

## Comparative Effects of Telmisartan versus Valsartan on serum Leptin level, in hypertensive type 2 diabetes mellitus patients

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### ABSTRACT

**Objective:** The aim of this study was to compare the effects of telmisartan and valsartan on blood pressure and serum leptin in hypertensive type 2 diabetes Mellitus patients.

**Study design:** A randomized control comparative clinical trial with open label design.

**Study period:** From 1st February, 2012 to 30th March, 2013.

**Patients and method:** Eighty eight type 2 diabetic hypertensive patients were randomly assigned to received either telmisartan ( $n = 46$ ) or valsartan ( $n = 42$ ) with body mass index (BMI)  $31.52 \pm 4.73$  kg/m<sup>2</sup>,  $30.39 \pm 3.95$  kg/m<sup>2</sup> respectively. Forty one diabetic normotensive patients ( $n=41$ ), age, sex, BMI, duration of diabetic disease, duration of diabetic treatment matched to the diabetic hypertensive patients groups were kept as control group. blood pressure (BP), leptin levels were measured at baseline and after 2 months of treatment.

**Results:** The study showed a significant higher systolic blood pressure (SBP), diastolic blood pressure (DBP) and serum leptin in the diabetic hypertensive patients before starting therapy as compared with the diabetic normotensive patients. Both telmisartan and valsartan significantly reduced serum leptin and BP. More reduction in DBP seen with valsartan than with telmisartan.

**Conclusion:** Monotherapy with telmisartan and valsartan produce a beneficial reduction effects on BP and reduce leptin level. The improvement of leptin sensitivity may play a role directly or indirectly in the induction of hypertension control.

**Key words:** Leptin, telmisartan, valsartan, blood pressure, type 2 Diabetes Mellitus

### الخلاصة

**أهداف الدراسة:** الهدف من هذه الدراسة هو مقارنة تأثير عقار التلزمزارتان مع عقار الفالزارتان على ضغط الدم ومستوى هورمون اللبتين، في مصلى المرضى المصابين بمرض السكري النمط الثاني المشخصين حديثاً بارتفاع ضغط الدم.

**تصميم الدراسة:** تم اعتماد تصميم الدراسة كمحاولة عشوائية ضابطة.

**فترة الدراسة:** من الأول من شهر شباط للعام 2012 إلى الثلاثين من شهر آذار للعام 2013.

**طرائق العمل:** تم اخذ 88 مريض سكري مشخص حديثاً بارتفاع ضغط الدم من الدرجة الخفيفة إلى المتوسطة، وقد تم توزيعهم بشكل عشوائي إلى مجموعتين، ليتم علاجهم إما بعقار التلزمزارتان (46) مريض أو عقار الفالزارتان (42) مريض. وكانت دلالة كتلة الجسم  $31,52 \pm 4,73$  كغم/م<sup>2</sup> و  $30,39 \pm 3,95$  كغم/م<sup>2</sup> على التوالي في كلا مجموعتي العلاج. وكذلك تم اخذ واحد وأربعون شخصاً مريضاً بالسكري ولديه ضغط دم طبيعي مطابقين لمرضى السكري المصابين بارتفاع ضغط الدم من حيث العمر، الجنس، دلالة كتلة الجسم، فترة المرض بمرض السكري النمط الثاني و فترة علاج مرض السكري النمط الثاني اخذوا كمجموعة ضبط. تم متابعة المرضى في كلا المجموعتين لمدة شهرين. تم قياس ضغط الدم ومستوى هورمون اللبتين قبل البدء بإعطاء العقارين وبعد شهرين من العلاج.

**النتائج:** أظهرت النتائج أن مرضى السكري من النمط الثاني المصابين بارتفاع ضغط الدم في كلا مجموعتي العلاج لديهم ارتفاعاً معنوياً في ضغط الدم الانقباضي والانقباضي ومستوى هورمون اللبتين قبل البدء بالعلاج مقارنة مع مجموعة مرضى السكري ذوات ضغط الدم الطبيعي. بعد شهرين من العلاج الأحادي كلا العقارين

التلمزرتان أو الفالزرتان اظهرا انخفاضا معنويا في مستوى هورمون الليبتين ، ضغط الدم الانقباضي والانسباضي مع ملاحظة انخفاض أكثر في ضغط الدم الانبساطي نتيجة عقار الفالزرتان مقارنة بالتلمزرتان. الاستنتاج: خلصت الدراسة إلى أن العلاج الاحادي بالتلمزرتان أو الفالسارتان قد يقدم فائدة بسبب خفضهما لضغط الدم ومستوى هورمون الليبتين. وان تحسين حساسية هرمون الليبتين قد تلعب دورا مباشرا أو غير مباشر في السيطرة على ارتفاع ضغط الدم

