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Comparative Effects of Telmisartan versus Valsartan on HOMA-IR in type 2 Diabetes Mellitus Patients with Hypertension

KEYWORDS: Homeostasis model assessment, body mass index, telmisartan, valsartan, type 2 Diabetes Mellitus

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ABSTRACT *The aim of this study was to Compare the effects of telmisartan and valsartan on homeostasis model assessment of insulin resistance (HOMA- IR) in type2 diabetes mellitus (T2DM) with hypertension (HT), a randomized control comparative trial (RCT), open label design was adopted. This study was conducted in the Department of Pharmacology, Mosul College of Medicine, University of Mosul and Al-Waffaa diabetic center, Mosul, Iraq from February 1st, 2012 to March 30th, 2013. Eighty-eight patients with oral hypoglycemic agents were randomly assigned to receive two month treatment telmisartan (n = 46) or valsartan (n = 42). with body mass index (BMI) 31.52±4.73, 30.39±3.95 respectivly. Forty one diabetic normotensive patients (n=41) ,and age ,sex ,BMI ,duration of diabetic disease ,duration of diabetic treatment matched to the diabetic hypertensive patients groups were kept as control group. the percentage of patients receiving each of oral hypoglycemic agents did not differ between groups, the oral hypoglycemic agents remained unchanged during the two- month study period. This study showed that diabetic hypertensive patients have a non significant difference in Glucose, serum insulin and (HOMA- IR) before starting therapy, as compared to diabetic normotensive patients group. telmisartan showed significant reduction in body mass index (BMI) (from 31.52±4.73 to 31.23±4.73), P=0.04, waist circumferences (WC) (from 107.07± 7.29 to 106.37± 6.76), P=0.05. valsartan showed insignificant reduction in BMI (from 30.39± 3.94 to 30.19 ±3.83) P=0.06. and in WC (from 106.43±10.34 to 106.17 ±10.47), P=0.17.*

The Homeostasis model assessment (HOMA-IR) as a marker of insulin resistance was decreased significantly in telmisartan group (from 6.32 ± 5.18 to 5.09 ± 4.48, p=0.01) as well as decreased in valsartan group but insignificantly (from 6.86± 6.50 to 5.67 ± 4.01, p=0.07).

Introduction

According to the World Health Organization's diabetes, HT, and obesity are one of the top five continuing risk factors for cardiovascular deaths in the world(1).

The driving forces linking obesity, HT, and diabetes due to the complex and multifactorial nature of the conditions that involve combinations of environmental, genetic, life style, and behavioural confounders. Additionally, it is recognized that neuroendocrine mechanisms, including insulin resistance (IR), sympathetic nervous activation, and stimulation of the rennin angiotensin aldosteron system (RAAS), are also involved(2).

In fact, blockade of Angiotensin II (Ang II) binding to the Angiotensin II type1 receptor(AT1) results in improvement of insulin and glucose metabolism at different levels, including an improvement in insulin secretion and peripheral insulin responses. Moreover, Ang II signaling is implicated in vascular injury associated with diabetes, and inhibition of AT1 receptors attenuates these responses markedly, including the diabetic pro inflammatory state(3).

There are some Angiotensin receptor blockers (ARBs) that can function as a partial agonist of Peroxisome proliferator-activated receptor gamma (PPAR- γ) and improve carbohydrate and lipid metabolism(4), even in the absence of a functional AT-II receptor(5). telmisartan, have significant PPAR- γ agonistic activity, as they enhance adipose differentiation of 3T3-L1 cells. PPAR-γ agonists also have an anti-inflammatory role, as shown by their inhibitory effects on the production of inflammatory cytokines such as tumor necrosing factor-alpha, in turn promoting the production of adiponectin and thereby normalizing obesity-related IR. Thus, the insulin-sensitizing effect of ARBs is considered to possibly be attributable to their PPAR- γ agonist activity(6). Furthermore telmisartan activates PPAR -δ–Dependent Pathways(7).

Valsartan had mechanisms of action different from those of thiazolidinediones or telmisartan with PPAR- γ activity, leading to improved insulin sensitivity of adipose tissues(8), in animal studies valsartan enhances insulin sensitivity in skeletal muscles of diabetic mice(9) valsartan suppresses the inflammatory response of macrophages, albeit not via PPAR- γ or the AT1 receptor. This suppression appears to secondarily improve adipose insulin resistance(6).

