RESEARCH ARTICLE

A prospective observational open-label study to evaluate the effect of telmisartan on glycosylated hemoglobin and fasting plasma glucose levels in hypertensive patients with impaired fasting glycaemia

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ABSTRACT

Background: In hypertensive patients with impaired fasting glycaemia (IFG), the incidence of Type 2 diabetes mellitus is 20%, which further worsens the situation. Currently, no approved drug is available for the treatment of IFG. Telmisartan has partial agonistic activity at the PPARγ receptor, thereby reducing insulin resistance. Hence, this study was undertaken.

Aim and Objectives: Primary objective: To evaluate the effect of telmisartan on glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG) levels. Secondary objective: To evaluate the effect of telmisartan on Body Mass Index (BMI).

Materials and Methods: In this prospective observational study, 100 newly diagnosed cases of hypertension with IFG were included. Before the treatment with telmisartan, baseline parameters such as Glycosylated haemoglobin (HbA1c), FPG, BMI, and blood pressure (BP) were recorded. Then, follow-up was done at 4, 8, and 12 weeks. BP and FPG were repeated at 4 and 8 weeks, whereas at 12 weeks all the four parameters were repeated. All the study endpoints were analyzed using paired t-test.

Results: In this study, telmisartan reduced mean HbA1c from 5.87 ± 0.09 to 5.66 ± 0.17%, FPG levels from 111.49 ± 3.82 to 104.28 ± 4.60 mg/dl, BMI from 24.20 ± 1.84 to 23.80 ± 1.75 kg/m² and SBP from 148.44 ± 3.64 to 133.43 ± 3.00, DBP from 91.90 ± 2.37 to 82.08 ± 2.45 mm of Hg at the end of 12 weeks of treatment (P < 0.001).

There were no serious adverse effects observed during the study period.

Conclusion: In this study, telmisartan reduced HbA1c, FPG, BMI, and BP values significantly. Hence, telmisartan is safe and has a significant effect on the reduction of both BP and insulin resistance.

KEY WORDS: Telmisartan; Impaired Fasting Glycaemia; Hypertension; Body Mass Index

INTRODUCTION

According to Joint National Committee 8 (JNC 8), hypertension is defined as a sustained rise in SBP ≥140 mm Hg or DBP ≥90 mm Hg or both.[¹] It is the most important contributing component for cardiovascular disease, and also it is one of the leading causes of morbidity and mortality worldwide. Sustained hypertension damages the heart, kidney, blood vessels, and brain which ultimately leads to ischemic heart disease, congestive cardiac failure, renal failure, and stroke.[¹]

According to the American Diabetes Association guidelines, abnormal glucose homeostasis is defined as² (1) Fasting Plasma Glucose (FPG) levels between 5.6 and 6.9 mmol/L (100–125 mg/dL), which is defined as impaired fasting glycemia (IFG); (2) Plasma glucose levels between 7.8
and 11 mmol/L (140 and 199 mg/dl) in an oral glucose challenge test, is termed as impaired glucose tolerance; or (3) Glycosylated hemoglobin (HbA1c) of 5.7–6.4%. All the three impairments are not seen in the same individual but individuals in all three groups are at high risk of developing type 2 diabetes mellitus (T2DM). Some use the terms pre-diabetes, increased risk of diabetes, or intermediate hyperglycaemia (WHO) for this category.[2]

Together hypertension, diabetes/impaired glucose regulation, dyslipidaemia and obesity form the metabolic syndrome. Increased intake of high calorie, low fiber foods and the adoption of more sedentary lifestyles are all contributing to increased prevalence of the metabolic syndrome in developing countries.[3] It has been observed that not only hypertensive patients with diabetes, but hypertensive patients without overt diabetes also tend to be resistant to insulin-dependent glucose uptake compared with normotensive people. Moreover, the prevalence of IFG among newly diagnosed hypertensive patients is very high, it is about 43%.[1]

About 20% of patients with hypertension having IFG are likely to develop T2DM in subsequent 3 years. Development of T2DM in hypertensive patients additionally complicates the disease and hastens the evolution of cardiovascular diseases and ultimately mortality.[4] The anti-hypertensive drugs, mainly Angiotensin II Receptor Blockers (ARBs) such as telmisartan >irbesartan >losartan have been shown to reduce the incidence of new-onset diabetes. Hence, these anti-hypertensives have shown differential effects on hypertensive patients with IFG.[5]