**الكلمات الدالة:** هورمون الليبتين ، عقار التلمزرتان، عقار الفالزرتان، ضغط الدم،مرض السكري النمط الثاني.

**L**eptin, a peptide hormone comprising 167 amino acids, is mainly released by adipocyte<sup>1</sup>, and its expression is proportional to size of adipocytes and to amount of adipose depots<sup>2</sup>.

Although leptin reduces food intake and body weight, obesity is characterized by high plasma leptin levels. In this regard, several studies have shown that attenuated leptin signaling is present in this metabolic disorder. This leptin resistance would explain why high leptin levels fail to induce the expected decreasing effects on feeding and body weight that would mitigate obesity. Several factors have been shown to mediate leptin resistance at the central level: impaired leptin transport in the blood–brain barrier, endoplasmic reticulum stress, and impaired leptin signaling<sup>3,4</sup>, leptin receptor internalization, receptor mutations and post-receptor signaling defects. Furthermore, the active hormone may be reduced by binding proteins or soluble receptors<sup>5</sup>.

Apparently, many patients are resistant to leptin satiety and weight reducing actions, where as sympathoexcitatory actions are preserved, a phenomenon referred to as selective leptin resistance<sup>6</sup>, this phenomenon might explain in part how hyperleptinemia could be accompanied by obesity (partial loss of appetite and metabolic actions of leptin) but still contribute to sympathetic over activity and hypertensive because of preservation of the sympathetic actions of leptin to some organs involved in BP regulation<sup>7</sup>.

Leptin is shown to be related to metabolic, inflammatory, and haemostatic factors involved in hypertension development<sup>8</sup>, chronic hyperleptinemia has been shown to enhance sympathetic nervous activity and reduces nitric oxide dependent vasodilation and natriuresis stimulates renin–angiotensin which may affect BP level in humans<sup>9</sup>.

Leptin has peripheral actions to stimulate vascular inflammation, oxidative stress, and vascular smooth muscle hypertrophy that may contribute to pathogenesis of T2DM, hypertension, Angiotensin II (Ang II) increases leptin synthesis in cultured adipose cells. Adipose tissue-derived Ang II and leptin may act synergistically to promote obesity-related hypertension<sup>10</sup>.

Insufficient suppression of the renin angiotensin aldosterone system (RAAS) has been implicated in the development of obesity-related high arterial pressure, and is linked with insulin resistance (IR) and T2DM<sup>11</sup>. Angiotensin receptor blockers (ARBs) are regarded as first-line treatments for T2DM with hypertension<sup>12</sup>.

The aim of the present study is to evaluate the effect of telmsartan and valsartan on serum leptin level in hypertensive type 2 diabetes Mellitus patients.

### Patients and methods

This is a randomized control comparative clinical trial 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. Eighty eight (88) hypertensive type 2 diabetic patients participated in this study. Forty six patients (21 male, 25 female) whose ages ranged between 41 and 70 year ( $54.41 \pm 7.19$  year), were kept on telmisartan 80 mg. (Telmi<sup>®</sup>, Diamond Pharma, Syria), once daily after breakfast for two month. The remaining forty two patients (20 male, 22 female) whose ages ranges from 40 and 67 year with ( $53.02 \pm 6.95$  year), were received valsartan 80 mg (DioStar<sup>®</sup>, Pharma International Co. Amman-Jordan) once daily for 2 months.

The patients have mild to moderate hypertension were either newly diagnosed or already diagnosed with hypertension, at some point used antihypertensive, but for various reasons, not currently taking drugs for hypertension. Patients with Type1 diabetes mellitus, Patients treated with thiazolidinediones, insulin, statins and smokers were excluded from the study. Forty one diabetic normotensive patients age, sex, BMI, duration of diabetic disease, duration of diabetic treatment matched to the diabetic hypertensive patients groups were kept as a control group. BP, leptin levels were measured at baseline (before treatment) and after 2 months of treatment .

Blood pressure was measured after 30 minutes rest in the sitting position. Mean values of 3 consecutive measurements, separated by about 15-20 minutes, were calculated and used for the analyses. The diabetic patients were classified as hypertensive if their

systolic blood pressure  $\geq 130$  mmHg, diastolic blood pressure  $\geq 80$  mmHg or both<sup>13</sup>.