Patients and methods

This is a randomized control comparative trial (RCT) with open label design study which was conducted in the Department of Pharmacology, College of Medicine, University of Mosul and Al-Wafa Diabetic Center in Mosul from 1st February, 2012 to 30th march, 2013. During the study period, more than 4000 patients with T2DM were screened for HT, However, only 88 diabetic hypertensive patients of them who were without any exclusion criteria were continued with the study's antihypertensive regimen. Forty six patients (21 male, 25 female) whose ages were between 41 and 70 (mean age 54.41±7.19) years, were kept on telmisartan 80 mg. (Telmi®, Diamond Pharma, Syria), once daily after breakfast for two month. Forty two patients (20 male, 22 female) whose ages ranges from 40 and 67 years with (mean age 53.02 ±6.95) years, were received valsartan 80 mg (Diostar®, Pharma International Co.Amman-Jordan), taken in the same way and period of telmisartan. T2DM patients (treated for diabetes with oral hypoglycemic agents) with mild to moderate hypertension should be either: Newly diagnosed or Already diagnosed with HT, at some point used antihypertensive, but for various reasons, not currently taking drugs for HT. The percentage of patients receiving each of oral hypoglycemic agents did not differ between groups, the oral hypoglycemic agents remained unchanged during the two- month study period. Patients with type 1 diabetes mellitus, Patients treated with thiazolidinediones or insulin, statin and smokers are excluded from the study. Forty one T2DM normotensive patient, (19 males and 22 females, age range from 40-75 years,

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with mean age ± SD of 52.45 ± 7.94 respectively, matched for sex, age and BMI,WC, duration of diabetic disease and duration of treatment with the diabetic hypertensive patients groups, were taken as control group. BMI, WC, Serum fasting glucose, serum fasting insulin were measured at basal time and after 2 months of treatment. The diabetic patients were classified as hypertensive if their SBP ≥130 mmHg, DBP ≥80 mmHg or both(10).

The BMI was calculated according to the following equation:
BMI = Weight (kg)/(height in meter)^2 (m^2)(11) obesity was defined as a BMI ≥ 30, WC in (cm) was determined with a standard tape measure, as the point midway between the costal margin and iliac crest in the mid-axillary line, with the subject standing and breathing normally(12).

Five ml of venous blood samples were collected from each patient after at least 12 hours fasting, Serum glucose was estimated by glucose-oxidase peroxidase colorimetric method (Lotta & Turner, 1975) using a kit supplied by Biocon Company (Germany). Serum insulin was measured by enzyme linked immune sorbent assay (ELISA) technique(13), using the insulin ELISA Kit which is a direct immunoenzymatic colorimetric method for the quantitative determination of insulin in human serum or plasma supplied from Gen Way Bio Tech, Inc. (USA).

Insulin resistance was measured by the following equation:
HOMA-IR=fasting insulin (μU/ml) x FBG (mmol/l)/22.5(14) The denominator of 22.5 is a normalizing factor; i.e, the product of normal fasting plasma insulin of 5μU/ml and normal fasting plasma glucose of 4.5 mmol/l typical of a "normal" healthy individual=22.5. Therefore, for an individual with "normal" insulin sensitivity, HOMA-IR=1(15) Patients were considered as insulin resistant when HOMA ≥ 2.6(16).

Result
(Table1) shows the characteristics of the study participants. The table shows the ages of the individual and the number of males and females, BMI, Waist circumference, Duration of disease and Duration of treatment in the studied groups. There were non-significant differences regarding the sex, age, BMI, waist circumference, duration of diabetic disease and Duration of treatment among the study groups.

Table (1): Characteristics of the Studied Patients

Groups / Parameters	Mean ± SD			
	Diabetic normotensive (n=41)	Telmisartan Group (n=46)	Valsartan Group (n=42)	*p*-value
Sex(No. and%)				
Male	19(46.3%)	21(45.7%)	20(47.6%)	0.98†
Female	22(53.7%)	25(54.3%)	22(52.4%)	
Age (Years)	52.54±7.94	54.41±7.19	53.02±6.95	0.44‡
BMI (kg/m^2)	30.29±5.36	31.52±4.73	30.39±3.95	0.40‡
Waist circumference(cm)	104.73±9.59	107.07±7.29	106.43±10.34	0.48‡
Duration of diabetic disease (Years)	3.90±1.69	3.89±2.00	4.31±1.84	0.38‡
Duration of diabetic treatment (Years)	3.32±1.24	3.01±1.57	3.05±1.20	0.70‡

† Chi-square test
‡ One-way ANOVA test

Comparison between fasting serum glucose , serum insulin fasting level and HOMA-IR of Diabetic hypertensive patients and Diabetic normotensive patients showed a non significant difference of all parameters. (Table2)

Table (2): Comparison of parameters between the studied groups.