PPARγ is a nuclear receptor in humans encoded by the PPARγ gene.[6,7]. It is mainly present in adipose tissue, colon and macrophages. It takes part in regulation of fatty acid storage and glucose metabolism.[8] Among ARBs telmisartan has structural similarity to a peroxisome proliferator-activated receptor-gamma (PPARγ) ligand pioglitazone, which is a selective agonist for the nuclear PPARγ. It enhances the transcription of several insulin-responsive genes, thereby helps reversing insulin resistance.[9] Thus, telmisartan being structurally similar to pioglitazone, it acts as a partial agonist of PPARγ.[9]

A study done by Derosa et al., has been shown that telmisartan improves glucose and lipid metabolism.[10] A study conducted by Benson et al., showed that telmisartan attenuated weight gain in rats fed with high-fat and high carbohydrate.[11]

Currently, pharmacotherapy with anti-diabetic drugs for individuals with IFG is controversial.[2] Hence, by understanding the insulin-sensitizing effect of telmisartan through PPARγ agonistic action, its use in hypertensive patients with impaired glycaemia can be beneficial for preventing/delaying the onset of T2DM subsequently in such patients,[12] the present study was conducted with the primary objective: To evaluate the effect of telmisartan on HbA1c, and FPG levels in hypertensive patients with IFG and secondary objective: To evaluate the effect of telmisartan on Body Mass Index (BMI) of hypertensive patients with IFG.

MATERIALS AND METHODS

Study Design and Source of Data

The present prospective observational open-label study was conducted in the outpatient department (OPD) of Medicine in Bapuji Hospital and Chigateri Government hospital, attached to J.J.M medical college, Davangere, Karnataka, India from April 2019 to October 2020 (18 months).

Ethics Committee Permission

The present study was initiated after obtaining permission from the Institutional Ethics Committee of J J M Medical College, Davangere (Ref No.:JJMMC/IEC-Sy-11-2018). The procedures followed were in accordance with the ethical standards of the IEC and with the Declaration of Helsinki.

Total sample size calculated using the prevalence based formula[13] including dropouts was 100, to provide 80% power of the study. Simple random sampling method was used to select the study participants from the OPD. The study was initiated on participants who fulfilled the inclusion criteria and gave consent for the participation. The written informed consent was prepared in both local regional and English language. The telmisartan 40 mg tablets for the study were procured from medical stores in Bapuji Hospital and Chigateri Government hospital, attached to J.J.M medical college, Davangere, Karnataka, India.

Inclusion Criteria

Patients of age between 25 and 60 years of either sex newly diagnosed with stage 1 essential hypertensive (≥140–159/≤90–99 (JNC8)) with IFG (100–125 mg/dl), who were prescribed Telmisartan and willing to give written consent were included in the study.

Exclusion Criteria

Patients with blood pressure (BP) ≥160/≥100 mm Hg and secondary hypertension, those already on other anti-hypertensive drugs, overt diabetes mellitus patients, pregnant and lactating females and those planning to conceive, Patients on hormone replacement therapy or oral contraceptives, associated medical illnesses such as cerebrovascular, serious cardiovascular, liver or renal diseases were excluded from the study.

Baseline parameters such as HbA1c, FPG levels, BMI and BP were recorded in case record form maintained for each patient.
Then, all of them were treated with tablet telmisartan 40 mg once daily in the morning on empty stomach as prescribed by the physician and they were advised to adopt appropriate lifestyle changes such as increasing physical activity, intake of low salt and high fiber diet and each patient were followed up once every month for 3 months and the following parameters were recorded in the Case record form maintained for each patient: FPG after 8hrs of fasting using glucose oxidase enzyme assay method: Baseline and at 4 weeks, 8 weeks and 12 weeks after initiation of treatment, HbA1c using High-performance liquid chromatography method: Baseline and after 3 months of treatment, BMI: Baseline and after 3 months of treatment was calculated using the formula:-BMI = Weight (kg)/[Height (m)]^2 and BP using sphygmomanometer: Baseline and at 4 weeks, 8 weeks, and 12 weeks after initiation of treatment.

**Statistical Analysis**

Categorical data were represented in the form of frequency and percentage. Quantitative data were represented as Mean and Standard Deviation. Comparison of variables before and after treatment in the same group of study participants has been done with paired t-test. A $P < 0.05$ was considered statistically significant. Data were analyzed with IBM Statistical Package for the Social Sciences Version 22 for windows.

