WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 5, 496-503. Review Article ISSN 2277– 7105

EFFICACY OF TELMISARTAN IN HYPERTENSIVE PATIENTS WITH METABOLIC SYNDROME

Shamna Haris[1]*, Sowparnika Treasa Sabu[2] and Prof (Dr.) Shaiju S. Dharan[3]

[1]5th Pharm D Student, Ezhuthachan College of Pharmaceutical Sciences, Kerala, India.

[2]Assistant Professor, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Trivandrum, Kerala, India.

[3]HOD, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Trivandrum, Kerala, India.

Article Received on
01 March 2021,

Revised on 22 March 2021,
Accepted on 11 April 2021

DOI: 10.20959/wjpr20215-20286

***Corresponding Author**
Shamna Haris
5th PharmD Student,
Ezhuthachan College of Pharmaceutical Sciences,
Trivandrum, Kerala, India.

ABSTRACT

Background: Metabolic syndrome is a cluster of conditions that occur together which includes elevated blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels. This results in an increase in the risk of Heart disease, Stroke and Type II Diabetes Mellitus. Telmisartan, an Angiotensin II receptor blocker (ARB) is found to have efficacy both in lowering Blood pressure and ameliorating metabolic syndrome in hypertensive patients mainly by its peroxisome proliferator-activated receptor (PPARγ) activity which has efficient actions on glucose and fatty acid metabolism. **Methods:** Previously published articles regarding the efficacy of telmisartan in ameliorating symptoms of metabolic syndrome in addition to efficient control of hypertension by PPAR γ activation. **Observations:** Telmisartan was found to be effective in partial activation of PPARγ that helps in controlling and improving the symptoms of metabolic syndrome which includes diabetes mellitus, dyslipidemia, obesity etc. Telmisartan showed improvement in insulin resistance by enhancing the expression of GLUT4, down regulating PEPCK and also by augmenting adiponectin production by the adipose cells which helped in increasing insulin sensitivity. It also helped in controlling dyslipidemia by inducing ABCA1/ABCG1 expression and suppressing MCP1 expression and macrophage proliferation by activating PPAR-Gamma which helped in providing anti-atherogenic action.

KEYWORDS: Telmisartan, Metabolic syndrome, PPARγ, Insulin resistance.

INTRODUCTION

Metabolic syndrome is a cluster of conditions that occur together, increasing the risk of Heart disease, Stroke and Type II Diabetes Mellitus. These conditions include increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels. The Prevalence of metabolic syndrome is rising rapidly worldwide.[1] About 31 % of the world's adult population is estimated to have metabolic syndrome.[2] A 2.5 fold increase in cardiovascular and diabetes related mortalities is found to be associated with metabolic syndrome. Diet is an important factor related with the increase in metabolic syndrome and the associated cardiovascular pathologies.[3]

It is a complex metabolic and vascular disorder which is related with inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) in the cardiovascular system with raised cardiovascular morbidity and mortality. Insulin activation of the phosphatidylinositol-3-kinase (PI3K) pathway can promote nitric oxide (NO) production in the endothelium and glucose uptake in insulin-sensitive tissues. Angiotensin II inhibits insulin-mediated PI3K pathway activation, thereby impairing endothelial NO production and Glut-4 translocation in insulin-sensitive tissues. This in turn can result in vascular and systemic insulin resistance, respectively.

Angiotensin II also increases insulin-mediated activation of the mitogen-activated protein kinase (MAPK) pathway, which can result in vasoconstriction and pathologic vascular cellular growth. Thus it is evident that the interaction of Angiotensin II with insulin signaling is fully operative not only in insulin-sensitive tissues but also in cardiovascular tissues, thereby linking insulin resistance and cardiovascular diseases.[4]

Telmisartan, an Angiotensin II receptor blocker (ARB) is found to have efficacy both in lowering Blood pressure and ameliorating other complications in hypertensive patients with metabolic syndrome mainly by its peroxisome proliferator-activated receptor activity which has efficient actions on glucose and fatty acid metabolism. Hence it can help in improving insulin sensitivity in patients with insulin resistance and also help control dyslipidemia and elevated cholesterol and triglyceride levels through various mechanisms associated with activation of PPAR γ which in turn can be beneficial in preventing or reducing the risk for cardiovascular and obesity related complications.

