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EFFICACY OF TELMISARTAN TO OTHER ANTI-HYPERTENSIVE DRUGS ON INSULIN SENSITIVITY

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ABSTRACT

Background: In individuals with hypertension and diabetes mellitus, elevated ET-1 (endothelin) levels and the existence of insulin resistance are important factors that lead to renal and cardiovascular complications. But in India, these subjects are not sufficiently studied.

Aim: The objective is to compare the effectiveness of telmisartan with other widely used anti-hypertensive medications in terms of insulin sensitivity with respect to HOMA-IR in individuals with diabetic hypertension.

Methods: 140 participants who reported to the Institute during the specified study period and had both diabetes and hypertension were evaluated. These subjects were split into two equal groups, with Group I subjects (n = 68) receiving telmisartan and Group II subjects (n = 72) receiving other antihypertensive medications for 12 weeks, including ramipril in 4 subjects, cilnidipine in 24 subjects, and amlodipine in 44 subjects. Change in insulin sensitivity on HOMA-IR was the primary outcome measured, and ET-1 levels were the secondary outcome.

Results: At baseline, the median HOMA-IR levels were 3.9 (2.0-5.7) for telmisartan and 3.7 (2.9-5.7) for another group. When compared to other antihypertensive groups, telmisartan significantly reduced median HOMA-IR after 12 weeks of treatment (p=0.001). Comparable outcomes were observed for ET-1, whose levels dropped in both groups after 12 weeks with a non-significant difference and p=0.88.

Conclusion: When compared to other antihypertensive medications, telmisartan dramatically increases insulin sensitivity after 12 weeks in individuals with type 2 diabetes and hypertension. ET-1 levels, however, showed a similar impact on endothelial function in both groups. Positive metabolic effects of telmisartan may aid in the management of macro and microvascular complications.

Keywords: Antihypertensives, Diabetes mellitus, Endothelin-1, HOMA-IR, Hypertension, Insulin resistance

INTRODUCTION

90% of cases of diabetes mellitus are caused by insulin resistance in afflicted individuals, which results in type 2 diabetes mellitus, a condition marked by hyperglycemia. Nearly 50–80% of individuals with type 2 diabetes mellitus have hypertension, indicating a shared pathophysiology. The overactivation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), which promotes the release of cytokines and endothelin-1 (ET-1), vascular shear stress, and oxidative stress, is the cause of this two-way relationship between T2DM and hypertension. Insulin resistance is characterized by hyperinsulinemia, which stimulates the production of ET-1 through a mitogen-activated protein kinase (MAPK)-dependent pathway that increases subsequent hypertension, arterial stiffening, and vascular insulin resistance.[1]

Despite being a popular anti-diabetic medication, metformin does not considerably lower the HOMA-IR (homeostatic model assessment for insulin resistance) for fasting blood glucose after six months. Additionally, individuals with diabetic hypertensives receive inadequate treatment for insulin resistance, which exacerbates the condition. Additionally, polypharmacy, poor glycaemic control, low adherence, and associated vascular complications make managing diabetic hypertension difficult. Angiotensin receptor blockers (ARBs) like telmisartan have been evaluated for partial PPAR-γ agonist activity (PPAR-γ) in a significant body of existing literature. One possible explanation is that PPAR-γ improves insulin sensitivity throughout the body by inhibiting the proliferation of fibroblasts and vascular smooth muscle cells, which lowers inflammation. The pleiotropic effects of calcium channel blockers (CCBs) in diabetic hypertension have also been evaluated.[2]

When compared to non-diabetic normotensive obese subjects, amlodipine significantly lowers fasting insulin and HOMA-IR in obese diabetic hypertensives. Conversely, in hypertensive subjects without pre-existing type 2 diabetes mellitus, other studies have found a higher incidence of diabetes with CCBs compared to ACEIs or ARBs, indicating the need for additional research, especially in developing countries like India. Although a few studies showed that both CCBs and ARBs improve endothelial function, it is still unclear which medication is better. While CCBs are said to have antioxidant qualities that both improve endothelial function and restore nitric oxide (NO) availability, telmisartan has been shown to improve endothelial health.[3]

There are conflicting findings in the literature, with some studies supporting the use of CCBs while others claim that ARBs are more effective. There aren't many studies comparing telmisartan to ARBs for improving metabolic markers like fasting blood sugar levels, and there aren't many that compare it to other antihypertensive medications like ACEIs and CCBs. Furthermore, these comparisons have not been made in an Indian context, which restricts how broadly they can be applied. There is conflicting evidence regarding the effects of telmisartan on ET-1, HOMA-IR, and fasting insulin; some studies show no benefit, while others show benefits.4 The purpose of the current study was to compare the effectiveness of telmisartan with other widely used anti-hypertensive medications on insulin sensitivity with regard to HOMA-IR in individuals with diabetic hypertension.

