Effect of losartan and atenolol on insulin sensitivity in nondiabetic hypertensive patients

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ABSTRACT

Objective: To study the effects of losartan and atenolol on glucometabolic parameters in nondiabetic hypertensive patients. **Materials and Methods:** In a prospective, open-label, parallel group study, nondiabetic patients with mild to moderate hypertension were randomized to either losartan (titrated from 50 to 100 mg/day, $n = 20$) or atenolol (titrated from 25 mg to 100 mg/day, $n = 20$) for period of 24 weeks. At baseline, 12 and 24 weeks fasting plasma glucose (FPG), fasting plasma insulin (FPI), homeostasis model assessment for insulin resistance (HOMA-IR) apart from lipid parameters, mean systolic, and diastolic blood pressures levels were determined. **Results:** At the end of study, losartan significantly ($P < 0.05$) reduced FPG, FPI, and HOMA-IR compared to atenolol and baseline. While atenolol increased the HOMA-IR levels significantly compared to the baseline. **Conclusions:** Losartan improved the insulin sensitivity while atenolol worsened it. Losartan is better than atenolol for its effects on the glucose-insulin metabolism.

Key words: Atenolol, hypertension, insulin resistance, losartan

INTRODUCTION

Different studies have shown that lowering blood pressure in patients of hypertension decreases the risk of death due to cardiovascular complications irrespective of the antihypertensive drug used for the treatment.[1] Various antihypertensive drug groups are used for the management of hypertension, including angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), thiazide diuretics, and calcium channel blockers (CCBs).[2] Irrespective of the identical benefits of lowering cardiovascular mortality, antihypertensive agents differ in terms of their adverse effects. Some antihypertensive drug groups may adversely affect the metabolic parameters including glucose-insulin metabolic parameters and lipid levels differently.[1] Hypertension itself induces a state of insulin resistance and impaired glucose tolerance culminating in the development of diabetes mellitus (DM) in hypertensive patients.[3] The occurrence of diabetes with hypertension increases the hazard of cardiovascular diseases by manifold.[4] Therefore, choosing antihypertensive medications that do not adversely affect the metabolic outcome and worsen the already insulin resistant state in

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hypertensive patients, instead prevent the new-onset of DM is important in nondiabetic patients with hypertension.[5] Different studies have shown the insulin sensitizing effects of ARBs especially that of telmisartan. Telmisartan is a mono-carboxylic acid, nontetrazole lipid soluble compound unlike other losartan such as ARBs with large tetrazole ring. Telmisartan is believed to have thiazolidinedione like agonistic activity at peroxisome proliferator-activated receptor, gamma (PPAR-γ) which explains its effects on glucose-insulin metabolism.[6] However, it remains unknown whether this is a class-effect or not. A metabolite of losartan, EXP-3174 can also have partial agonistic activity at PPAR-γ receptor.[7]

Regarding the effects of losartan on insulin resistance results have been conflicting. Recently, a few studies have demonstrated the favorable effects of losartan on the glucose-insulin metabolism.[8] A study demonstrated that losartan lowered the relative risk of incidence of type 2 DM by 25% compared to atenolol.[9] However, other studies have failed to demonstrate the insulin resistance lowering effect of losartan.[10,11]

The present study was undertaken with the aim of studying the influence of commonly used antihypertensive drugs losartan and atenolol on glucometabolic parameters in nondiabetic hypertensive patients.

MATERIALS AND METHODS

Study population
Forty nondiabetic patients of mild (systolic blood pressure [SBP]: 140–159 mmHg and/or diastolic blood pressure [DBP]: 90–99 mmHg) to moderate hypertension (SBP: 160–179 mmHg and/or DBP: 100–109 mmHg) between 18 and 75 years, male or female subjects attending medicine out-patient department of a tertiary care hospital and consenting to participate were enrolled in the study. The exclusion criteria were as follows: Type 1 or type 2 DM, secondary hypertension, history of hypersensitivity to ARBs/BB, one or both sided renal artery stenosis, acute or chronic renal failure, serum creatinine ≥2.5 mg/dl, serum potassium >5.5 mEq/l, patients who are known case of chronic obstructive pulmonary disease or bronchial asthma, smokers, patients with significant electrocardiogram abnormality, significant cardiovascular disease, history of hypertensive encephalopathy/stroke/transient ischemic attack (TIA) within last 6 months, pregnant/lactating women, or women intending for pregnancy.

