Original Article

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The Effects of Telmisartan and Losartan on Insulin Sensitivity

Hipertansif Tip 2 Diyabetiklerde Telmisartan ve Losartanın İnsülin Duyarlılığına Etkileri

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Abstract

Purpose: Telmisartan has been reported to increase insulin sensitivity by acting as a partial PPAR-gamma agonist, regardless of its renin-angiotensin system inhibition, but losartan has no such activity. In this study, we compared the effects of telmisartan and losartan on insulin sensitivity among type 2 diabetic patients.

Material and Method: Age, sex and weight-matched patients, who had been on telmisartan or losartan treatment for at least 3 months, were included. Their anthropometric measurements were performed, blood pressures were recorded. Fasting venous blood samples were obtained for analyzing the levels of glucose, HbA1C, insulin and adiponectin. HOMA-IR was calculated. An euglycemic hyperinsulinemic clamp procedure was performed in each subject and M index was calculated. Thereafter, telmisartan and losartan were withdrawn in both groups. A cross-over design was planned; following a wash-out period of 15 days, losartan group (Group 1) was given telmisartan 80 mg/day, telmisartan group (Group 2) was administered losartan 50 mg/day. After 12 weeks of therapy, all measurements, calculations and the euglycemic hyperinsulinemic clamp test were re-performed.

Results: General characteristics of the patients at inclusion were similar. Nine cases in group 1 and 8 cases in Group 2 concluded the follow-up. In Group 1, among all follow-up parameters, only weight exhibited a significant decrease at final evaluation (p=0.034). In Group 2, only M value was found to increase (p=0.028).

Discussion: Our findings indicated that losartan improved insulin sensitivity in patients with concomitant hypertension and type 2 diabetes, and telmisartan use resulted in more weight loss. *Turk Jem 2013; 17: 92-97*

Key words: Telmisartan, losartan, insulin resistance

Özet

Amaç: Anjiotensin Reseptör Blokörleri (ARB) insülin direncini düzeltmektedir. ARB grubundan telmisartanın Renin-anjiotensin- sistemi inhibisyonundan bağımsız, parsiyel PPAR-gamma aktivitesi göstererek insülin duyarlılığını arttırdığı gösterilmiştir. Bir başka ARB olan losartanda bu aktivite bulunamamıştır. Çalışmamızda tip 2 diyabetik hastalarda telmisartan ve losartanın insülin direnci üzerine etkilerini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya üç aydır telmisartan yada losartan alan, sulfonilüre tedavisi ile metabolik kontrolü sağlanmış 2 diyabetli hastalar alındı. Hastaların antropometrik ölçümleri alındı, açlık plazma glukozu, HbA1C, bazal insülin ve serum adiponektin düzeyleri belirlendi; HOMA-IR hesaplandı. Hiperinsülinemik-öglisemik klemp testiyle insülin duyarlılığını yansıtan M değerleri bulundu. Takiben hastaların almış olduğu ARB kesildi. On beş günlük ilaçtan temizlenme periyodunu takiben önceden losartan almış olan gruba (Grup 1) telmisartan (80 mg/gün), önceden telmisartan almış gruba (Grup 2) losartan (50 mg/gün) verildi. On iki hafta takip sonunda hastalara bahsedilen antropometrik ölçümler ve laboratuvar testleri ile hiperinsülinemik öglisemik klemp testi tekrarlandı.

Bulgular: Çalışmayı 1. Gruptan dokuz, 2. Gruptan sekiz hasta tamamladı. Başlangıç özellikleri açısından gruplar arasında anlamlı farklılık yoktu. Çalışma bitiminde Grup 1'de kan basıncı, açlık plazma glukozu, HbA1C, bazal insülin düzeyi, serum adiponektin düzeyileri, HOMA-IR ve M değerlerinde başlangıca göre anlamlı farklılık yokken vücut ağırlığı ve vücut kitle indeksinde istatistiksel anlamlı azalma tespit edildi (p=0,034 ve p=0,023). Buna karşın Grup 2'deki hastalarda bahsedilen hiçbir parametrede çalışma başlangıcı ve bitişi arasında fark yokken hiperinsüliemik-öglisemik klemp testiyle belirlenen insülin duyarlılığında anlamlı artış saptandı (p=0,028).

