The Medical Journal Of Tikrit University (2019) 25 (1): 165-174

ISSN: 1813-1638

The Medical Journal of Tikrit University

Available online at: www.mjotu.com

العراقية
المجلات الاكاديمية العلمية
IRAQI
Academic Scientific Journals

Beneficial Effects of Telmisartan in Treatment of Hypertension With Type Two Diabetic Patients in Salahaddin Society

Sabah A. Khuder (1)

Rafal K. Farhan *(2)

(1) Saladdin Health Directorate
Ministry of Health
Salahaldeen
Iraq

(2) Department of Microbiology
College of Medicine
Tikrit University
Salahaldeen
Iraq

Keywords:

Type II D.M,
Microalbuminuria,
SBP,
DPB,
MAP,
Telmisartan

ARTICLE INFO

Article history:

Received	12 Mar 2019
Accepted	15 Apr 2019
Available online	01 June 2019

ABSTRACT:

Background Diabetes is a chronic illness lead to acute complications that required patient self-management education and life style care to prevent complication

This study **aims** is to determine the degree of 12 weeks telmisartan therapy on the level of systolic blood pressure (SBP) & diastolic blood pressure (DPB), mean arterial pressure (MAP), serum glucose level, glycated hemoglobin(HbA1c) level and microalbuminuria (MA) as a marker of renal deterioration recently diagnosed hypertensive type two diabetes mellitus (T2DM) patients.

Patients & Methods: Forty six newly diagnosed hypertensive patients with types 2 diabetes mellitus participated in the study(2017); 22 males and 24 females, their mean age was 52.93± 7.69 years. Eighty one apparently healthy persons (36 male and 45 female), who had no chronic disease and didn't receive any chronic therapy participated in the study as a control group. Both groups were matched regarding age and sex. BP was measured using a mercury sphygmomanometer with the subject waiting for a 5-minutes rest. Fasting serum glucose (FSG) concentration was estimated using a kit supplied by Biocon (Germany). HbA1c is measured in whole blood sample by ion-exchange resin quantitative colorimetric determination using a kit supplied from Stanbio (USA). Microalbuminuria measured by detecting protein-creatinine ratio (PCR) which include determination of urine protein by sulphosalicylic acid 3%, measuring urine creatinine by using a kit supplied from SyrBio company and finally calculation of PCR by dividing protein concentration in urine upon creatinine concentration in urine .

Result: Showed that T2DM patients having a significant rise in SBP, DBP and MAP, also persistent hypertension lead to overt diabetic nephropathy, and there is diabetes and hypertension have a close relationship between due to resistance to insulin action on glucose uptake in peripheral tissues as compared with the control group. After a 12 weeks telmisartan monotherapy there was a significant reduction in SBP, DBP, MAP, FSG and microalbuminuria level.

Conclusion: Telmisartan has a valuable renal protective effect by decreasing proteinuria, also it have a specific antihyperglycemic effect beyond angiotensin II receptor antagonism in addition to its hypotensive effects.

Key words: Type two diabetes mellitus, microalbuminuria, Telmisartan

DOI: http://dx.doi.org/10.25130/mjotu.25.01.16

*Corresponding author E mail : drrafal1989@gmail.com/

Introduction

Diabetes is a chronic illness lead to acute complications that required patient self management education and life style care to prevent complication (1). In type 2diabetes, hypertension is often present as a part of metabolic syndrom of insulin resistance, also including central obesity and dyslipidemia(2). Increase urinary albumin excretion (UAE) is the first marker of kidney damage, this leads to diabetic nephropathy (DN)(8).

The renin angiotensin system (RAS) plays a vital role in the path-physiology of diabetic proteinuria, with AG II mediator (19). Agents that targeted Renin-Angiotensin-System (RAS) are the antihypertensive agents of choice in all DM patients with microalbuminuria or diabetic kidney disease (9).