Participants of the study were made aware of the nature and purpose of this study and written informed consent was obtained. The study was conducted after obtaining approval from the Institutional Ethical Committee. This study was done in Unison with the Declaration of Helsinki.

Study design
This was a prospective, randomized controlled, open-label, parallel group study conducted in a tertiary care teaching hospital. The patients included in the study were randomized, using lottery method into two groups of 20 each to receive following treatments orally: Group I: Losartan titrated from 50 to 100 mg daily, Group II: Atenolol titrated from 25 to 100 mg daily. Titration of the doses was done similar to the study by Reneland et al.[12] A rescue therapy of indapamide was given to patients in whom the blood pressure was not controlled on titration to the highest possible doses of individual drugs. Patients received the medicines for 24 weeks and were followed at 12 and 24 weeks to study the effects on SBP, DBP, and heart rate (HR) and following metabolic parameters:

- Fasting plasma glucose (FPG) and fasting plasma insulin (FPI) were measured using standard techniques on samples obtained from the subjects after overnight fasting. Insulin was estimated by enzyme-linked immunosorbent assay technique. The homeostasis model assessment for insulin resistance (HOMA-IR) was computed as:
  HOMA-IR = FPI (μU/ml) × FPG (mmol/L)/22.5
  HOMA-IR: It is a computer model of glucose-insulin interactions proposed by Matthews et al. based on the supposition that is averagely weighing healthy persons under 35 years had 100% β-cell function and labeled having insulin resistance of one.[13] Various studies have correlated the insulin resistance obtained from HOMA-IR with that from the gold standard hyperinsulinemic-euglycemic glucose clamp technique.[14]
- Lipid parameters namely serum high-density lipoprotein cholesterol, serum triglycerides, and total cholesterol were measured using standard methods. Low-density lipoprotein cholesterol levels were calculated using Friedewald's formula.

Blood pressure measurement
Mercury sphygmomanometer with appropriate sized cuff, i.e., to encircle at least 80% of the arm was used to record the blood pressure. Each patient was made to sit for at least 5 min in a chair with feet touching the floor and arm supported at heart level in a private, quiet setting with a comfortable room temperature. The auscultatory method of blood pressure measurement was used. Mean of the two recordings was noted.

Body mass index
Also called as Quetelet index was calculated using formula:

$$BMI = Weight\ (kg)/height\ (m^2)$$

Sample size calculation
The sample size was computed based on earlier studies of Yavuz et al. of the effect of losartan on insulin sensitivity in essential hypertensive patients.[15] The HOMA-IR (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. Assuming alpha risk 5%, power 95%, and ratio of sample size (n2/n1) 1, and then the total sample size required is 18 patients.

Statistical analyzes
Data were analyzed using GraphPad Instat® version 3.10, 32 bit for Windows, GraphPad Software, Inc. 7825 Fay Avenue, Suite 230, La Jolla, CA 92037 USA. Data are stated as means ± SD for data following a normal distribution and expressed as median (range) for the skewed data. After testing the data for normality (Kolmogorov–Smirnov test), intergroup analyses between losartan and atenolol groups for the data at baseline, at 12 weeks and 24 weeks and percent change from baseline till 12 weeks and till 24 weeks were assessed using the unpaired Student's t-test for Gaussian data with or without Welch correction and using Mann–Whitney test for non-Gaussian data.

For intragroup (or within-group) comparison, repeated measure analysis of variance (RM-ANOVA) was applied for comparing different parameters with normal distribution in the same group at different time points. For non-Gaussian data, Kruskal–Wallis test was used. Tukey Kramer test and Dunn's test were used as a posttest with multiple comparisons to detect the group responsible for the difference for the Gaussian and non-Gaussian data, respectively. The results were evaluated at a significance level of $P < 0.05$ and with 95% confidence intervals.