MATERIALS AND METHODS

The purpose of the current prospective randomized clinical study was to compare the effectiveness of telmisartan with other widely used anti-hypertensive medications on insulin sensitivity with regard to HOMA-IR in individuals with diabetic hypertension. The Institute's Department of Medicine provided the study participants. Prior to their involvement in the study, all participants provided written and verbal informed consent.

The study evaluated 140 participants who reported to the Institute during the specified study period and had both diabetes and hypertension. These subjects were split into two equal groups, with Group I subjects (n = 68) receiving telmisartan and Group II subjects (n = 72) receiving other antihypertensive medications for 12 weeks, including ramipril in 4 subjects, cilnidipine in 24 subjects, and amlodipine in 44 subjects.

Adult subjects of any gender between the ages of 18 and 75 who had a history of type 2 diabetes mellitus and a HbA1c in the range of 7 to 10% on dipeptidyl peptidase-4 (DPP-4) inhibitors, sulphonylureas (SU), metformin, or a combination of these medications, as well as newly diagnosed hypertension with a mean systolic blood pressure (mean SBP) of at least twice using a validated sphygmomanometer. Lactating and pregnant women, people with type 1 diabetes mellitus, people taking steroids, immunosuppressants, insulin, traumatic brain injury, ischemic hemorrhagic stroke, heart failure, and people with an active cancer diagnosis were all excluded from the study.

Following the start of the intervention, each subject was monitored for 12 weeks. Along with taking a blood sample, the blood pressure was measured at baseline and after 12 weeks. Ramipril 2.5 mg OD, cilnidipine 10 mg OD, amlodipine 5 mg OD, and telmisartan 40 mg OD were the maintenance stable doses used to continue the antihypertensive treatment. Throughout the study, no subject received an escalation dose.

Change in insulin sensitivity on HOMA-IR after 12 weeks was the main outcome evaluated, and ET-1 levels before and after the treatment were the secondary outcome. Before the initial antihypertensive dose and at 12 weeks, fasting blood samples were drawn intravenously under stringent aseptic conditions. A chemiluminescence immunoassay analyzer was used to measure fasting insulin.

HOMA-IR (fasting glucose (mmol/L) × fasting insulin (μU/mL)/22.5) was used to estimate insulin resistance. Competitive enzyme-linked immunosorbent assay (ELISA) was used to measure serum ET-1 in fasting samples at baseline and 12 weeks. Throughout the entire study, participants were asked to report any adverse events in order to monitor their safety and adherence. Monthly phone follow-ups and pill counting during visits were used to gauge therapy

adherence. If any SAEs (serious adverse events) occurred, they were reported and documented in accordance with standard pharmacovigilance protocols.

Statistical tests, including the chi-square test, Fisher's exact test, Mann Whitney U test, and SPSS, were used to analyze the data. The significance level was considered at a p-value of <0.05.

RESULTS

The purpose of the current prospective randomized clinical study was to compare the effectiveness of telmisartan with other widely used anti-hypertensive medications on insulin sensitivity with regard to HOMA-IR in individuals with diabetic hypertension. The study evaluated 140 participants who reported to the Institute during the specified study period and had both diabetes and hypertension. These subjects were split into two equal groups, with Group I subjects (n = 68) receiving telmisartan and Group II subjects (n = 72) receiving other antihypertensive medications for 12 weeks, including ramipril in 4 subjects, cilnidipine in 24 subjects, and amlodipine in 44 subjects. With p=0.14, the mean age and gender distribution of study participants taking telmisartan and those in other groups were statistically comparable.