Blocking of angiotensin II receptors with the angiotensin Type1 receptor antagonist (AT1-RA) inhibit angiotensin more directly(3) , the angiotensin converting enzyme (ACE) inhibitor reduce albumin excretion (AE) more than other agents in patient with T2DM nephropathy(11). Previously clinical trials demonstrated the effectiveness of AT1-RA in reducing the Albumin Excretion Rate (AER) in patient with hypertension and MA in T2DM (15).

Telmisartan displays insurmountable , but reversible binding to the AT1 receptor, and it has the highest binding affinity for this receptor among other type ARBs. Also providing long term blockade of the AT1 receptor, telmisartan has minimal affinity for the AT2 receptor or for acetylcholine, catecholamine, dopamine, histamine, serotonin, or imipramine receptors (7).

Telmisartan is commonly used for management of hypertension. It also have beneficial effects on hypertension related cardiovascular end-organ damage, at least in part through a reduction of oxidative stress and inflammation. Also it substantially minimize the risk of type-two diabetes in comparison to other antihypertensive therapies, probably by regulating insulin sensitivity(14).

Telmisartan have stronger effective than other antihypertensive agents, both in minimizing glomerular injury& in lowering the intraglomerular pressure. Thus, the blockade of RAS is the most potened effect to induce regression of renal disease in DM nephropathy(13).

Patients and Methods

Forty six newly diagnosed hypertensive diabetic type2 patients participated in the study; (22males and

24 females). Their mean age was (52.93 ± 7.69) years.

These participants were clinically examined by the physicians of the clinic and they were put on oral telmisartan(80 mg/day) for 12weeks. Eighty one healthy subjects (36males and 45females)of matching age, sex, were participated in this study as a control group .All type 1 diabetics Patients, patients on another drugs(other than glibenclamide), angina or myocardial infarction (MI), renal or hepatic diseases, resistant or malignant hypertension, smoker, pregnant and lactating women also excluded from the study.

Regional research committees at College of Medicine and Salah Alddin Health Administration approved the study protocol. This comparative controlled interventional clinical trial study was conducted during the period from the first of January to the first of August 2017 in Tikrit teaching hospital one of the biggest hospital in Tikrit center served a large proportion of community.

The biochemical investigation includes fasting serum glucose (FSG) {was estimated using a kit supplied by Biocon (Germany)}, HbA1c{measured by using a kit supplied from Stanbio (USA)}, microalbuminuria measured by detecting protein-creatinine ratio (PCR) which include determination of urine protein by sulphosalicylic acid 3%, measuring urine creatinine by using a kit supplied from SyrBio company and finally calculation of PCR by dividing protein concentration in urine upon creatinine concentration in urine. BP was measured by the use of a mercury sphygmomanometer with the subject waiting of after a 5-minutes rest.

Blood samples for laboratory assay of the control group are also taken after persons fasting for 11-14 hours. 10 ml of venous blood have been collected by using a sterile disposable syringe and separated into 2 unequal parts:

1. 2.5 ml were transferred into an anticoagulant EDTA tube with gentle shaking to obtain whole blood sample that was used for HbA1c measurement at approximately 2-days intervals.
2. The remaining blood was transferred into a plain tube, allowed to clot at room temperature and then serum was separated by centrifugation for 25 minutes at 3000 rpm and kept at -15 to -20°C until it analyzed.
3. 10ml of random voided urine were collected in a sterile container from patients and control participants, transferred and kept in a plain tube, checked by dip stick, allowed to be frozen at -20°C, and analyzed at approximately 7-days intervals. The

samples were used for the determination of proteinuria and microalbuminuria.

Standard statistical methods were used to detect the mean& SD. Unpaired t-test can used to compare the results of various biochemical parameters of DM patients with the controls.

P value ≤ 0.05 was considered to be statistically significant(10).

Result:

Forty six newly diagnosed hypertensive diabetic type2 patients participated in the study; (22males and 24 females). Their mean age was (52.93 ± 7.69) years. Also, Eighty one apparently healthy persons (36 male and 45 female), who had no chronic disease and didn't receive any chronic therapy participated in the study as a control group. Both groups were matched regarding sex and age. Their mean ± SD age was (52.55 ± 9.82) years.