Tartışma: Bu bulgularla kısa süreli tedavide tip 2 diyabetik hastalarda losartanın insülin duyarlılığını, telmisartan anlamlı kilo kaybı yaptığı halde bu ilaca göre daha belirgin düzelttiği sonucuna varıldı. *Turk Jem 2013; 17: 92-97*

Anahtar kelimeler: Telmisartan, losartan, insülin direnci

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Introduction

The relation between hypertension, insulin resistance and hyperinsulinemia is well known. In untreated essential hypertensive patients, fasting and postprandial insulin levels were higher than the results in normotensive controls and when adjusted for body mass index, a direct relationship was found between plasma insulin levels and blood pressure (1,2,3). According to large prospective studies conducted in several populations, the risk of developing type 2 diabetes is greater in patients with essential hypertension compared to non-hypertensive individuals (4).

The renin-angiotensin system (RAS), which plays a key role in the regulation of blood pressure, is known to have an effect on the development of insulin resistance and diabetes. In the same manner, insulin resistance also has effects on the RAS tissue. In insulin resistance, by means of postranscriptional mechanisms, angiotensin receptor 1's (AT1) upregulation in tissues and an increase in activity and production of angiotensin II (AT II) production occur (5). There is evidence that AT II inhibits insulin-induced vasodilatation and glucose transport (6,7). Inhibition of RAS may reduce insulin resistance by improving blood flow in muscle tissues (8), by reducing sympathetic activity (9), by making changes in the levels of serum ions (10), by regulating the insulin signaling pathway independently of vasodilation and thus by increasing peripheral glucose utilization (11) and with the effects of adipokines with fatty tissue (12) . At the same time, it is thought that RAS inhibition has positive contributions to insulin secretion by its corrective effect on the ionic balance of potassium and magnesium and by improving microcirculation of pancreatic beta-cells (13).

RAS inhibition drugs such as angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) significantly lower insulin resistance and have antidiabetic effects. Because of their positive metabolic effects, they are popular agents in terms of development of diabetes. ACEI's and ARB's protective effects on the inhibition of the RAS have been found to be similar, the conducted meta-analyses calculated that RAS inhibition decrease approximately 22% of the relative risk of developing type 2 diabetes by using this group of drugs (14).

Recently, antidiabetic effects of ARBs were found to be seen as partial PPAR-gamma agonism (peroxisome proliferator-activated receptor-gamma) (15). PPAR-gamma activation provides differantiation of preadipocytes to mature adipocytes in fatty tissue, and it provides insulin sensitivity enhancing effect in adipose tissue. Again, the secretion of cytokines which have negative effect on insulin resistance, such as free fatty acids, tumor necrosis factor alpha, interleukin-6 and resistin, decrease and insulin-sensitizing adiponectin secretion increases (16). At At1r removed cell models, this PPAR-gamma activity was found to be maintained, thus it was concluded that inhibition of this activity was independent of RAS (15). Among ARBs, only telmisartan has a PPAR-gamma-stimulating effect at therapeutic concentrations, where high doses of irbesartan (partially) and candesartan (a little less) have similar activity (17). No PPAR-gamma activity was observed at any concentration of the other ARBs or losartan (17,18).

In our study, we aimed to compare the effects of telmisartan and losartan on insulin resistance in patients with treated type 2 diabetes. In this way, we aimed to investigate if there is significant advantage of telmisartan, a dual-acting drug which has the RAS inhibition and partial PPAR-gamma activity at therapeutic doses, over classical ARBs which, do not have known PPAR-gamma activity in clinical practice.

