that losartan plays a positive role in glucose-insulin metabolism [8]. For example, research has shown that losartan cut the risk of developing type 2 diabetes mellitus by 25%, contrasted with atenolol [9]. Meanwhile, studies by others did not find large improvements in insulin resistance with losartan [10,11]. This study therefore looked at how antihypertensive drugs losartan and atenolol might influence glucometabolic parameters in nondiabetic hypertensive participants.

Materials and Methods

The study enrolled 80 patients between 18 and 75 years old, all with hypertension. The patients were seen at the medicine outpatient department of the tertiary care hospital and due to be treated. Participants were excluded if they had type 1, type 2 diabetes, only one or both renal arteries narrowed, a history of ARB or beta-blocker allergy, kidney failure or low kidney function, elevated potassium, lung conditions such as COPD or asthma, smokers, severe changes on electrocardiogram, narrowened heart arteries, inside of the brain issues such as hypertensive encephalopathy, stroke or TIA within the last six months or were pregnant, nursing mothers or planning to become pregnant. Every participant was told what the study was about and gave written permission.

A parallel-group, open-label, randomized, controlled and prospective study was performed at the hospital. Eligible participants were randomly separated by lottery into two groups, each with twenty participants, who received medication as follows: Group I had losartan raised from 50 to 100 mg daily and Group II received atenolol titrated from 25 to 100 mg daily. Patients in whom blood pressure was still not controlled with titrated medications were switched to adding indapamide. Patients were given treatment for 24 weeks and continued to be checked at both 12 and 24 weeks to monitor their SBP, DBP, HR and the listed metabolic parameters.

After overnight fasting, fasting plasma glucose (FPG) and fasting plasma insulin (FPI) were measured using standard techniques. An enzymelinked immunosorbent assay was used to estimate insulin levels. Homeostasis model assessment of insulin resistance (HOMAIR) was calculated as follows:

HOMA-IR = FPI (μU/ml) × FPG (mmol/L)/22.5

Standard methods were used to measure serum triglycerides, serum high density lipoprotein cholesterol, and total cholesterol. Calculating low-density lipoprotein cholesterol levels was based on Friedewald's formula.

Blood pressure measurement

Mercury sphygmomanometers were used to measure blood pressure in conjunction with cuffs large enough to cover at least 80% of the arm. During the testing procedure, patients were required to sit for five minutes in a comfortable environment with their feet touching the ground and their arms supported at heart level. An auscultatory method was used to measure the blood pressure.

Body mass index

Also called as Quetelet index was calculated using formula:

BMI = Weight (kg)/height (m2)

Sample size calculation

Using previous studies of losartan's effect on insulin sensitivity in essential hypertensive patients, a sample size was calculated [15]. The HOMAIR (mean ± standard deviation [SD]) levels before and after 6 months of losartan treatment in hypertensive patients were 2.3 ± 0.6 and 1.5 ± 0.7, respectively. According to the alpha risk 5%, the power 95%, and the ratio of sample size (n2/n1) 1, 18 patients are necessary for a valid study.

Means and standard deviations are expressed for data following a normal distribution, and medians and ranges are expressed for data that follow a skewed distribution. The data were tested for normality (Kolmogorov–Smirnov test), and intergroup analyses were conducted for data at baseline, 12 weeks, and 24 weeks. Using the unpaired Student's t-test with or without Welch correction for Gaussian data and Mann-Whitney test for non-Gaussian data, we assessed the percentage change from baseline until 12 weeks and 24 weeks.

RM - ANOVA was used to compare different parameters with normal distribution within the same group at different time points for intragroup (or withingroup) comparisons. The Kruskal-Wallis test was used to analyze non-Gaussian data. As a post-test, the Tukey Kramer test and Dunn's test were used to identify the group responsible for the difference in Gaussian and non-Gaussian data, respectively. A significance level of $P < 0.05$ and a 95% confidence interval were used to analyze the results.

Results and Discussion

Results

Baseline parameters

A total of 80 patients were enrolled in the study, of which 40 were randomized to each of the treatment groups. A detailed description of the baseline clinical characteristics of the study patients can be found in Table 1. The variables measured in this study did not show any significant difference between the two groups for any of the variables measured.

Systolic blood pressure, diastolic blood pressure, and heart rate

It is concluded that there are no significant differences between the SBP and DBP levels at each time point in the study as a result of the intergroup analysis [Table 2]. Based on the 12-week and 24-week follow-up analyses. When losartan and atenolol were added at the end of the study, HR was significantly reduced (P < 0.001).