Table (1) shows that the blood pressure parameters of SBP, DBP and MAP were significantly higher ($p<0.0001$) in type 2 diabetic patients before starting therapy in comparison with the control group.

Table (1): Comparison of SBP, DBP and MAP parameter between control and type 2 diabetic patients before Telmisartan therapy.

Parameters	Mean ± SD		p-value
	Control (n=81)	Before Telmisartan (n=46)	
SBP(mmHg)	120.27 ± 6.44	163.47 ± 12.15	<0.0001
DBP(mmHg)	78.01± 6.11	110.10 ± 7.78	<0.0001
MAP(mmHg)	92.21±5.67	127.89±7.96	<0.0001

Significant at p-value<0.05 using unpaired t-test

Table (2) shows that after 12weeks of telmisartan therapy, SBP, DBP and MAP levels although reduced but still there were highly significant differences ($p<0.0001$) from the control values.

Table (2): Comparison of SBP, DBP and MAP parameters between control and type 2 diabetic patients after Telmisartan therapy.

Parameters	Mean ± SD		p-value
	Control (n=81)	After Telmisartan (n=46)	
SBP(mmHg)	120.27± 6.44	126.39±9.05	<0.0001
DBP(mmHg)	78.01± 6.11	86.19± 10.91	<0.0001
MAP(mmHg)	92.21±5.67	97.26±15.84	<0.0001

Significant at p-value<0.05 using unpaired t-test

Table (3) shows that the levels of FSG, HbA1c, Urine Protein, Urine Creatinine and PCR were significantly higher (p<0.0001) in type 2 diabetic patients before starting therapy in comparison with the control group.

Table (3): Comparison of FSG, HbA1c, Urine Protein, Urine Creatinine and PCR levels between control and type 2 diabetic patients before Telmisartan therapy.

Parameters	Mean ± SD		p-value
	Control (n=81)	Before Telmisartan (n=46)	
FSG (mmol/l)	4.96 ± 0.62	9.72 ± 2.84	<0.0001
HbA1c (%)	5.51±0.28	8.32 ± 1.07	<0.001
Urine Protein (mg/l)	43.65±5.32	282.93±137.12	<0.0001
U. Creatinine(mmol/l)	5.85±0.95	9.06±5.83	<0.0001
PCR (mg/mmol)	7.57±1.08	51.36±53.20	<0.0001

Significant at p-value<0.05 using unpaired t-test

Table (4) shows that the levels of FSG, HbA1c, Urine Protein, Urine Creatinine and PCR were significantly higher (p<0.0001) in type 2 diabetic patients after starting therapy in comparison with the control group.

Table (4): Comparison of FSG, HbA1c, Urine Protein, Urine Creatinine and PCR levels between control and type 2 diabetic patients after Telmisartan therapy.

Parameters	Mean ± SD		p-value
	Control (n=81)	After Telmisartan (n=46)	
FSG (mmol/l)	4.96 ± 0.62	7.67 ± 1.99	<0.0001
HbA1c (%)	5.51±0.28	7.56 ± 1.30	<0.001
Urine Protein (mg/l)	43.65±5.32	115.67±95.80	<0.0001
U. Creatinine(mmol/l)	5.85±0.95	6.78±3.98	<0.0001
PCR (mg/mmol)	7.57±1.08	22.98±25.80	<0.0001
Parameters	Mean ± SD		p-value
	Control (n=81)	After Telmisartan (n=46)	
FSG (mmol/l)	4.96 ± 0.62	7.67 ± 1.99	<0.0001
HbA1c (%)	5.51±0.28	7.56 ± 1.30	<0.001
Urine Protein (mg/l)	43.65±5.32	115.67±95.80	<0.0001
U. Creatinine(mmol/l)	5.85±0.95	6.78±3.98	<0.0001
PCR (mg/mmol)	7.57±1.08	22.98±25.80	<0.0001

Significant at p-value<0.05 using unpaired t-test

Discussion

Diabetes mellitus(DM), is a common metabolic disorder that caused by defects in insulin secretion or action or both . is diagnosed by hyperglycemia often accompanied by glycosuria, polyuria & polydipsia(6).