Materials and Methods

Patient Selection

This study includes 20 patients who applied to Başkent University Adana Teaching and Research Hospital, Endocrinology and Metabolic Diseases. Patients were newly diagnosed with type 2 diabetes, they were medically untreated and had mild to moderate hypertension. All type 2 diabetes diagnoses were based on The American Diabetes Association Guide published in 2004 (19). Patients were diagnosed with mild to moderate hypertension if they had stage 1 hypertension according to Joint National Committee VII criterias (20). Smokers, patients with chronic alcoholism problem, uncontrolled hypertensive patients with arterial blood pressure averaged 140/90 mm / Hg in last three weeks, type 1 diabetic patients, poorly controlled diabetics with glucosyl hemoglobin (HbA1c)> 8%, pregnant women, patients with single kidney or malignancy, patients with any endocrinological chronic disease, liver or kidney failure and patients over the age of 65 were excluded from the study. After approval of the Başkent University Faculty of Medicine central ethics committee with project number KA-05/256, the patients included in the study read and approved volunteers' information sheet.

Preparatory Period

Insulin secretogog monotherapy (sulfonylurea or meglitinide) was started for diabetes patients enrolled in the study group and patients were divided into two groups based on their antihypertensive treatment. Group 1 patients (n=10; 5 females, 5 males) was started losartan 50 mg / day and group 2 patients (n=10; 3 females, 7 males) was started telmisartan 80 mg / day. Both groups were advised with proper nutrition diets. Blood glucose and blood pressure regulation was provided with monthly visits.

Study Design

At the end of three months of treatment, patients received standard-carbohydrate diet for 3 days and after 12 hours fasting; their arterial blood pressures, waist circumferences and body weights were measured; body-mass index (BMI) was calculated as kg/m^2. Serum potassium, creatinine, glucosyl hemoglobin (HbA1c) levels, fasting plasma glucose levels and basal insulin were measured from patients' venous blood samples. HOMA-IR values were calculated with the {Fasting Glucose (mmol / l) x fasting insulin (mU/mL)} / 22.5 formula. A portion of the venous blood plasma was stored to analyze adiponectin levels later. For each patient, hyperinsulinemic euglycemic clamp test (HECT) was applied based on the method described by de Fronzo and calculated M values were recorded (21).

Lag period: Then both groups' anti-hypertensive treatments (telmisartan and losartan) were stopped for a period of two weeks (wash-out period). In this process, patients' daily blood pressure

monitoring were collected against the risk of hypertensive emergencies and none of the patients had an increase at their blood pressure, which might have required their removal from the study.

Follow-up period: After two weeks of drug-free period, group 1 (the group who started with losartan treatment) was given 80 mg/day telmisartan and Group 2 (the group who started with telmisartan) was given 50 mg/day losartan. Patients were recommended not to make a significant change in their dietary compliance and physical activity, and their blood pressure and blood sugar were followed through monthly visits. None of the patients required a change in their oral antidiabetic or antihypertensive medication dose.

End of study

At the end of third month, all patients' biochemical and anthropometric measurements were re-taken, blood samples were taken for serum adiponectin levels and M values were recorded by performing HECT.

Height and body weight of patients were measured in a standard scale. Blood pressure was recorded by calculating the average of three measurements taken with standard arm sleeve sphygmomanometer after 5 minutes of resting. Plasma glucose was measured with enzymatic colorimetric method (glucose oxidase method), creatinine was measured with kinetic colorimetric method; and potassium levels were measured with ion selective electrode method in biochemistry analyzer (Roche Modular DP). Plasma fasting insulin levels were measured with microparticle enzyme immunassey method (Axsym Abbott Diagnostics Division), and adiponectin levels were measured with enzyme linked immunosorbent assey (ELISA) method (BIOVENDOR Human adiponectin Elise, Tecan Sunrise).