There is a significant difference between the fasting plasma glucose (FPG) and fasting plasma insulin (FPI) levels at the end of treatment between the two groups, as shown in the intergroup analysis [Table 2] of the fasting plasma glucose (FPG) levels. In both groups, the fasting plasma glucose levels were statistically significant (P = 0.0018, P < 0.0001) at the end of the treatment. HOMAIR levels proved to be significantly different in the study groups after 12 and 24 weeks, respectively, indicating a significant difference in HOMAIR levels between the study groups (P = 0.0144 and P = 0.0001). Besides a comparison of the groups based on percent change measured between baseline and the end of 12 and 24 weeks after a baseline, it was also conducted to determine if there were any differences. The difference in the percentage change in HOMAIR over a period of 12 weeks was significantly different between losartan and atenolol (P = 0.0386) and over a period of 24 weeks (P = 0.0001). A comparative intragroup analysis of the FPG, FPI, and HOMAIR levels at 12 and 24 weeks post-discharge showed that atenolol increased the levels of all three drugs, whereas losartan decreased the levels of all three drugs.

Lipid metabolic parameters

Losartan and atenolol groups did not differ significantly in lipid metabolic parameters at 12 and 24 weeks followup [Table 2]. No significant differences were found between baseline and 12- and 24-week follow-up levels.

Table I: Characteristics of patients in the study groups at baseline

Variable	Atenolol (*n*=40)	Losartan (*n*=40)	*P*
Age (year) (range)	49.5±8.34 (41-73)	51.2±8.23 (39-70)	NS
Gender (male/female)	26/14	26/14	
BMI (kg/m2)	22.7±4.01	22.41±3.97	NS
HR (per min)	74.5±6.51	73.4±8.01	NS
SBP (mmHg)	162.5±8.71	162.3±8.78	NS
DBP (mmHg)	94.6±7.01	95.7±7.98	NS
FPG (mg/dL)	100.84±14.31	100.79±9.24	NS
FPI (μIU/mL)	10.74±4.87	10.31±2.74	NS
HOMA-IR	2.68±2.42	2.77±1.01	NS
LDL-C (mg/dL)	115.78±19.68	114.±26.71	NS
HDL-C (mg/dL)	36.1±10.62	36.7±10.41	NS
TG (mg/dL)	149.91±78.51	150.4±62.14	NS
Total-C (mg/dL)	182.61±27.62	182.42±33.47	NS

Table 2: A comparison of atenolol and losartan on different variables: an intergroup analysis

Variable	Time points (weeks)	Treatment Groups (n=40)		*P*
		Atenolol	Losartan	
HR (per min)	Baseline	74.4±6.74	74.3±7.76	NS
	12	64.5±7.13	74.8±6.06	<0.0001
	24	61.6±6.60	74±5.23	<0.0001
SBP (mmHg)	Baseline	162.4±8.47	163.4±10.52	NS
	12	154.1±8.16	151.4±11.33	NS
	24	145.7±6.47	144.72±8.42	NS
DBP (mmHg)	Baseline	95.7±6.43	96.9±8.11	NS
	12	84.2±5.30	87.6±5.67	NS
	24	83.4±5.58	83.4±4.59	NS
FPG (mg/dL)	Baseline	99.5 (81-125)	100.5 (89-122)	NS
	12	96.5 (84-130)	94.5 (89-112)	NS
	24	104.9±13.12	94.7±3.38	0.0018
FPI	Baseline	10.83±3.97	11.53±3.61	NS

(μIU/mL)	12	12±3.86	9.49±4.68	NS
	24	16.08±5.24	7.65±2.12	<0.0001
HOMA-IR	Baseline	2.79±1.25	2.88±0.91	NS
	12	2.89 (1.51-5.48)	2.01 (1.11-5.74)	0.0144
	24	4.12±1.28	1.79±0.51	<0.0001
LDL-C (mg/dL)	Baseline	114.65±21.78	115.95±27.66	NS
	12	115.4±20.18	114.45±20.68	NS
	24	115.5 (76-156)	120 (80-144)	NS
HDL-C (mg/dL)	Baseline	37.15±10.58	37.8±11.64	NS
	12	36 (25-56)	39 (26-53)	NS
	24	37.45±10.25	40.6±7.71	NS
TG (mg/ dL)	Baseline	150.75±79.83	152.7±60.31	NS
	12	144 (70-296)	141 (78-258)	NS
	24	147.75±63.14	144.5±50.25	NS
Total-C (mg/dL)	Baseline	181.95±28.14	184.29±31.74	NS
	12	181.99±24.19	181.89±23.95	NS
	24	179.54±24.14	179.88±20.14	NS

