

Original Article

Telmisartan vs. other antihypertensives on cardiometabolic and vascular outcomes in diabetic hypertension: A randomised trial

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Background and objectives: Insulin resistance and elevated endothelin-1 (ET-1) levels are key contributors to cardiovascular and renal complications in patients with type 2 diabetes mellitus (T2DM) and hypertension. This study compared the effects of telmisartan with other commonly used antihypertensive agents on insulin sensitivity in terms of homeostatic model assessment for insulin resistance (HOMA-IR) and vascular endothelial function in terms of ET-1 levels in patients with T2DM and hypertension.

Methods: In this randomised, open-label study, 182 patients with coexisting T2DM and hypertension were screened between May 2023 and September 2024. The study was registered with the Clinical Trials Registry–India (CTRI; CTRI/2023/04/051878). Seventy eligible patients were enrolled and randomised 1:1 to receive telmisartan (n=34) or other antihypertensive agents (amlodipine, n=22; cilnidipine, n=12; ramipril, n=2; total n=36) for 12 weeks. The primary outcome was the change in insulin sensitivity as measured by the HOMA-IR. ET-1 levels were evaluated as a secondary outcome.

Results: At baseline, the median HOMA-IR values were 4.1 [interquartile range (IQR): 2.2–5.9] in the telmisartan group and 3.9 (IQR: 3.1–5.9) in the comparator group. After 12 weeks, the median HOMA-IR significantly decreased in the telmisartan group to 1.79 (IQR: 1.30–2.63) compared to 3.45 (IQR: 2.43–5.12) in the other antihypertensive group ($P=0.001$). Baseline ET-1 levels were 19.23 pg/mL (IQR: 10.8–29.9) and 17.1 pg/mL (IQR: 10.3–26.48) in the telmisartan and comparator groups, respectively. At 12 weeks, median ET-1 levels decreased to 12.49 pg/mL (IQR: 5.70–18.70) and 11.22 pg/mL (IQR: 4.84–23.20), respectively ($P=0.90$).

Interpretation and conclusions: Telmisartan significantly improved insulin sensitivity at 12 weeks compared to other antihypertensive agents in patients with T2DM and hypertension. However, the reduction in ET-1 levels was similar across groups, suggesting a comparable effect on endothelial function over 12 weeks. These findings suggest that, beyond its antihypertensive action, telmisartan may offer favourable metabolic benefits that could help limit diabetes-related micro- and macrovascular complications compared with other commonly prescribed antihypertensives.

Keywords Antihypertensive agents; Diabetes mellitus; Endothelin-1; Hypertension; Insulin resistance

Diabetes mellitus is a spectrum of disorders characterised by hyperglycaemia, with 90% of cases due to the insulin-resistant form, Type 2 Diabetes Mellitus (T2DM).¹ Hypertension (HTN) occurs in 50–80% of people with T2DM, reflecting shared pathophysiology.^{2,3} This bidirectional relationship between HTN and T2DM,⁴ is driven by over activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic system, which promote oxidative

stress, vascular shear stress, and the release of cytokines and endothelin-1 (ET-1).⁵ Hyperinsulinemia, a hallmark of insulin resistance, also promotes the production of ET-1 through a mitogen-activated protein kinase (MAPK)-dependent pathway,^{6,7} augmenting vascular insulin resistance, arterial stiffening, and subsequent hypertension.⁸⁻¹⁰

Biguanides and thiazolidinediones are known insulin-sensitizing agents.¹¹⁻¹³ However, a systematic

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review and meta-analysis (SRMA) of 11 trials in obese/overweight children and adolescents found that metformin did not significantly reduce homeostatic model assessment for insulin resistance (HOMA-IR) or fasting glucose beyond 6 months.¹⁴ Another SRMA in T2DM patients reported thiazolidinediones improved insulin sensitivity indices such as quantitative insulin sensitivity check index (QUICKI) and homeostatic model assessment for insulin sensitivity (HOMA-S) more than metformin ($P = 0.003$),¹⁵ but their adverse effects as full peroxisome proliferator activated receptor gamma (PPAR- γ) agonists limit their use.¹² Consequently, insulin resistance remains sub optimally managed in diabetic hypertensives, contributing to disease progression. Furthermore, management of diabetic hypertension is challenging due to polypharmacy, poor glycaemic control, low adherence, and associated vascular complications.¹⁶⁻¹⁸