RESULTS

Baseline parameters
A total of 40 patients were enrolled, with 20 randomized to each treatment group, baseline clinical characteristics of study patients are shown in Table 1, and no significant differences were noted between groups for different variables.

Systolic blood pressure, diastolic blood pressure, and heart rate
Intergroup analysis [Table 2] shows no significant difference in the SBP and DBP levels at different times points of follow-up. Intragroup analysis [Table 3] shows that both groups had significant reductions in SBP and DBP levels at the 12 and 24 weeks follow-up ($P < 0.0001$, vs. baseline). At the end of study, atenolol decreased the HR significantly as compared to losartan ($P < 0.0001$).

Fasting plasma glucose, fasting plasma insulin, and homeostasis model assessment for insulin resistance
Intergroup analysis [Table 2] shows the FPG and FPI levels in the two groups are statistically significant at the end of treatment ($P = 0.0018$ and $P < 0.0001$). The HOMA-IR

Table 1: Baseline characteristics of patients in the study groups

Variable	Atenolol (n=20)	Losartan (n=20)	P
Age (year) (range)	53.4±9.28 (40-71)	50.3±9.09 (40-68)	NS
Gender (male/female)	13/7	13/7	
BMI (kg/m²)	23.6±3.39	23.64±4.34	NS
HR (per min)	75.6±7.88	74.3±7.76	NS
SBP (mmHg)	164.3±9.29	163.4±10.52	NS
DBP (mmHg)	95.7±6.43	96.9±8.11	NS
FPG (mg/dL)	101.95±15.26	101.35±8.13	NS
FPI (µIU/mL)	10.83±3.97	11.53±3.61	NS
HOMA-IR	2.79±1.25	2.88±0.91	NS
LDL-C (mg/dL)	114.65±21.78	115.95±27.66	NS
HDL-C (mg/dL)	37.15±10.58	37.8±11.64	NS
TG (mg/dL)	150.75±79.83	152.7±60.31	NS
Total-C (mg/dL)	181.95±28.14	184.29±31.74	NS

Data expressed as mean±SD. NS=Not significant, SD=Standard deviation, BMI=Body mass index, HR=Heart rate, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, FPG=Fasting plasma glucose, FPI=Fasting plasma insulin, HOMA-IR=Homeostasis model assessment for insulin resistance, LDL-C=Low density lipoprotein cholesterol, HDL-C=High-density lipoprotein cholesterol, TG=Triglycerides, Total-C=Total cholesterol

levels in study groups were significantly different at 12 and 24 weeks ($P = 0.0144$ and $P < 0.0001$). Groups were also compared in terms of percent change from baseline to the end of 12 and 24 weeks. Effect of losartan versus atenolol on percent change in HOMA-IR is significant at 12 weeks ($P = 0.0386$) and 24 weeks ($P < 0.0001$) as shown in Figures 1 and 2. Intragroup analysis at 12 and 24 weeks follow-up shows that atenolol increased whereas losartan decreased FPG, FPI, and HOMA-IR levels. The statistical significance levels for these changes compared to baseline are shown in Table 3.

Lipid metabolic parameters
There was no significant difference between the losartan and atenolol groups at 12 and 24 weeks follow-up in the lipid metabolic parameters [Table 2]. Intragroup analysis [Table 3] showed no difference in the levels of different lipid metabolic variables at 12 and 24 weeks follow-up compared to baseline.

DISCUSSION

The present study provides evidence that losartan has an insulin-sensitizing effect in nondiabetic hypertensive patients. Furthermore, the antihypertensive drugs losartan and atenolol have distinct metabolic effects despite similar antihypertensive efficacy.