The baseline mean systolic blood pressure, mean diastolic blood pressure, fasting insulin, and fasting blood sugar levels all showed similar non-significant differences (p=0.82, 0.13, 0.61, 0.54, and 0.15, respectively). Additionally, the two study groups' Endothelin-1 and HOMA-IR levels were statistically comparable, at 0.57 and 0.34, respectively. The two study groups' use of anti-diabetic medications was likewise similar, with p=0.719 (Table 1).

According to the study's findings, the telmisartan and other medication groups' ET-1 levels were similar in terms of intergroup comparison for changes in vascular and metabolic parameters after 12 weeks in research participants (p=0.88). Fasting blood glucose levels showed similar results, with p=0.07 for telmisartan and other groups.

However, HOMA-IR was significantly lower in the telmisartan group compared to the other medicine group (p<0.001), and fasting insulin levels were significantly higher in the other medicine group and significantly lower in the telmisartan group (Table 2).

ET-1 levels at baseline were 19.21 and at follow-up were 12.2, which was significantly higher at baseline (p<0.001) for intragroup changes in vascular and metabolic variables in the telmisartan group. At baseline, fasting blood glucose levels were 133 mg/dl; at the 12-week follow-up, they were 118 mg/dl, a significant decrease with p<0.001. At baseline, fasting insulin levels were 12.07; at 12 weeks, they significantly dropped to 5.63 (p<0.001). Additionally, HOMA-IR levels dropped significantly (p<0.001) between baseline and 12 weeks (Table 3).

ET-1 values significantly dropped from baseline to the 12-week follow-up period, with a p-value of less than 0.001, when evaluating intergroup changes in vascular and metabolic variables in the other antihypertensive group. However, fasting blood glucose, fasting insulin, and HOMA-IR values did not significantly change from baseline to 12 weeks (p-values of 0.24, 0.15, and 0.12, respectively) (Table 4).

DISCUSSION

The current study evaluated 140 participants who reported to the Institute within the specified study period and had both diabetes and hypertension. These subjects were split into two equal groups, with Group I subjects (n = 68) receiving telmisartan and Group II subjects (n = 72) receiving other antihypertensive medications for 12 weeks, including ramipril in 4 subjects, cilnidipine in 24 subjects, and amlodipine in 44 subjects.

With p=0.14, the mean age and gender distribution of study participants taking telmisartan and those in other groups were statistically comparable. The baseline mean systolic blood pressure, mean diastolic blood pressure, fasting insulin, and fasting blood sugar levels all showed similar non-significant differences (p=0.82, 0.13, 0.61, 0.54, and 0.15, respectively). Additionally, the two study groups' Endothelin-1 and HOMA-IR levels were statistically comparable, at 0.57 and 0.34, respectively. The two study groups' anti-diabetic medication intake was likewise similar (p=0.719). These findings were similar to those of earlier research by Tehrani AY et al.5 in 2022 and Ayza MA et al.6 in 2020, in which the authors evaluated participants with clinical and demographic characteristics of diabetes and hypertension.

ET-1 levels were similar in the telmisartan and other medication groups with p=0.88 when it came to intergroup comparison for changes in vascular and metabolic parameters in study participants after 12 weeks. Fasting blood glucose levels showed similar results, with p=0.07 for telmisartan and other groups. However, HOMA-IR was significantly lower in the telmisartan group compared to the other medicine group (p<0.001), and fasting insulin levels were significantly higher in the other medicine group and significantly lower in the telmisartan group. These findings were in line with those of Ersoy C et al. (7) and Liontos A et al. (8), who also reported comparable changes in vascular and metabolic parameters following different antihypertensives.

The telmisartan group's ET-1 level was 19,21 at baseline and 12.2 at follow-up, which was significantly higher at baseline with $p<0.001$ for intragroup changes in vascular and metabolic variables. At baseline, fasting blood glucose levels were 133 mg/dl; at the 12-week follow-up, they were 118 mg/dl, a significant decrease with $p<0.001$. At baseline, fasting insulin levels were 12.07; at 12 weeks, they significantly dropped to 5.63 ($p<0.001$). HOMA-IR levels also dropped significantly ($p<0.001$) between baseline and 12 weeks. These results were consistent with those of Fukao K et al. (9) and Cakir L et al. (10), who reported similar vascular and metabolic variables following telmisartan use.