Telmisartan, is an angiotensin receptor blocker (ARB) studied for its partial PPAR- γ agonist activity (PPAR- γ) in many preclinical and clinical studies.¹⁹ The possible mechanism explained is the PPAR- γ mediated improvement of whole-body insulin sensitivity, exerting anti-proliferative effects on vascular smooth muscle cells and fibroblasts thereby reducing inflammation.¹⁹⁻²² Similarly, calcium channel blockers (CCBs) have been investigated for pleiotropic effects in diabetic hypertension. A trial on amlodipine showed significant reductions in HOMA-IR and fasting insulin in obese diabetic hypertensive patients compared with normotensive non diabetic obese subjects.²³ In contrast, a meta-analysis reported a higher incidence of diabetes with CCBs than with angiotensin converting enzyme inhibitors (ACEIs) or ARBs, in hypertensives without pre-existing T2DM,²⁴ highlighting the need for further research across diverse populations.

Some clinical studies indicate that both ARBs and CCBs positively impact endothelial function, but the superiority of one class over the other remains unclear. Telmisartan has been shown to improve endothelial health^{25,26} whereas studies on CCBs suggest they possess antioxidant properties that restore nitric oxide (NO) availability, thereby also improving endothelial function.²⁷ However, existing evidence is mixed, with some studies favouring CCBs^{28,29} while others support the superior efficacy of ARBs.³⁰⁻³²

Although a systematic review has shown telmisartan's superiority over other ARBs in improving metabolic markers such as fasting plasma glucose,³³ comprehensive comparisons against a broader, more

diverse group of first-line antihypertensive agents, such as CCBs and ACEIs, are lacking. Moreover, these effects have not been evaluated in the Indian population, limiting generalizability. Evidence on telmisartan's impact on fasting insulin, HOMA-IR, and ET-1 is also mixed, with some studies reporting no significant changes³⁴ and others showing benefits.^{35,36} This randomized controlled trial aims to compare telmisartan's effect on insulin resistance and endothelial dysfunction against a composite group of commonly prescribed first-line antihypertensives in patients of T2DM with hypertension.

Methods

This was a prospective, randomised, active-controlled, parallel-group, open-label clinical trial study which was conducted by the department of Pharmacology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India after obtaining the ethical approval from the Institutional Ethics Committee (IEC) and subsequently registered with the Clinical Trials Registry-India (CTRI; CTRI/2023/04/051878).

Study design and randomisation: Patient recruitment began after clinical trial registration. (Eligible participants, after screening, were randomly allocated in a 1:1 ratio to either the telmisartan group or a comparator group receiving an alternative antihypertensive agent (excluding ARBs) in optimal once-daily doses, as decided by the treating physician. Written informed consent was obtained from all participants prior to enrolment. Randomisation was carried out using a permuted block sequence (blocks of size six and eight) generated with online software. The allocation sequence was concealed by the principal investigator, and during enrolment, the junior resident disclosed the group assignment to the treating physician only after confirmation with the principal investigator.

Inclusion/exclusion criteria: All adult patients of either sex and aged between 18 and 75 yr who visited the General medicine or Endocrinology outpatient department with previously diagnosed T2DM and an HbA1C value between 7% and 10% and taking metformin, sulphonylureas (SU), dipeptidyl peptidase-4 (DPP-4) inhibitors, or combination of any of these class of medications and newly diagnosed hypertension with office mean systolic blood pressure (mean SBP) of ≥ 140 mmHg and office mean diastolic BP of ≥ 90 mmHg (3 measurements taken 1 min apart and calculating the mean of the last 2 readings) measured manually using validated sphygmomanometer for at

least two occasions were included in the study. Those who were pregnant/lactating/diagnosed with type 1 diabetes mellitus/on insulin/immunosuppressants/steroid therapy/diagnosed with active malignancy/heart failure/stroke- either ischemic haemorrhagic/traumatic brain injury (TBI) was excluded from the study.³⁷

Patient recruitment and follow up: The study duration was two years. Participants were followed up for 12 weeks after starting the intervention. The assessment of office blood pressure and blood sample collection was done at baseline and at 12 weeks of starting the allocated treatment. Recruitment was conducted over the predefined study period, and enrolment was closed when the study duration ended. Although the estimated sample size was 65, a total of 70 patients were recruited. Of these, 60 patients completed the full follow up protocol. The efficacy analyses were conducted according to the intention-to-treat principle, with all 70 enrolled patients included in the final analysis.³⁶ Missing data were addressed using regression imputation, incorporating baseline and other observed covariates to generate predicted values. The antihypertensive therapy was maintained at stable doses (telmisartan 40 mg OD/amlodipine 5 mg OD/cilnidipine 10 mg OD/ramipril 2.5 mg OD) throughout the study, and no dose escalation was done during the trial period.