Parameters	Diabetic hypertensive patients N=88	Diabetic normotensive patients N=41	P-value
	Mean ±SD	Mean ±SD	
Glucose (mmol/l)	9.87±2.70	9.81±2.61	0.91
Insulin (μU/ml)	14.95±12.43	13.29±12.84	0.49
HOMA-IR	6.58±5.82	6.02±7.27	0.64

Unpaired *t*-test

telmisartan showed significant reduction BMI (from 31.52±4.73 to 31.23±4.73), P=0.04, WC (from 107.07± 7.29 to 106.37± 6.76), P=0.05, in fasting serum Insulin (from 15.21±12.44 to12.73±11.34), p=0.02, HOMA-IR (from 6.32 ± 5.18 to 5.09 ± 4.48, p=0.01. telmisartan showed insignificant reduction in fasting serum Glucose (from 9.43±2.43 to 9.04±2.43), p=0.28, (Table3).

Table (3): parameters changes in telmisartan administered patients before and after treatment

Telmisartan					
parameters Mean ±SD	Before treatment	After treatment	Mean difference	95% CI of difference	P-value
BMI (kg/m^2)	31.52±4.73	31.23±4.73	-0.28	0.01_0.55	0.04
Waist circumference	107.07±7.29	106.37±6.76	-0.70	0.01_1.38	0.05
Glucose (mmol/l)	9.43±2.43	9.04±2.43	-0.39	0.33_1.12	0.28
Insulin (μU/ml)	15.21±12.44	12.73±11.34	-2.48	0.44_4.51	0.02
HOMA-IR	6.32±5.18	5.09±4.48	-1.23	0.26_2.21	0.01

paired *t*-test

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valsartan showed significant improvement in fasting serum glucose (from 10.35± 2.92 to 8.93±1.87) at p=0.001, but insignificant improvement of serum fasting insulin level (from 14.67±12.57 to 14.19±9.38) at p=0.66, HOMA-IR (from 6.86± 6.50 to 5.67 ± 4.01) at p=0.07, BMI (from 30.39± 3.95 to 30.19±3.83) at P=0.06, WC (from 106.43±10.34 to 106.17±10.47) at P=0.17.

Table (4): parameters changes in valsartan administered patients before and after treatment

Valsartan					
parameters Mean ±SD	Before treatment	After treatment	Mean difference	95% CI of difference	P-value
BMI (kg/m²)	30.39±3.95	30.19±3.83	-0.21	-0.01_0.42	0.06
Waist circumference	106.43±10.33	106.17±10.47	-0.26	-0.12_0.64	0.17
Glucose (mmol/l)	10.35± 2.92	8.93±1.87	-1.41	0.65_2.18	0.001
Insulin (µU/ml)	14.67±12.57	14.19±9.38	-0.48	-1.71_2.67	0.66
HOMA-IR	6.86±6.50	5.67±4.01	-1.19	-9.10_2.46	0.07

Paired *t*-test

Table (5) summarizes the mean difference variations of parameters .

Table (5): The Parameters mean difference variations between telmisartan and valsartan

Parameter	Mean differences		P-value
	Telmisartan Mean ±SE	Valsartan Mean ±SE	
BMI(Kg/ m²)SBP (mmHg)	-0.28±0.13	-0.21±0.11	0.26
Waist circumferance	-0.70±0.34	-0.26±0.18	0.18
Glucose (mmol/l)	-0.39±0.36	-1.41±0.38	0.77
Insulin (µU/ml)	-2.48±1.00	-0.48±1.08	0.59
HOMA-IR	-1.23±0.48	-1.19±0.63	0.73

Unpaired *t*-test

Discussion

The patients in this study were obese as evident (BMI ≥ 30 (kg/m²), hyperglycemic as evident by the high concentration of fasting serum glucose. and have IR as evident by HOMA ≥ 2.6, these results go with the hypothesis that obesity is associated with an increased risk of developing IR and T2DM. In obese individuals, adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors that are involved in the development of IR(17).