When evaluating the intergroup changes in vascular and metabolic variables in the other antihypertensive group, ET-1 values showed a significant decrease from baseline to the 12-week follow-up period (p-value <0.001). However, fasting blood glucose, fasting insulin, and HOMA-IR values showed a non-significant change from baseline to 12 weeks, with p-values of 0.24, 0.15, and 0.12, respectively. These results were consistent with those of Gomaz SM et al and Saeed ZI et al, who reported similar changes in vascular and metabolic variables following antihypertensive medication.

CONCLUSION

Telmisartan considerably increases insulin sensitivity in subjects with hypertension and type 2 diabetes mellitus after 12 weeks when compared to other antihypertensive medications, the current study concludes despite its limitations. ET-1 levels, however, showed a similar impact on endothelial function in both groups. Compared to other antihypertensive medications, telmisartan has favorable metabolic effects in addition to its antihypertensive action that may aid in the management of macro and microvascular complications.

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S. No	Characteristics	Others (n=72)	Telmisartan (n=68)	Overall (n=140)	p-value
1.	**Mean age (years)**	53±8.8	55.8±7.6	54.8±7.7	0.14
2.	**Gender**				
a)	Male	34	30	64	
b)	Female	38	38	76	
3.	**Mean systolic BP**	143 (142, 146)	145 (142,146)	143 (142,146)	0.82
4.	**Mean diastolic BP**	88 (88, 90)	88 (88, 90)	88 (88, 90)	0.13
5.	**Endothelin-1**	16.9 (10.1, 26.46)	19 (10.6-29.7)	18 (10.1, 29.4)	0.57
6.	**HOMA-IR**	3.7 (2.9, 5.7)	3.9 (2.0, 5.7)	3.8 (2.3, 5.8)	0.34
7.	**Fasting blood sugar**	154 (127, 174)	133 (114, 160)	143 (118, 173)	0.15
8.	**Fasting insulin**	13 (16, 16)	10 (3, 15)	9 (5, 15)	0.54
9.	**HbA1c**	7.5 (7.18-8.63)	7.7 (7.21, 8.73)	7.6 (7.0, 8.5)	0.61
10.	**Anti-diabetic drugs n (%)**				
a)	Metformin+ sulfonyl urea+ dipeptidyl peptidase 4 inhibitor	26 (36)	28 (41.7)	54	0.719
b)	Metformin + dipeptidyl peptidase 4 inhibitor	18 (25)	6 (23.)	34	
c)	Metformin+ sulfonyl urea	28 (39)	24 (35)	52	

Table 1: Demographic and clinical data in study subjects at baseline

S. No	Parameter	Telmisartan (n=68)	Others (n=72)	p-value
1.	**ET-1**	12.2 (5.60, 18.72)	11.0 (4.82, 23.0)	0.88
2.	**Fasting blood glucose**	118 (107, 128)	122 (113, 196)	0.07
3.	**Fasting insulin**	5.5 (3.6, 8.9)	9.6 (7.0, 11.9)	**0.001**
4.	**HOMA-IR**	1.77 (1.28, 2.61)	3.43 (2.41, 5.10)	**<0.001**

Table 2: Intergroup comparison for changes in vascular and metabolic parameters after 12 weeks in study subjects

S. No	Parameter	Baseline median IQR	Follow-up median IQR	p-value
1.	**ET-1**	19.21 (20.77- 29.92)	12.2 (5.64-18.72)	**<0.001**
2.	**Fasting blood glucose**	133 (116.23-161.48)	118 (109.23-129.98)	**<0.001**
3.	**Fasting insulin**	12.07 (5.28-16.70)	5.63 (3.73- 9.09)	**<0.001**
4.	**HOMA-IR**	4.11 (2.22-5.88)	1.77 (1.28-2.61)	**<0.001**

Table 3: Intragroup changes in vascular and metabolic variables in telmisartan group

S. No	Parameter	Baseline median IQR	Follow-up median IQR	p-value
1.	**ET-1**	17.14 (10.28- 26.46)	11.21 (4.82-23.24)	**<0.001**
2.	**Fasting blood glucose**	156 (128.48-176)	124 (115-197.48)	0.24
3.	**Fasting insulin**	10.93 (7.96-17.87)	9.73 (7.20- 12.12)	0.15
4.	**HOMA-IR**	3.93 (3.08-5.86)	3.43 (2.41-5.14)	0.12

Table 4: Intragroup changes in vascular and metabolic variables in other antihypertensives group