Telmisartan is one from Angiotensin Receptor Blockers (ARBs), which the more effect antihypertensive agent that provide a smooth control of BP, with low rates of side effect profile compared with placebo, and without cough that is frequently associated with Angiotensin Converting Enzyme Inhibitors (ACEIs). Lipophilic nature of its molecule should rise its tissue penetration in comparison other ARBs(21).

Telmisartan increases renal perfusion flow, urine flow and glomerular filtration rate in a concentration-dependent manner (20). Combination ACEI- ARB therapy is more antiproteinuric than ACEI alone(13). Using a telmisartan with routine treatment present additional albuminuria reduction in patients with diabetic nephropathy.

Improvement of the renal blood flow by selective vasodilator produced by specific blockage of Renin Angiotensin Aldosteron System (RAAS) was brought about by ACEIs and/or ARBs may successfully decrease the progressive of renal injury in patients with hypertension (12).

The advantage of telmisartan in preserving renal function could be related to the reduction of urine protein levels& reduction in blood pressure , and so decreases the rate of decline of renal function (16).

Telmisartan may have a specific anti hyperglycemic effect beyond angiotensin II receptor antagonism. This is because its partial Peroxisome Proliferator Activated Receptor- γ (PPAR-γ) action and biological effect that is not present to the same extent in other ARBs (17).

Telmisartan improve flow of blood to skeletal muscles, by this way, improving insulin and glucose delivery to the insulin sensitive tissues, facilitating insulin signaling at the cellular level and improved secretion of insulin from □ -cells(4).

Our findings are in agreements with many studies, In a comparative study between telmisartan and ramipril, Thomas (2009) reported that telmisartan 80-mg gave significantly lower mean 24 hour bP than amlodipine 10-mg, & remarkably greater reductions in systolic and diastolic blood pressure during the last 6 hour of the dosing interval, the incidence of cough was higher in the ramipril in comparsion with the telmisartan.

In another study, comparison of telmisartan against losartan in hypertensive type two diabetic patients with nephropathy, indicated that telmisartan was superior to losartan in reducing proteinuria in hypertensive patients with Diabetic Kidney Disease (DKD) and relatively the same reductions in blood pressures. Further, the superiority of telmisartan could be due to its intrinsic PPAR-γ agonist properties (5).

Conclusion:

Telmisartan had a significant effect on reducing blood pressure, it was effective in reducing microalbuminuria in hypertensive patients with T2DM. This study conferred a beneficial renal protective effect of telmisartan because significant reduction in proteinuria (measured as PCR) occurred after using telmisartan daily for 12 weeks. Also telmisartan has a significant improvement in metabolic parameters mainly those reflecting carbohydrate and lipid metabolism which lower the serum level of FSG after 12 weeks therapy due to its partial PPAR-γ.

References:

1.ADA (2010). Standards of medical care in diabetes. *Diabetes care*; volume 33: supplement 1, S11-S18.

2.ADA (2003).Treatment of Hypertension in Adults With Diabetes. *Diabetes Care*; 26 (Suppl. 1): S80-S82.

3.American Diabetes Association (2007). Diagnosis and classification of diabetes mellitus. *Diabetes Care*.,1:42–47.

4.Arthur B, Haralambos G, (2006). Angiotensin II antagonists-clinical experience in the treatment of hypertension, Prevention of cardiovascular outcomes and renal protection in diabetic nephropathy and proteinuria. *Arq Bras Endocrinol Metab* ;50: 327-333.

5.Bichu P. Nistala R, Khan A, Sowers R and Adam W,(2009). Angiotensin receptor blockers for the reduction of proteinuria in diabetic patients with overt nephropathy: results from the AMADEO study. *Vascular Health and Risk Management* ; 5: 129–140.