The results of this study showed that in nondiabetic hypertensive patients, losartan reduced the insulin resistance index, HOMA-IR more than atenolol. Different studies support that ARBs including losartan decrease the

Table 2: Effect of atenolol versus losartan on different variables: Intergroup analysis

Variable	Time points (weeks)	Treatment groups (n=20)		P
		Atenolol	Losartan	
HR (per min)	Baseline	75.6±7.88	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	164.3±9.29	163.4±10.52	NS
	12	154.1±8.16	151.4±11.33	NS
	24	147.9±7.58	146.1±9.18	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 (μIU/mL)	Baseline	10.83±3.97	11.53±3.61	NS
	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	183.65±26.19	181.95±22.04	NS

Data expressed as mean±SD except for non-Gaussian data where data is expressed as median (range). #Unpaired *t*-test with welch correction, $Mann-Whitney test, NS=Not significant, *Significant, **Very significant, ***Extremely significant. SD=Standard deviation, HR=Heart rate, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, FPG=Fasting plasma glucose, FPI=Fasting plasma insulin, HOMA-IR=Homeostasis model assessment for insulin resistance, LDL-C=Low density lipoprotein cholesterol, HDL-C=High-density lipoprotein cholesterol, TG=Triglycerides, Total-C=Total cholesterol

insulin resistance.[16-18] In a study by Jin and Pan Losartan (100 mg daily) was compared with amlodipine (10 mg daily) administered for a period of 3 months in patients of type 2 diabetes with nephropathy. Insulin resistance was measured using HOMA-IR. Significant reductions of FPI concentrations and HOMA-IR were also observed at the end of treatment for the losartan group when compared with the baseline. However, reductions were not statistically significant in comparison to the amlodipine group.[16] In a study by Aksnes *et al.*, insulin resistance was studied by glucose clamp technique in patients of hypertension. Glucose disposal rate were found to be significantly higher after treatment with losartan 100 mg + amlodipine 5 mg compared to amlodipine 10 mg (4.97 ± 0.4 vs. 4.27 ± 0.5 mg/kg/min,

P = 0.039). HOMA-IR levels in the losartan + amlodipine group significantly reduced after 8 weeks compared to the baseline (4.4 ± 0.8 vs. 3.1 ± 0.6, P = 0.007).[17] Nishimura *et al.* studied the effects of losartan (50–100 mg/day) versus a CCB administered for 3 months in patients of impaired glucose tolerance. Losartan caused a significant reduction in HOMA-IR (23.9%).[18]

Renin angiotensin system plays a role in the development of insulin resistance. Angiotensin II induced vasoconstriction may impair the tissue blood flow thereby impairing glucose utilization.[19] In addition, angiotensin II through its AT1 receptor-associated jannus kinase 2 (JAK2) phosphorylates insulin receptor substrate (IRS)-1 which further decreases the activation of phosphatidylinositol (PI) 3-kinase. This action of angiotensin II is implicated to affect the insulin signaling and induce a state of insulin resistance.[20] Angiotensin II is also implicated in upregulation of oxidative stress, which in turn affects insulin sensitivity. Renin angiotensin system is involved in upregulating tumor necrosis factors, TNF-α in skeletal muscle which decreases translocation of glucose transporter (GLUT) thus play a role in inducing insulin resistance. Angiotensin II through its AT1 and AT2 receptors induces adipose tissue hypertrophy and preadipocyte differentiation, respectively. Hypertrophied adipose tissue, in turn, secrete cytokines which are involved in the development of insulin resistance.[21] ARBs may exert beneficial effects on glycemic control through a variety of mechanisms related to the inhibition of angiotensin-II.[22]

Our study is in contrast to the studies which show that losartan does not improve the insulin sensitivity.[10,15,23,24] Bahadir *et al.* investigated the effect of telmisartan (80 mg/day) versus Losartan (50 mg/day) given for 8 weeks on insulin resistance in hypertensive patients with metabolic syndrome where insulin resistance was evaluated by using HOMA-IR. Mean HOMA-IR levels at baseline and at the end of the study, in losartan group were 1.8 ± 0.6 and 1.8 ± 0.6 (P > 0.05).[10] Yavuz *et al.* compared the effects of enalapril (5–40 mg/day) with losartan (50–100 mg/day) administered for 6 months on insulin resistance and endothelial function. HOMA-IR levels for the losartan group decreased from 2.3 + 0.6 to 1.5 + 0.7 at the end of 6 months but this change was not significant (P > 0.05).[15] Huang *et al.* studied the effects of telmisartan against losartan given for 16 weeks on body fat distribution and insulin sensitivity in Chinese patients with hypertension and obesity. HOMA-IR levels showed no improvement in the losartan group.[23] Perl *et al.* studied the vascular, antihypertensive, and metabolic effects of 12 weeks treatment of telmisartan or losartan in patients of hypertension with impaired glucose tolerance. Insulin resistance was assessed by HOMA-IR. Losartan did not show improvement in insulin