Five ml of venous blood samples were collected from each patient after at least 12 hours fasting. Serum leptin was measured using the GenWay human leptin ELISA kit (USA) which is based on standard sandwich enzyme linked immuno-sorbent assay (ELISA)<sup>14</sup>.

### Statistical data analysis

The data obtained in the current study has analyzed using Statistical package for social sciences (SPSS) program (version17), ANOVA method were used to analyze the comparison between the groups. Standard statistical methods were used to determine the mean and standard deviation ( $M \pm SD$ ). Unpaired Student *t*-test was used to compare the results of various biochemical parameters of diabetic hypertensive patients with the comparative group. Paired Student *t*-test was used to compare the results of various biochemical parameters in diabetic hypertensive patients before and after therapy in each group. P-value  $\leq 0.05$  was considered to be statistically significant.

### Results

The demographic characteristic and mean baseline data of all studied groups were shown in (Table1) the patients were relatively obese, BMI  $\geq 30$  kg/m<sup>2</sup>). There were non-significant differences regarding the sex, age, BMI, waist circumference, duration of diabetic disease and duration of diabetic treatment among the study groups.

Table 1. Characteristics of the studied patients

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

† Chi-square test

‡ One-way ANOVA test

NS: Non significant

The diabetic hypertensive patients at baseline have a significantly higher SBP, DBP than diabetic normotensive patients. the serum

leptin in diabetic hypertensive at baseline is significantly higher than serum leptin in diabetic normotensive patients (Table 2)

Table 2. Comparison SBP, DBP and serum leptin between the studied groups

parameters	Diabetic hypertensive patients N=88	Diabetic normotensive patients N=41	P-value
	Mean $\pm$ SD	Mean $\pm$ SD	
SBP (mmHg)	151.75 $\pm$ 8.38	118.02 $\pm$ 4.78	<0.000
DBP (mmHg)	99.38 $\pm$ 6.80	77.73 $\pm$ 8.06	<0.000
Serum leptin (ng/ml)	16.76 $\pm$ 7.66	13.94 $\pm$ 6.75	0.05

Unpaired *t*-test

Table 3. Comparison of SBP, DBP and serum leptin between telmisartan and valsartan groups at baseline

Parameters	Telmisartan group N=46	Valsartan group N=42	P-value
	Mean $\pm$ SD	Mean $\pm$ SD	
SBP (mmHg)	150.52 $\pm$ 9.21	153.10 $\pm$ 7.24	0.15(NS)
DBP (mmHg)	97.83 $\pm$ 5.42	101.07 $\pm$ 7.77	0.03
Serum leptin (ng/ml)	17.08 $\pm$ 8.16	16.41 $\pm$ 7.15	0.68(NS)

Unpaired t-test

NS: Non significant

No significant difference was found between SBP and serum leptin of valsartan group and telmisartan group at baseline. Whereas, DBP showed significant differences (Table 3).

A significant reduction of DBP, SBP and leptin level after 2 months treatment with telmisartan and valsartan (Table 4 and 5).

Table 4. SBP, DBP and serum leptin level before and after treatment with telmisartan

Telmisartan					
parameters Mean $\pm$ SD	Before treatment	After treatment	Mean difference	95% CI of difference	P- value
SBP (mmHg)	150.52 $\pm$ 9.21	129.35 $\pm$ 7.65	-21.17	18.32_24.03	<0.000
DBP (mmHg)	97.83 $\pm$ 5.42	89.89 $\pm$ 6.28	-7.94	5.94_9.93	<0.000
Serum leptin (ng/ml)	17.08 $\pm$ 8.16	14.97 $\pm$ 8.93	-2.12	0.05_4.19	0.05

paired t-test

Table 5. SBP, DBP and serum leptin level before and after treatment with valsartan

Valsartan					
Parameters Mean $\pm$ SD	Before treatment	After treatment	Mean difference	95% CI of difference	P-value
SBP (mmHg)	153.10 $\pm$ 7.24	128.75 $\pm$ 6.81	-24.35	21.90_26.79	<0.000
DBP (mmHg)	101.07 $\pm$ 7.77	87.26 $\pm$ 4.84	-13.81	11.06_16.56	<0.000
Serum leptin (ng/ml)	16.41 $\pm$ 7.15	14.84 $\pm$ 6.91	-1.57	-0.003_3.15	0.05