Body mass index, waist circumferance in current study decreased significantly in telmisartan. The telmisartan effects on body weight in the current study were similar to the study reported by HE H *et al.*, where they reported that telmisartan prevents weight gain(7), so as the study done by Benson in 2005(18), the explanation base on the hypothesis that telmisartan has been reported to function as a partial agonist of PPAR- γ, a member of the ligand-activated nuclear receptor super family that is expressed at high levels in adipose tissue(19). PPAR-γ regulates genes that modulate lipid utilization and storage, lipoprotein metabolism, adipocyte differentiation, and insulin action(19) and affect fat cell differentiation(20).

In contrast to these result, Derosa in 2004 reported no change in (BMI) with telmisartan in patients with mild hypertension and type 2 diabetes mellitus(21), wohl in 2010 also reported that telmisartan treatment induced no differences in body weight when compared to placebo treatment(22).

The current study reported insignificant effect of valsartan on BMI, WC. Fogari *et al.,* in 2005 reported that valsartan significantly decrease BMI in hypertensive obese patients(23).

The significant effect of telmisartan and the insignificant effect of valsartan with regard BMI, WC in agreement with the study of Sugimoto et al in 2006. They reported that telmisartan showed excellent effects in controlling body weight and fat accumulation in the internal organ and reduce adipose tissue cell size better than valsartan(24).

In this current study the improvement of insulin sensitivity occur with both Telmisatan and valsartan treatment but only significant in telmisartan group.

Contrasting results have been reported in the literature about the effects of telmisartan on insulin sensitivity, In 2006, a study conducted by Nagel *et al*, reported that telmisartan at a dose of 40 mg resulted in a significant improvement in glucose metabolism in insulin-resistant subjects(25) Pershadsingh *et al* in 2004, reported insulin-sensitizing effects of telmisartan: implications for treating insulin-resistant hypertension(26), many other studies go with the same findings(18),(27). while other studies reported no improvement in insulin sensitivity(21,22).

The effect of valsartan on insulin sensitivity were controversial, valsartan lack or have minimal PPAR- γ agonist activity(28), but the improvement of insulin resistance (IR) may occurs by interrupting rennin-angiotensin system(29). valsartan induces neither proliferation nor enlargement of adipocytes, and it would presumably improve insulin sensitivity without inducing obesity(6). However, animal studies showed that valsartan enhances insulin sensitivity in skeletal muscles of diabetic mice(9).

Several studies have already shown that valsartan could ameliorate insulin sensitivity in hypertensive obese patients(23,30).

This study shown that treatment for 2 months may improve insulin sensitivity (as measured by HOMA-IR) although insignificant by valsartan, but significantly in telmisartan group. These result may be explained by the high lipophilicity of telmisartan compared with valsartan and other ARBs, this pharmacological profile might be involved in the strong insulin-sensitizing effect of telmisartan(24), and the PPAR- γ modulating effect of telmisartan(18).

The improvement of the body weight and IR in this study might suggest that in addition to insulin sensitivity mediated by AT1R blocking, the insulin sensitivity improvement by telmisartan may be attributed, at least in part, to the reduction of adipose tissue weight, and this is go with the hypothesis that dysfunctional adipocytes of obese subjects produce angiotensin II, contributing to systemic blood pressure levels(31). The Local RAS in adipose tissue plays a role in regulating adipogenesis in human adipose tissue(32), hypothesized that large adipocytes produce increased amounts of Ang II, which then inhibits the differentiation of preadipocytes. This causes a failure of adequate expansion of adipose tissue and the resulting deposition of lipids in other tissues(22).

Inspite of telmisartan significantly improved HOMA-IR, valsartan not significantly improved IR, this study showed no sig-

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nificant difference in the mean difference variations of parameters, Therefore, we could not conclude that valsartan does not have an insulin-sensitizing effect, but we could clarify the relatively strong contribution of telmisartan to insulin sensitivity compared to the effect of valsartan.

These results suggest that both valsartan and telmisartan are appropriate anti-hypertensive agents providing improvement of some obesity-related metabolic disorders such as insulin resistance. however, telmisartan is the more beneficial agent due to compared to valsartan.

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