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPAR)

Peroxisomes are subcellular organelles which are found in most plant and animal cells which are involved in performing various metabolic functions including H_2O_2-based respiration, β-oxidation of fatty acids (FAs), and cholesterol metabolism.

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors of nuclear hormone receptor superfamily.

It consists of mainly three subtypes.

PPARα – It is mainly found in liver and to a limited extent in muscle, heart and bone. Activation of PPAR-α reduces triglyceride level and is involved in regulation of energy homeostasis.

PPARβ/δ - Activation of PPAR-β/δ elevates metabolism of fatty acids. PPAR-δ is present extensively in the body and regulates energy expenditure.

PPARγ - Activation of PPAR-γ causes insulin sensitization and increases glucose metabolism. It is expressed mostly in endothelial cells and vascular smooth muscle cells. PPAR-γ is subdivided into four isoforms:

γ1 - expressed in virtually all tissues, including heart, muscle, colon, kidney, pancreas and spleen.

γ2 - expressed mainly in adipose tissue (30 amino acids longer).

γ3 - expressed in macrophages, large intestine, and white adipose tissue.

γ4 - expressed in endothelial cells.

It is thus evident that PPAR receptors have a major role in regulating energy homeostasis and metabolic function.[5]

INDICATIONS AND BENEFITS OF TELMISARTAN

The various indications for which telmisartan is used include hypertension, diabetic nephropathy, stroke prevention, proteinuria, left ventricular hypertrophy, diabetic microalbuminuria, intolerance to ACE inhibitors due to cough, combination therapy etc. It has multiple advantages when compared to other ARBs and antihypertensives in managing both hypertension, proteinuria in CKD, dyslipidemia and insulin resistance together known as metabolic syndrome. The various benefits of telmisartan include longer half life, better distribution, low renal excretion, activates PPAR – gamma, trough-peak ratio and also blunts effectively the early morning blood pressure surge (EMBPS). It is relatively safe in renal cases and has minimal drug interactions.