**RESULTS**

A total of 100 newly diagnosed cases of hypertension with IFG were enrolled in the study, out of which three were lost to follow up and 97 patients completed the study. In this study, it was observed that among the study population 48% were male and 52% were female. The frequency distribution of age in the study population has been represented in Table 1.

**Table 1: Frequency distribution of age in the study population**

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Frequency (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–39</td>
<td>13 (13%)</td>
</tr>
<tr>
<td>40–49</td>
<td>29 (29%)</td>
</tr>
<tr>
<td>50–59</td>
<td>45 (45%)</td>
</tr>
<tr>
<td>60–69</td>
<td>13 (13%)</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

The results in the current study showed that telmisartan 40 mg once daily dose was effective in reducing HbA1c, FPG, BMI [Table 2] and BP [Table 3], from the baseline successively after 4 weeks, 8 weeks, and 12 weeks of treatment. The results were statistically highly significant ($P < 0.001$).

**DISCUSSION**

In this study, it was observed that among the study population 48% were male and 52% were female. The results in the current study showed that telmisartan 40 mg once daily dose was effective in reducing HbA1c, FPG, BMI and BP from the baseline successively after 4 weeks, 8 weeks, and 12 weeks of treatment. The results were statistically highly significant ($P < 0.001$). However, no serious adverse effects were observed during the study period.

The findings of our study are consistent with the results of Mattam et al., study, “effect of telmisartan in hypertensive patients with IFG” except for HbA1c and BMI because the parameters were not studied by them. A study conducted by Cristiana et al., “metabolic effect of telmisartan and losartan in hypertension with metabolic syndrome” also concluded that besides providing superior 24 h BP control, telmisartan unlike losartan displays insulin-sensitizing activity, which may be explained by its partial agonistic activity at PPARy receptor.

The present study results showed statistically highly significant reduction of BMI from baseline after 12 weeks of treatment with telmisartan, the findings are supported by a study conducted by Benson et al. which has been already discussed above, showed that telmisartan attenuated weight gain despite the use of a pair-feeding (high-fat diet) protocol that ensured comparable food intakes among all experimental groups. The present results can also be reinforced with Masaki et al. Study found the effect of telmisartan on insulin in Japanese T2DM-in which it was concluded that BP and FPG levels, reduced significantly following treatment with telmisartan.

A study done by Ralf et al. Telmisartan improves insulin sensitivity in prediabetic patients with essential hypertension, concluded that telmisartan improved insulin sensitivity.

Novel findings of this study include, that telmisartan showed statistically highly significant ($P < 0.001$) reduction in HbA1c
Table 3: Comparison of baseline mean BP with different study periods using paired t-test

<table>
<thead>
<tr>
<th>Study period</th>
<th>Mean SBP/DBP±SD (mm of Hg)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>148.44±3.64/91.90±2.37</td>
<td></td>
</tr>
<tr>
<td>After 4 weeks of treatment</td>
<td>143.30±4.35/88.68±2.02</td>
<td>0.001*</td>
</tr>
<tr>
<td>After 8 weeks of treatment</td>
<td>137.98±3.34/85.36±2.92</td>
<td>0.001*</td>
</tr>
<tr>
<td>After 12 weeks of treatment</td>
<td>133.43±3.00/82.08±2.45</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*Statistically highly significant, BP: Blood pressure, SBP: Systolic blood pressure , DBP: Diastolic blood pressure

from baseline after 12 weeks, which has actually not been studied till date as per our literature search and the present study also showed statistically highly significant (P < 0.001) reduction in BMI from baseline after 12 weeks of treatment with telmisartan, which was not showed in the previous studies. Hence, further studies are required to confirm these findings.

CONCLUSION

ARBs, particularly telmisartan has partial agonistic activity at PPARγ receptor, leading to enhanced transcription of several insulin-responsive genes, thereby helps in reversing insulin resistance. In this study, it was observed that in HTN with IFG patients treated with telmisartan showed a significant reduction in HbA1c, FPG, BMI, and BP. Hence, in patients with HTN with IFG telmisartan is safe and helps in delaying or even prevention of the onset of T2DM, by reducing insulin resistance due to its partial agonistic activity at PPARγ receptor.

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