Paired t-test

Table 6. The reduction of the mean of SBP, DBP and serum leptin between telmisartan and valsartan

Parameter	Mean differences		P-value
	Telmisartan Mean $\pm$ SE	Valsartan Mean $\pm$ SE	
SBP (mmHg) DBP (mmHg)	-21.17 $\pm$ 1.42	-24.35 $\pm$ 1.21	0.10(NS)
DBP (mmHg)	-7.94 $\pm$ 0.99	-13.81 $\pm$ 1.36	0.001
Serum leptin (ng/ml)	-2.12 $\pm$ 1.03	-1.57 $\pm$ 0.78	0.18(NS)

Unpaired t-test

NS: Non significant

Comparison between the reduction of the mean of SBP, DBP and serum leptin of telmisartan and valsartan showed as insignificant difference only in DBP (Table 6).

### Discussion

Angiotensin receptor blockers have become an important class of drugs, with clinical benefits in the treatment of hypertension in patients with diabetes<sup>15</sup>, and all of the drugs in this class bind to the AT1receptor thereby inhibiting the multiple actions of Ang II that are mediated by that receptor,

including vasoconstriction, mitogenic activity, cytokine production, reactive oxygen species formation. increases aldosterone release and sympathetic activity<sup>16,17</sup>. Some ARBs can function as a partial agonist of peroxisome proliferator-activated receptor gamma (PPAR-  $\gamma$ ) and improve carbohydrate and lipid metabolism<sup>17</sup>. Leptin and RAS mediate sympathetic activation and parasympathetic withdrawal<sup>16</sup>.

Leptin showed high levels in diabetic hypertensive patients when compared with diabetic normotensive patients, and SBP, DBP were significantly

higher in diabetic hypertensive patients when compared with diabetic normotensive. These results may be due to the sympathetic system activation throughout leptin activity, this result were in agreement with the evidence which found that chronic hyperleptinemia has been shown to enhance sympathetic nervous system activity and reduces nitric oxide dependent vasodilation and natriuresis<sup>18</sup>. Leptin stimulates renin-angiotensin and sympathetic system<sup>19</sup>, natriuresis which may affect BP level in human and that a blunted effect of leptin may predispose to hypertension in human<sup>9</sup>.

At the end of the 2-month treatment period, there was a significant reductions in SBP and DBP from baseline values in both treatments. The ability of valsartan and telmisartan to reduce BP have resulted primarily from its antagonistic action on angiotensin type 1 (AT1) receptors.

The results of telmisartan and valsartan therapy on blood pressure in the present study were in agreement with many previous study(20-23). In this study valsartan significantly reduced DBB greater than telmisartan. These results suggest that the superiority of valsartan on DBP lowering effect might be related to its strength rather than to the duration of its pharmacological action .

A meta analysis study<sup>24</sup> showed no differences between telmisartan's BP-lowering capabilities and valsartan BP-lowering capabilities as monotherapy, but when combined with hydrochlorothiazide, telmisartan was more effective than valsartan.

By the end of the 2-month treatment period, the present study showed reductions in serum leptin level from baseline values, in both treatment. In the literature, both increase<sup>25</sup> and decrease<sup>26-28</sup>, in fasting leptin concentrations have been reported after administration of telmisartan, moreover, the lack of effect of telmisartan on circulating leptin also has been reported<sup>29</sup>. With regard valsartan reports conflicting between increase<sup>28</sup> or decrease serum leptin level<sup>30</sup> or having no effect<sup>31</sup>.

Angiotensin II regulates the production of adipokines, it increases the expression and the release of pro-inflammatory cytokines<sup>32</sup>, increases leptin ob gene expression and secretion<sup>33</sup>. Thus, inhibition of Ang II by ARBs might result in reduced leptin production.

Renin angiotensin system blockade by (ARBs) promotes the differentiation of adipocytes via angiotensin II type 1 receptor blocking<sup>10</sup>, and by Peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) activation with subset of ARBs. PPAR- $\gamma$  agonists have an anti-inflammatory role, as shown by their inhibitory effects on the production of inflammatory cytokines<sup>34</sup>, the formation and release of adipocytokines are partly regulated via PPAR-dependent pathways<sup>27</sup>.

### **Conclusion**

Monotherapy with telmisartan and valsartan produce a beneficial reduction effects on BP and reduce leptin level. The improvement of leptin sensitivity may play a role directly or indirectly in the induction of hypertension control.

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