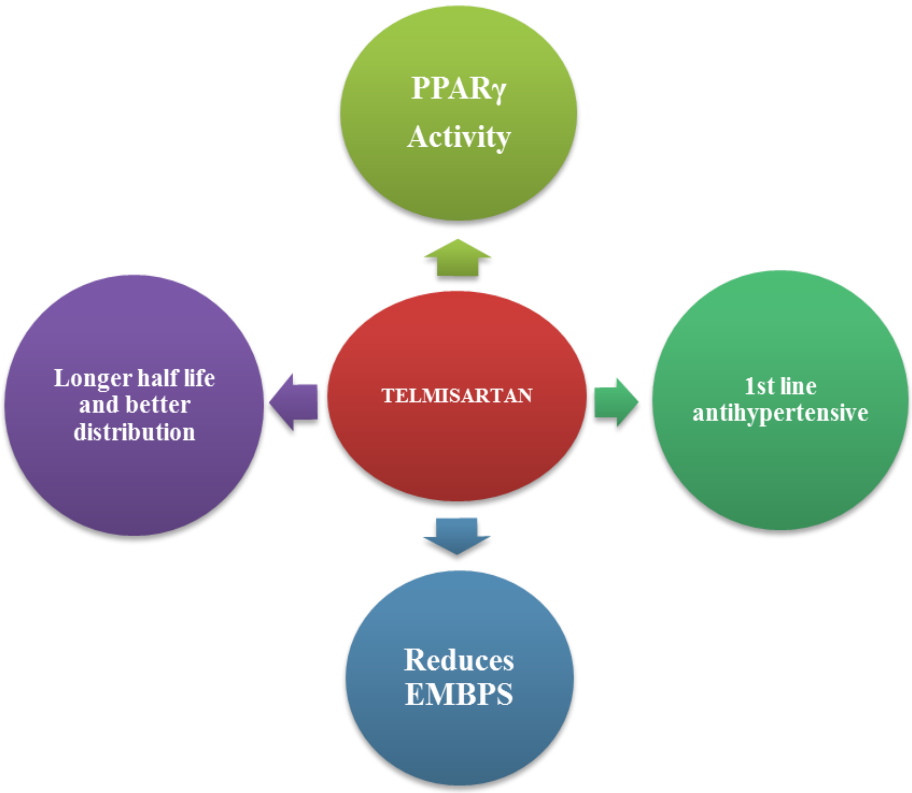

Figure 1: Benefits of Telmisartan.

Telmisartan can significantly reduce the Systolic and Diastolic blood pressure (SBP and DBP) and also serum levels of triglyceride compared to other ARBs in a much efficient and beneficial manner. Hence Telmisartan is found to be more efficacious than other ARBs like Losartan or Candesartan in improving metabolic syndrome and controlling High blood pressure in hypertensive patients.

EFFECTS ON INSULIN RESISTANCE

Telmisartan's agonistic action at the peroxisome proliferator-activated receptor γ (PPAR-γ) has made it relevant in being considered the first choice of treatment in diabetic patients with hypertension.

Telmisartan is found to have Peroxisome proliferator-activated receptor-gamma (PPAR-gamma) activity which helps to decrease insulin resistance and improve insulin sensitivity. PPAR-gamma can regulate and has effects on the gene expression involved in carbohydrate metabolism. In animal study, it was evident that administration of telmisartan caused a significant reduction of weight gain, glucose, and triglyceride levels in rats which were fed a high-fat, high-carbohydrate diet, compared with treatments of losartan, another type of ARB.

In addition, some recent clinical papers also reported the insulin-sensitizing effects of telmisartan in hypertensive patients.[8]

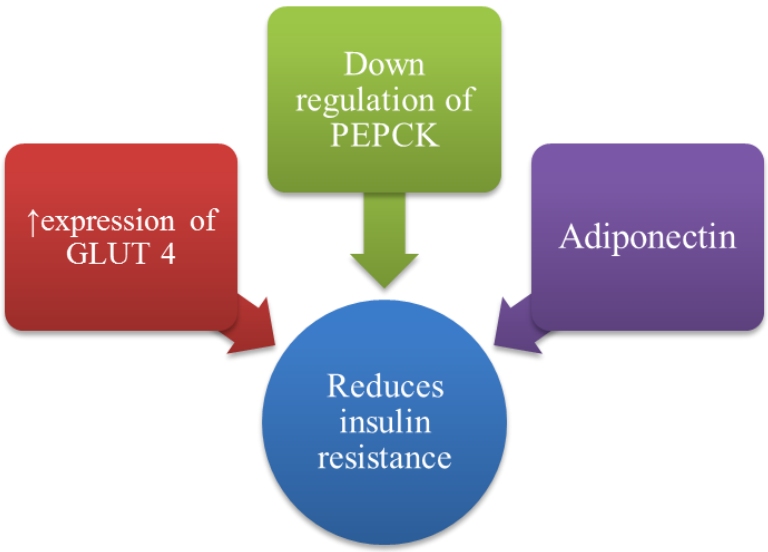

Figure 2: Mechanism of reduction of insulin resistance.