Outcomes and assessments: The primary endpoint was the change in insulin sensitivity after 12 weeks of treatment, assessed using HOMA-IR. The secondary endpoint was the change in serum ET-1 concentrations before and after the treatment. Fasting blood samples were collected before the first antihypertensive dose and at 12 weeks. Fasting insulin was measured on a Liaison chemiluminescence immunoassay analyser and plasma glucose on a Beckman Coulter AU 680. Insulin resistance was estimated using HOMA-IR (fasting glucose (mmol/L) × fasting insulin (μU/mL)/22.5). Serum ET-1 was quantified by competitive enzyme-linked immunosorbent assay (ELISA) on fasting samples at baseline and 12 weeks.

Safety monitoring and adherence: Participants were instructed to report adverse events at any time during the treatment period. Adherence to therapy was evaluated through monthly telephone follow-ups and by pill count verification during clinic visits. Serious adverse events (SAEs), if observed, were

recorded and reported in accordance with standard pharmacovigilance guidelines.

Sample size: Assuming 80% power, α error of 0.5, and an effect size of 0.8 for HOMA-IR using the G power software, the calculated sample size was 52 patients (26 in each group). Assuming a dropout rate of 20%, 65 patients were expected to be recruited.

Statistical analysis: Analyses of end points were performed on the intention-to-treat (ITT) population, defined as all randomized subjects who had taken at least one dose of anti-hypertensive medication. To ensure adequate sample size for meaningful comparison, participants receiving amlodipine (n=22), cilnidipine (n=12), and ramipril (n=2) were combined into a single “other antihypertensives” group (N=36), as the numbers in each individual drug class were insufficient for separate analysis. Data were presented as mean ± standard deviation (SD), or as median and interquartile range (IQR) depending upon the distribution. Data were checked for normality using Shapiro-Wilk test. Independent Student t-test was used to compare quantitative variables between two groups (Mann-Whitney U test, if data do not follow normal distribution). Chi-square test was used to compare categorical variables. Intragroup differences were evaluated by paired t-test or Wilcoxon signed rank test for non-parametric data. $P < 0.05$ was considered statistically significant. Statistical analysis was done using SPSS version 22 (IBM Corp., NY, USA).