Table 3: Effects of atenolol and losartan on different variables at different time points of follow-up: Intragroup analysis

Variable	Treatment groups	At different time points			Posttest (multiple comparison test)		
		Baseline	12 weeks	24 weeks	P (12 weeks vs. baseline)	P (24 weeks vs. baseline)	P (24 weeks vs. 12 weeks)
SBP (mmHg)	Atenolol	164.3±9.29	154.1±8.16	147.9±7.58	<0.0001***	<0.0001***	<0.01**
	Losartan	163.4±10.52	151.4±11.33	146.1±9.18	<0.0001***	<0.0001***	NS
DBP (mmHg)	Atenolol	95.7±6.43	84.2±5.30	83.4±5.58	<0.0001***	<0.0001***	NS
	Losartan	96.9±8.11	87.6±5.67	83.4±4.59	<0.0001***	<0.0001***	<0.05*
HR (per min)	Atenolol	75.6±7.88	64.5±7.13	61.6±6.60	<0.0001***	<0.0001***	NS
	Losartan	74.3±7.76	74.8±6.06	74±5.23	NS	NS	NS
FPG (mg/dL)	Atenolol	101.95±15.26	102.7±15.45	104.9±13.12	NS	NS	NS
	Losartan@	100.5 (89-122)	94.5 (89-112)	94.5 (90-102)	<0.05*	<0.05*	NS
FPI (µIU/mL)	Atenolol	10.837±3.97	12±3.86	16.08±5.24	NS	<0.01**	<0.05*
	Losartan@	12.09 (5.23 -16.6)	8.37 (4.72-25.5)	7.55 (4.90-11.5)	NS	<0.01**	NS
HOMA-IR	Atenolol	2.79±1.25	3.04±1.08	4.12±1.28	NS	<0.01**	<0.05*
	Losartan@	2.84 (1.30-4.47)	2.01 (1.11-5.74)	1.78 (1.10-2.58)	<0.05*	<0.0001***	NS
LDL-C (mg/dL)	Atenolol	114.65±21.78	115.4±20.18	116.65±20.38	NS	NS	NS
	Losartan	115.95±27.66	114.45±20.68	112.45±20.06	NS	NS	NS
HDL-C (mg/dL)	Atenolol	37.15±10.58	36.7±8.35	37.45±10.25	NS	NS	NS
	Losartan	37.8±11.64	38.2±8.67	40.6±7.71	NS	NS	NS
TG (mg/dL)	Atenolol	150.75±79.83	149.45±68.86	147.75±63.14	NS	NS	NS
	Losartan	152.7±60.31	146.2±48.97	144.5±50.25	NS	NS	NS
Total-C (mg/dL)	Atenolol	181.95±28.14	181.99±24.19	183.65±26.19	NS	NS	NS
	Losartan	184.29±31.74	181.89±23.95	181.95±22.04	NS	NS	NS

Data expressed as mean±SD except for non-Gaussian data where data is expressed as median (range). @Kruskal-Wallis test, *Significant, **Very significant, ***Extremely significant. NS=Not significant, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, HR=Heart rate, FPG=Fasting plasma glucose, FPI=Fasting plasma insulin, HOMA-IR=Homeostasis model assessment for insulin resistance, LDL-C=Low density lipoprotein cholesterol, HDL-C=High-density lipoprotein cholesterol, TG=Triglycerides, Total-C=Total cholesterol, SD=Standard deviation
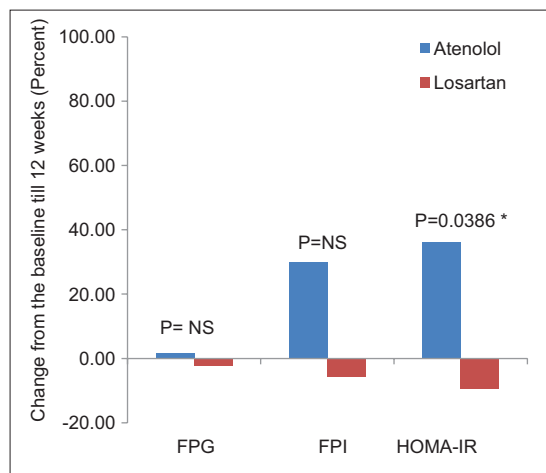