Telmisartan reduces the insulin resistance through increased expression of GLUT4 and down-regulation of phosphoenol pyruvate carboxykinase (PEPCK) via PPARγ dependent mechanisms. Telmisartan has the ability to enhance glucose transporter type 4 protein expression and 2-deoxyglucose uptake in the basal and insulin-stimulated states of adipocytes. It also enhances GLUT 4 localization to the plasma membrane and augments glucose uptake through PPARγ in adipocytes.[9] PPAR-γ being an intracellular hormone receptor, plays a significant role in carbohydrate and lipid metabolism. Activation of PPARγ is also assumed to stimulate adiponectin production by the adipose cells, which can help in increasing insulin sensitivity.[10] High-molecular-weight adiponectin levels were found to be increased by telmisartan in diabetic patients with hypertension and thus helped in improving insulin resistance, through partial PPARγ activation. The binding of adiponectin to its receptors can mediate the insulin-sensitizing effect, which is of particular importance in diabetic patients.[9]

Moreover, the control of blood glucose level in patients with diabetes mellitus can be described by its ability to improve lipid metabolism in the body, attenuate oxidative stress responses of body, lessen the damage to blood vessels caused by oxygen-free radicals, lower the vascular endothelin level, improve vasodilation functions and relieve insulin resistance.[11]

Studies has shown the efficacy of Telmisartan in ameliorating the consequences of metabolic syndrome more effectively compared to other ARB's like Valsartan, Eprosartan etc. It can prevent the onset of diabetes in hypertensive patients and improve insulin resistance in diabetic patients.

EFFECTS ON DYSLIPIDEMIA

ARBs were found to have significant effect on lipid metabolism in experimental models and in some clinical trials. ARBs showed the ability to reduce excessive production and build up of triglycerides in liver, in experimental models, through mechanisms which were independent of their anti-hypertensive action.[12]

Telmisartan induces ABCA1/ABCG1 expression (ABCA1 and ABCG1 are genes that encode cholesterol transporter proteins which is involved in playing an important role in phospholipids and cholesterol homeostasis) and suppresses monocyte chemoattractant protein 1 (MCP1) expression and macrophage proliferation by activating PPAR-Gamma.[13] These effects may induce anti-atherogenic effects in hypertensive patients. Telmisartan has the ability to increase PPARγ activity and PPAR ligand binding activity in macrophages. Whereas the other ARBs like losartan, valsartan and olmesartan does not affect the PPARγ activity.[14]

In addition, when compared to other ARBs, relatively low concentrations of telmisartan were found to increase the expression of phosphoenol-pyruvate carboxykinase (PEPCK) gene in human visceral adipocytes. PEPCK is a key target gene that is related to the ability of PPAR-γ activators in reducing the fatty acid levels. Additional evidence that telmisartan can activate PPAR-γ arise from the findings that telmisartan can induce adipocyte differentiation in vitro and is much more efficient than other ARBs in decreasing serum concentrations of glucose and triglyceride in rats which were maintained with a diet rich in fats and carbohydrates.[12] Telmisartan inhibited lipopolysaccharide-induced mRNA expression of monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor-α, and these effects were abolished by PPARγ small interfering RNA, where as other ARBs did not have this property. In addition, telmisartan suppressed oxidized low-density lipoprotein-induced macrophage proliferation through PPARγ activation.[14]

When compared to glitazones, telmisartan behaves as a selective PPARγ modulator which only activates a subset of genes and hence has fewer adverse effects when compared to full

PPAR-γ agonists. Telmisartan has a high mean volume of distribution of 460-510 L along with high lipophilicity which indicates that it may have significant higher capacity to move into intracellular compartments and obtain greater access to PPAR-γ than other ARBs.[12]

CONCLUSION

Telmisartan was found to be effective in partial activation of PPARγ that helps in controlling and improving the symptoms of metabolic syndrome which includes diabetes mellitus, dyslipidemia, obesity and thus helps to prevent and reduce the risk of heart disease, stroke and other cardiovascular morbidities. Being an Angiotensin II receptor blocker (ARB) it has renal protective effects and is considered a first line treatment in diabetic patients with hypertension or in patients with associated renal dysfunctions. Telmisartan showed improvement in insulin resistance by enhancing the expression of GLUT4, down regulating phosphoenol pyruvate carboxykinase (PEPCK) and also by augmenting adiponectin production by the adipose cells which helped in increasing insulin sensitivity. It also helped in controlling dyslipidemia by inducing ABCA1/ABCG1 expression and suppressing monocyte chemoattractant protein 1 (MCP1) expression and macrophage proliferation by activating PPAR-Gamma which helped in providing anti-atherogenic action. Thus telmisartan can be considered beneficial in reducing or preventing onset of metabolic syndrome in hypertensive patients and further research on these actions of telmisartan can provide confirming results which if found positive can help many people suffering from metabolic syndrome worldwide in addition to efficient control of high blood pressure.