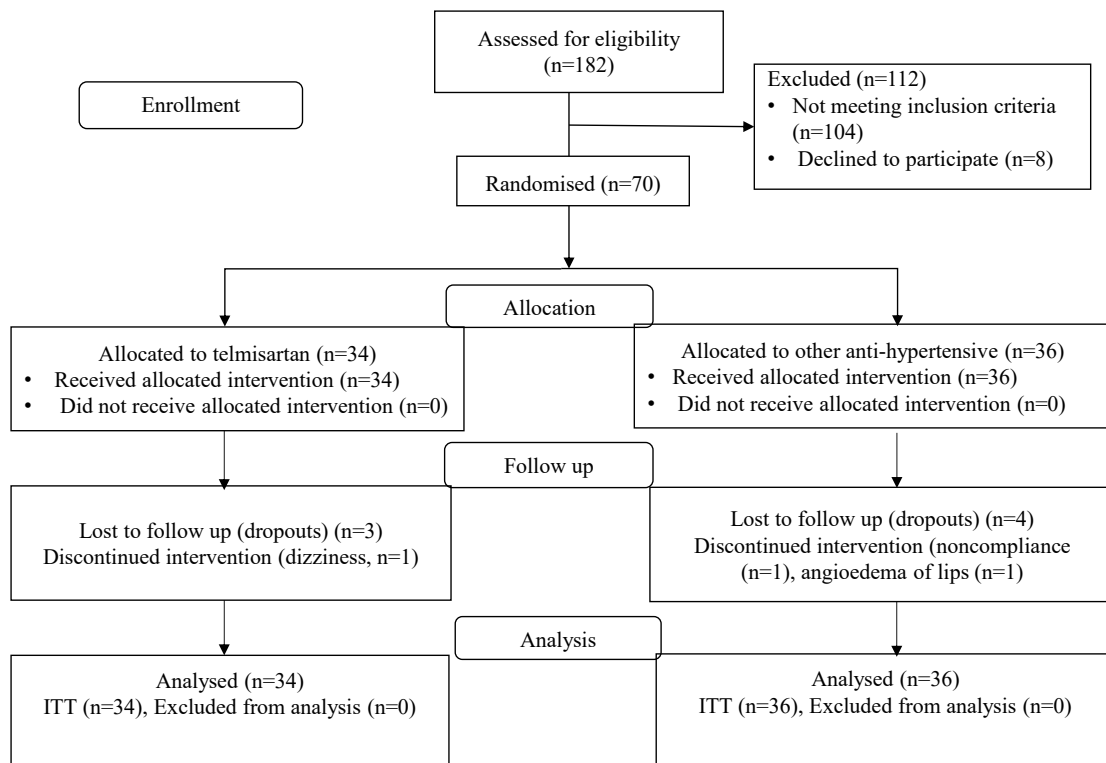
Results

Between May 2023 and September 2024, a total of 182 patients with type 2 diabetes mellitus and newly diagnosed hypertension were screened. Of these, 70 eligible participants were enrolled and randomised in a 1:1 ratio to receive either telmisartan (n=34) or other antihypertensive agents [amlodipine (n=22), cilnidipine (n=12), ramipril (n=2); total n=36]. Sixty participants completed the 12-week follow up; however, all 70 were included in ITT analysis. Baseline demographic and clinical characteristics were comparable across study arms (**Table I**). Concomitant use of standard antihyperglycaemic agents (metformin, sulfonylureas, and DPP-4 inhibitors) was permitted as per ongoing prescriptions, with similar distribution between groups³⁶ (**Table I**). Three participants discontinued treatment: one in the telmisartan group due to dizziness, and two in the comparator group; one owing to ramipril-induced angioedema and the other

Table I. Baseline demographic and clinical characteristics of study participants

Baseline characteristics	Overall (N=70)	Telmisartan (n=34)	Other anti-hypertensive(s) (n=36)	P value
Age (yr) [#]	55 (8)	56 (8)	53(9)	0.16
Sex (Female/Male)	38/32	19/15	19/17	-
Mean diastolic BP [§]	90 (90,92)	90 (90,92)	90 (90,92)	0.11
Mean systolic BP [§]	145 (144,148)	145 (144, 148)	145 (144, 148)	0.84
HbA1C [§]	7.8 (7.2, 8.7)	7.9 (7.23, 8.75)	7.7 (7.20, 8.65)	0.63
F _{INS} (µL/mL) [§]	11 (7, 17)	12 (5,17)	11 (8,18)	0.56
Fasting plasma glucose [§] (mg/dL)	145 (120, 175)	135 (116, 162)	156 (129,176)	0.17
HOMA-IR [§]	4.0 (2.5, 6.0)	4.1 (2.2, 5.9)	3.9 (3.1,5.9)	0.36
Endothelin-1 [§] (pg/mL)	18.2 (10.3–29.6)	19.2 (10.8–29.9)	17.1 (10.3-26.48)	0.59
Anti-diabetic medications, n (%)				
MF + SU	26	12 (35.3%)	14 (38.8%)	0.721
MF + DPP-4i	17	8 (23.5%)	9 (25%)	
MF+ SU+ DPP-4i	27	14 (41.7%)	13 (36.1%)	

[#]mean (Standard Deviation); [§]median (interquartile range); N, total number of patients; n, number of patients in each group; BP, blood pressure; F_{INS}, fasting insulin; HOMA-IR, homeostasis model assessment for insulin resistance; MF, metformin; SU, sulphonyl urea; DPP-4i, dipeptidyl peptidase-4 inhibitors

**Figure.** Participant flow diagram (CONSORT) illustrating recruitment, allocation, follow up, and analysis.

due to noncompliance after switching to ayurvedic medication. No serious adverse events occurred. Overall medication adherence was high, as confirmed

through monthly telephone follow ups and pill count verification at clinic visits. Details of participant flow are summarized in **Figure**.