Figure 1: Effect of atenolol versus losartan on glucometabolic factors after 12 weeks. FPG: Fasting plasma glucose, FPI = Fasting plasma insulin, HOMA-IR = Homeostasis model assessment index-insulin resistance, NS = Not significant, * = Significant
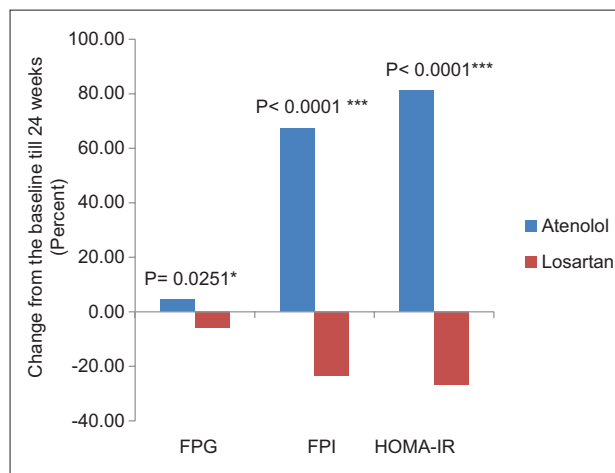

Figure 2: Effect of atenolol versus losartan on glucometabolic factors after 24 weeks. FPG: Fasting plasma glucose, FPI = Fasting plasma insulin, HOMA-IR = Homeostasis model assessment index-insulin resistance, NS = Not significant, * = Significant, *** = Extremely significant

sensitivity (baseline: 3.04 ± 0.60, after losartan treatment: 3.38 ± 0.84, $P > 0.05$).[24]

In a study by Moan et al., losartan was administered at a dose of 50–100 mg/day for 4 weeks in patients of mild hypertension. Euglycemic glucose clamp technique was used to evaluate the effects on glucose insulin metabolism. Losartan did not

significantly alter insulin sensitivity.[25] Same author found that losartan significantly improved the insulin sensitivity in severe hypertensive patients.[26] The discrepancy between these studies and our study might because of differences in the dose of losartan, duration of the treatment, severity of hypertension, or other unknown variables.

Our study shows that insulin sensitivity is decreased in atenolol group. Results of this study in relation to the effects of atenolol on glucose-insulin metabolism match with that of previous studies.[12,27] BB may affect insulin sensitivity and glycemic control in different ways. Antagonism at the pancreatic β2 receptors reduces the insulin release. This effect is more pronounced with nonselective BBs but can also be seen with higher doses of β1 selective blockers. Insulin sensitivity is further impaired by weight gain associated with the use of BBs. In normal people, vasodilatation induced by insulin increases blood flow to the skeletal muscles. Nonselective BBs decrease blood flows to muscles because of unrestricted α1-activity mediated vasoconstriction. This compromises insulin-stimulated glucose uptake and leads to a state of insulin resistance.[28] BBs affect the first phase of insulin secretion by reducing β2-mediated insulin release. Attenuation of the early phase of insulin secretion is an important predictor of the development of type 2 DM.[29]

This study emphasizes the importance of choosing an antihypertensive drug that does not increase the risk of developing DM in patients of hypertension.

CONCLUSION

The findings of this study showed that irrespective of the similar antihypertensive efficacy, losartan improved while atenolol worsened insulin resistance in nondiabetic hypertensive patients. Losartan appears to be superior to atenolol as far as the effects on the glucometabolic parameters are concerned. Further studies are needed to elucidate the mechanisms by which losartan improves insulin sensitivity.

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Conflicts of interest
There are no conflicts of interest.

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