6.Celik I, Yegin F, Odabasoglu E (2002). Effect of experimental diabetes mellitus on plasma lactate dehydrogenase and glutamic oxaloacetic transaminase levels in rabbits, *Turkish Journal of. Biology*; 26:151–154

7.Galzerano D, Capogrosso C, Sara D, Galzerano A, Paparello P, Diana L et al .,(2010).New Standards in Hypertension and Cardiovascular Risk Management: focus on telmisartan. *Vascular Health and Risk Management*; 6: 113-133.

8.Gross JL, Azevedo MJ, Silverio SP, Canani LH, Caramori NL, Zelmanovitz T (2005). Diabetic nephropathy: diagnosis, prevention and treatment. *Diabetic care*; 28:176-188.

9.Kidney Disease outcome Quality Initiative (KDOQI) (2004). clinical practice guidelines on hypertension and antihypertensive agent in chronic kidney disease. *AM J Kidney Dis* ;43:S1-S290.

10.Kirkwood, BR (1988). Essentials of Medical Statistics. 1st ed., Blackwell scientific publication, *Oxford*;12 : 43-56.

11.Lacoureiere Y, Nadeall A, Poirier L etal,(1993). Captopril or conventional therapy in hypertensive type 2 diabetic: three year analysis . *Hypertension* ;21:786-794.

12.Long DA, Price KL, Herrera-Acosta J, Johnson RJ(2004). How does angiotensin II cause renal injury ? *Hypertension*;43:722-723.

13.Mazerska M and Mysliwiec M, (2009). Telmisartan lowers albuminuria in type 2 diabetic patients treated with angiotensin enzyme inhibitors. *Advances in Medical Sciences* ;54(1) : 37-40.

14.Nakayama SH et al., (2009). Comparison of Effects of Olmesartan and Telmisartan on Blood Pressure and Metabolic Parameters in Japanese Early-Stage Type-2 Diabetics with Hypertension. *Hypertens Res* ; 31: 7–13.

15.Parving HH, Lehnert H, Brochner Mortensen J et al., 2001). For the Irbesartan in patient with type 2 diabetes and microalbuminuria study Group: The effect of irbesartan on the development of diabetic nephropathy in patient with type 2 diabetes. *N Engl J Med* ;345:870-878.

16.Priscilla K, Kenneth F, David P, (2002). Randomized controlled crossover study of the effect on proteinuria and blood pressure of adding angiotensin II receptor antagonist to an Angiotensin converting enzyme inhibitors in normotensive patients with chronic renal disease and proteinuria. *Nephrol Dial Transplant* ;17: 597-601.

17.Rosano GM, Vitale C, Castiglioni C, Cornoldi A, Fini M, Raffaele S (2004). Comparative effect of Telmisartan and Losartan on glucose metabolism in hypertensive patients with the metabolic syndrome. *Circul;* 110 (Supp III):60-65.

18.Thomas U, (2009). The rationale for choosing telmisartan and ramipril in the ONTARGET program. *European Heart Journal Supplements* ;11: 3–8.

19.Touyz RM, (2005). Molecular and cellular mechanisms in vascular injury in hypertension: role of angiotensin II. *Curr opin Nephrol. Hypertens*;14:125-131.

20.Wienen Wolfgang, Entzeroth Michael, Meel Jacobus C.A. van, Stangier Joachim, Busch Ulrich, Ebner Thomas, et al.,(2000). A review on telmisartan: a novel, long-acting angiotensin II receptor antagonist. *Cardiovasc Drug Rev*; 18: 127-154.

21.Zou Z, Xi G-L, Yuan H-B, Zhu Q-F, and Shi X-Y, (2008). Telmisartan Versus Angiotensin Converting Enzyme Inhibitors in the Treatment of Hypertension : A meta-analysis of Randomized controlled trials. *Journal of Human Hypertension* ; 1 : 1-11.