Table II. Between-group comparison of changes in metabolic and vascular parameters at 12 weeks (Mann–Whitney U test)

Variable	Telmisartan (n=34) Median (IQR)	Other anti-hypertensives (n=36) Median (IQR)	<i>P</i> value (2 sided)
HOMA-IR	1.79 (1.30, 2.63)	3.45 (2.43, 5.12)	<0.001*
F _{INS}	5.7 (3.8,9.1)	9.8 (7.2, 12.1)	0.002*
FPG	120 (109, 130)	124 (115,198)	0.06
ET-1	12.4 (5.62, 18.74)	11.2 (4.84, 23.2)	0.90

*P** < 0.05. HOMA-IR, homeostatic model assessment for insulin resistance; F_{INS}, fasting insulin; FPG, fasting plasma glucose; ET-1, endothelin-1; IQR, inter quartile range

Table III. Within-group changes in metabolic and vascular parameters in the telmisartan group (Wilcoxon signed-rank test)

Variable	Baseline Median (IQR)	Follow up Median (IQR)	Median difference (IQR)	95% CI	<i>P</i> value
HOMA-IR	4.13 (2.24-5.90)	1.79 (1.30-2.63)	-1.41 (-4.13, -0.49)	-2.21, -0.63	<0.001*
F _{INS}	12.09 (5.30-16.72)	5.65 (3.75-9.11)	-3.34 (-10.04, -0.59)	-5.04, -1.20	<0.001*
FPG	135 (116.25-161.50)	120 (109.25-130.00)	-10.50 (-35.75, -4.75)	-24.51, -8.00	<0.001*
ET-1	19.23 (10.79–29.94)	12.4 (5.62, 18.74)	-6.83 (-13.40, -3.55)	-10.71, -4.40	<0.001*

*P** < 0.05. CI, confidence interval

Table IV. Within-group comparison of metabolic and vascular parameters in the comparator group (amlodipine/cilnidipine/ramipril group) using Wilcoxon signed-rank test

Variable	Baseline median (IQR)	Follow up median (IQR)	Median difference (IQR)	95% CI	<i>P</i> value
HOMA-IR	3.91 (3.10-5.88)	3.45 (2.43-5.12)	-0.67 (-2.66-0.89)	-1.98, 0.09	0.10
F _{INS}	10.95 (7.98-17.89)	9.75 (7.22-12.14)	-1.36 (-6.13-2.13)	-3.70, 1.04	0.17
FPG	156.00 (128.50-176.00)	124.0 (115.0-197.50)	-4.00 (-37.50-14.00)	-32.52, 8.01	0.26
ET-1	17.16 (10.30-26.48)	11.23 (4.84-23.22)	-3.58 (-9.74--1.36)	-6.52, -2.15	<0.001*

*P** < 0.05

At 12 weeks, HOMA-IR was significantly lower in the telmisartan group compared to the comparator. Within-group analysis showed a significant reduction with telmisartan, whereas the comparator group showed no significant change. For fasting blood glucose, the between-group difference did not reach statistical significance. Within-group analysis showed a significant reduction with telmisartan but not with the comparator. For fasting insulin, the between-group difference favoured telmisartan. Within-group analysis showed a significant reduction in the telmisartan group, but not in the comparator group. For ET-1, the between-group difference was not significant. Within-group analysis showed significant reductions in both groups. **Table II** summarizes the between-group comparisons of metabolic and vascular parameters at 12 weeks, and **Supplementary Table** provides the mean changes from baseline with the corresponding between-group differences. **Tables III** and **IV** present the within-group changes for the telmisartan and other antihypertensives groups, respectively.

Discussion

Telmisartan demonstrated consistent improvements in metabolic parameters compared to other antihypertensives group, with significant within-group reductions in HOMA-IR, fasting plasma glucose (FPG), fasting insulin (F_{INS}). The other antihypertensives group showed non-significant changes in HOMA-IR, FBS, and F_{INS}. Between-group differences were statistically significant for HOMA-IR and F_{INS} and, trended toward significance for FPG. Both groups showed significant reductions in ET-1 over 12 weeks, with no significant between-group difference on primary analysis, indicating broadly comparable effects on endothelial function. Effect size estimates were broadly consistent with the main results, showing greater improvements in fasting glucose and insulin with telmisartan, a trend toward reduction in HOMA-IR, and a more pronounced decline in ET-1 compared to the comparator.

Collectively, these findings suggest a potential beneficial effect of telmisartan on glucose homeostasis,

consistent with earlier studies,^{33,37} which also reported better glycaemic outcomes with telmisartan compared to other ARBs. The significant reductions in fasting insulin in the telmisartan group at 12 weeks suggests an enhancement in the body's ability to utilize insulin more effectively.^{31,38} The RAAS blockade by telmisartan also counteracts the impairment of insulin signalling caused by angiotensin-II.³⁹ In contrast, other antihypertensive agents like amlodipine, ramipril, and cilnidipine primarily target vascular resistance to manage hypertension and have limited direct metabolic effects. Amlodipine and cilnidipine are calcium channel blockers, while ramipril is an ACE inhibitor, and their effects on insulin sensitivity might be less pronounced than those of telmisartan.⁴⁰ Therefore, while effective for managing hypertension, these drugs might lack a significant influence on insulin signalling pathways, thereby having little effect on insulin resistance in T2DM and its related complications.