REFERENCES

1. Misra A, Singhal N, Khurana L. Obesity, the metabolic syndrome, and type 2 diabetes in developing countries: role of dietary fats and oils. J Am Coll Nutr, 2010; 29(3): 289S−301S.
2. Engin A. The definition and prevalence of obesity and metabolic syndrome. Adv Exp Med Biol, 2017; 960: 1−17.
3. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA, 2002; 288(21): 2709−2716.
4. Zhou MS, Schulman IH, Zeng Q. Link between the renin-angiotensin system and insulin resistance: implications for cardiovascular disease. Vasc Med, 2012; 17(5): 330-341.

5. Tyagi S, Gupta P, Saini AS, Kaushal C, Sharma S. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. J Adv Pharm Technol Res, 2011; 2(4): 236-240.
6. Cheng KC, Li Y, Chang WT, Kuo FY, Chen ZC, Cheng JT. Telmisartan is effective to ameliorate metabolic syndrome in rat model – a preclinical report. Diabetes Metab Syndr Obes, 2018; 11: 901-911.
7. De Luis DA, Conde R, González-Sagrado M, Aller R, Izaola O, Duenas A, Perez Castrillon JL, Romero E. Effects of telmisartan vs olmesartan on metabolic parameters, insulin resistance and adipocytokines in hypertensive obese patients. Nutricion Hospitalaria, 2010; 25(2): 275-279.
8. Yamagishi S, Takenaka K, Inoue H. Role of insulin-sensitizing property of telmisartan, a commercially available angiotensin II type 1 receptor blocker in preventing the development of atrial fibrillation. Med Hypotheses, 2006; 66(1): 118-120.
9. Ayza MA, Zewdie KA, Tesfaye BA, Gebrekirstos ST, Berhe DF. Anti-Diabetic Effect of Telmisartan Through its Partial PPARγ-Agonistic Activity. Diabetes Metab Syndr Obes, 2020; 13: 3627-3635.
10. Naruse M, Koike Y, Kamei N, Sakamoto R, Yambe Y, Arimitsu M. Effects of azilsartan compared with telmisartan on insulin resistance in patients with essential hypertension and type 2 diabetes mellitus: An open-label, randomized clinical trial. PLoS One, 2019; 14(4): e0214727.
11. Chen T, Xing J and Liu Y: Effects of telmisartan on vascular endothelial function, inflammation and insulin resistance in patients with coronary heart disease and diabetes mellitus. Exp Ther Med, 2018; 15: 909-913.
12. Vanitha M, Vijayal K. Effect of telmisartan on serum lipid profile in patients with hypertension and dyslipidemia. Int J Med Res Health Sci, 2013; 2(4): 745-749.
13. Zahra Tavoosi, Hemen Moradi-Sardareh, Massoud Saidijam, Reza Yadegarazari, Shiva Borzuei, Alireza Soltanian, Mohammad Taghi Goodarzi. Cholesterol Transporters ABCA1 and ABCG1 Gene Expression in Peripheral Blood Mononuclear Cells in Patients with Metabolic Syndrome. Cholesterol, 2015; 682904.
14. Takeshi Matsumura, Hiroyuki Kinoshita, Norio Ishii, Kazuki Fukuda, Hiroyuki Motoshima, et al. Telmisartan exerts antiatherosclerotic effects by activating peroxisome proliferator-activated receptor in macrophages. Arteriosclerosis, Thrombosis, and Vascular Biology, 2011; 31(6): 1268–1275.