DISCUSSION

Results from the study demonstrate that losartan improves insulin sensitivity in nondiabetic hypertensive patients. Even though losartan and atenolol control high blood pressure similarly, they differ in how they affect metabolic functions.The study found that those with high blood pressure without diabetes responded better to insulin resistance changes when treated with losartan than with atenolol. A number of studies point to ARBs such as losartan, as a factor in lowering insulin resistance [16–18]. Approximately 120 patients were given either losartan (100 mg daily) or amlodipine (10 mg daily) over three months because they all had type 2 diabetes and nephropathy. Using HOMA-IR, insulin resistance was found to improve in the losartan group, while fasting insulin levels decreased, although not to a level that was statistically different when compared to amlodipine. The researchers evaluated insulin resistance with the glucose clamp on diabetic patients with hypertension. Following treatment with losartan (100 mg) plus amlodipine (5 mg), glucose was removed faster from the bloodstream than after treatment with amlodipine (10 mg) alone (4.97 ± 0.4 vs. 4.27 ± 0.5 mg/kg/min, P = 0.039). Similarly, HOMA-IR readings in the group using losartan plus amlodipine were much lower after eight weeks than at the start (4.4 ± 0.8 vs. 3.1 ± 0.6, P = 0.007). Found that in patients with impaired glucose tolerance, losartan (50–100 mg/day) helped reduce HOMA-IR by 23.9% more than a calcium channel blocker after three months.

Insulin resistance often results from the important part that the renin-angiotensin system (RAS) plays. Tissue blood flow may be decreased by the vasoconstrictive effect of angiotensin II which can reduce glucose use by those tissues [19]. As a result, angiotensin II and its target receptor activate JAK2 which then activates IRS-1, stopping PI3K activation and reducing insulin signaling, making the body resistant to insulin.[20]Angiotensin II works to increase oxidative stress which leaves insulin less efficient in the body. In addition, turning on RAS raises TNF-α in skeletal muscle which lowers GLUT movement and contributes to insulin resistance. AT1 receptors on adipose tissue result in its growth and differentiation of the precursor cells, while AT2 receptors induce differentiation. Hypertrophied adipose tissue then produces cytokines which make insulin less effective. Using ARBs may lower blood sugar levels in several ways by blocking angiotensin II [20 - 22].

In contrast to our results, some papers say that losartan does not help insulin sensitivity. Compared telmisartan and losartan among hypertensive metabolic patients for eight weeks, using HOMA-IR. Higher levels of HOMA-IR were observed at both baseline and the end of treatment in the losartan group, with no major differences (mean 1.8 at basline and 1.8 at the study end, P > 0.05) [10].The team at Yavuz found that over six months, losartan (50–100 mg/day) caused a non-significant drop in HOMA-IR compared to enalapril (5–40 mg/day). The use of telmisartan improved both body fat and insulin sensitivity among overweight Chinese hypertensive patients, but losartan did not show a remarkable change in HOMA-IR [23]. In hypertensive patients with impaired glucose tolerance, Perl et al. studied the vascular, antihypertensive and metabolic responses to telmisartan and losartan over 12 weeks, finding there was no major reduction in insulin resistance when patients were given losartan [24]. Later, the same study group found that losartan made it easier for patients with severe hypertension to use insulin [26]. The differences in outcomes might be related to the dosage, how long someone was given losartan, how severe their hypertension was at the start or other unknown elements.

Results from our study indicate that atenolol decreased insulin sensitivity in a manner seen in previous trials [12,27]. Many factors allow beta-blockers to make it harder for the body to use insulin and control its blood sugar. Activating pancreatic β2 receptors decreases insulin secretion, but slightly more when using nonselective beta-blockers and a bit when using larger quantities of β1-selective beta-blockers. Gaining weight because of beta-blockers also worsens how sensitive the body is to insulin. Normal insulin works by making blood vessels dilate in muscles; still, nonselective beta-blockers prevent insulin from widening blood vessels, leading to insulin resistance. In addition, beta-blockers affect early insulin release by decreasing β2 cells' activity and decreased early insulin response is often a sign of upcoming type 2 diabetes [29].

Conclusion

According to the results, while both drugs manage blood pressure similarly, losartan improved insulin resistance, whereas atenolol made it worse in nondiabetic people with hypertension. Regarding glucometabolic effects, losartan seems to outperform atenolol. More investigation needs to be carried out to understand how losartan improves insulin sensitivity.

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