Both groups demonstrated significant within-group reductions in ET-1 levels; with the decline in the telmisartan arm trending toward greater magnitude compared to the other antihypertensives (**Supplementary**), indicating a more pronounced improvement in vascular endothelial function. While improved blood pressure control in both groups likely contributed to the overall reduction in ET-1 through hemodynamic mechanisms, the comparatively better effect observed with telmisartan suggests a class-specific benefit. RAAS blockade by telmisartan may attenuate angiotensin II-mediated ET-1 expression, in addition to exerting anti-apoptotic and anti-proliferative effects in endothelial cells.^{25,32} In contrast, CCBs and ACEIs may reduce ET-1 release by enhancing NO bioavailability,^{41,42} thereby providing endothelial benefits, though possibly less pronounced than with telmisartan.

The randomised design minimised selection bias and balanced confounders, supporting causal inference. By focusing on a high-risk population with T2DM and hypertension, the findings address an important clinical need and enhance real-world relevance. This study also tested the reproducibility of telmisartan's reported antidiabetic effects across different populations. We also assessed cardiometabolic outcomes such as HOMA-IR and ET-1, which are key follow-up parameters in this group. Given the challenges of managing coexisting diabetes and hypertension, particularly in elderly patients with high pill burden, a single agent with dual

benefits and established long-term safety represents a clinically valuable option.

This study has some limitations such as small sample size, short 12-week follow up, and heterogeneity of the comparator group, which may restrict generalizability, and class-specific conclusions to some extent. The open-label design may have influenced adherence and reporting, though biochemical endpoints are less prone to such bias. Lifestyle factors could be confounding but randomization may have eliminated it to some extent. To fully capture endothelial function, warrants study of parameters like euglycaemic clamp, flow-mediated dilation, nitric oxide metabolites, *etc.* in future studies.

Although our findings suggest potential metabolic benefits of telmisartan, they are based on surrogate endpoints, short follow up, and a small sample, and should therefore be considered exploratory and hypothesis-generating rather than definitive. We recommend conducting longer trials evaluating cardiovascular outcomes, major adverse cardiovascular events (MACE), renal outcomes (time to onset of CKD stage V) *etc.*, to confirm these observations. We also recommend analysis of parameters like adiponectin,^{43,44} leptin,³⁸ euglycemic clamp, flow mediated dilatation, *etc.*,⁴⁵⁻⁴⁷ along with the hard clinical endpoints to bring light to extended clinical implications of telmisartan and, also develop newer drugs with selective action to fit into the treatment of other chronic inflammatory diseases with insulin resistance specifically.

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शोध-संदेश

इस अध्ययन में टाइप-2 मधुमेह और उच्च रक्तचाप से ग्रसित रोगियों में इन्सुलिन संवेदनशीलता (insulin sensitivity) और रक्त वाहिकाओं के कार्य पर टेलमिसार्टन (Telmisartan) के प्रभाव की तुलना अन्य सामान्य रूप से प्रयुक्त एंटीहाइपरटेंसिव दवाओं से की गई। इन्सुलिन संवेदनशीलता का आंकलन HOMA-IR के माध्यम से तथा एन्डोथीलियल कार्य का मूल्यांकन एंडोथेलिन -1 (ET-1) स्तरों के आधार पर किया गया। 12 सप्ताह के उपचार के बाद टेलमिसार्टन से इन्सुलिन संवेदनशीलता में अन्य दवाओं की तुलना में अधिक सुधार देखा गया, जबकि ET-1 स्तरों में कमी सभी समूहों में लगभग समान रही। ये निष्कर्ष दर्शाते हैं कि टेलमिसार्टन न केवल रक्तचाप नियंत्रण में प्रभावी है, बल्कि इसके अतिरिक्त इसके लाभकारी अन्य प्रभाव भी हो सकते हैं, जो मधुमेह से संबंधित सूक्ष्म एवं स्थूल रक्तवाहिकाओं की जटिलताओं को सीमित करने में सहायक हो सकते हैं।

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