SPSS 11.0 for Windows was used for statistical evaluation. Both groups' patient characteristics and the parameters' mean values were determined by cross-tabs. Intergroup comparisons were performed by using independent samples t-test. In each group, the change in patients' own characteristics and parameters at the beginning and at the end were compared with paired samples t-test. For statistical significance p value was considered to be smaller than 0.05.

Results

Initially, 20 patients were included in the study, (2 groups including 10 patients). One patient from the first and 2 patients from the second group were excluded from the study for not attending visits regularly. Nine patients (4 female, 5 male) from group 1 and eight patients (one female, 7 male) from group 2, a total of 17 patients, completed the study. The average age of the patients was 51.2 ± 6.4 years for group 1; and 44.6 ± 6.2 years for group 2. Characteristics of the patients at the beginning and at the end are given in Tables 1 and 2.

1- Body weight and BMI: At the beginning of the study there was no significant difference between two groups in terms of average body weight and BMI (p=0.39). At the end of the study, there was a significant decrease in group 1 patients' body weights and BMI in Group 1 (p=0.034 and p=0.023). At the end of the study, Group 2 patients mean body weight and BMI did not change significantly compared to the beginning (p=0.27 and p=0.34).

2- Blood pressure: At the beginning of the study, both groups had similar systolic blood pressure (SBP) values (p=0.67). In Group 2 patients, the mean diastolic blood pressure (DBP) levels were significantly lower compared to Group 1 patients DBP (p=0.043). At the end of the study, in both groups, there was no statistically significant change in terms of SBP and DBP compared to the initial measurements (Table 1 and 2).

3- Fasting Plasma Glucose (FPG) and glycosylated hemoglobin (HbA1c) levels: At the beginning of the study, in both groups, starting FPG levels did not differ statistically (p=0.49). HbA1c levels were significantly lower in Group 2 (p=0.032). At the end of the study, in both groups, mean FPG and HbA1c levels did not differ significantly compared to the initial measurements (Tables 1 and 2).

4- Adiponectin: At the beginning of the study, there was no statistically significant difference between two groups in terms of average adiponectin levels (p=0.38). At the end of the study, there was no statistically significant difference at the adiponectin levels compared to initial measurements (p=0.27 and p=0.087).

5- Insulin, HOMA-IR, and M value: At the beginning of the study, there was no statistically significant difference between two groups in terms of fasting plasma insulin, HOMA-IR and M values calculated with HECT (p=0.072, p=0.39 and p=0, 48).

At the end of the study, in Group 1 patients, there was no significant change compared to initial values in terms of median fasting plasma insulin levels, HOMA-IR and M values calculated by HECT (Table 1).

In Group 2 patients, there was a slight but statistically insignificant decrease compared to the initial values in terms of fasting insulin level and HOMA-IR values (Table 2). However, in Group 2, there was a statistically significant increase in M values calculated by HECT compared to the initial values (p=0.028).

6- Serum creatinine and potassium levels: During follow-up, none of the patients enrolled in the study had any elevation in serum creatinine or potassium levels that would have changed the treatment.

Discussion

In our study, the group switched from losartan to telmisartan (Group 2) showed more improvement in insulin sensitivity determined by HECT than the group switched from telmisartan to losartan (Group 1). In contrast, in the group that switched to telmisartan, significantly decreased body weight values were recorded compared to the other group. In both groups, there were no difference between blood pressure, fasting plasma glucose, basal insulin levels, HOMA-IR values and adiponectin levels.

In several experimental and clinical studies, telmisartan and losartan have been shown to increase insulin sensitivity, reduce the occurrence of diabetes and lower fasting plasma glucose and HbA1c levels in diabetic patients (18,22,23,24,25). These two ARBs' beneficial effects on insulin resistance and glucose metabolism are due to their RAS blockade ability. In addition to that, it has been reported that telmisartans' partial PPAR-gamma agonistic feature increases insulin sensitivity indepently from RAS blocade

effect (17). Telmisartan is the only ARB which has PPAR-gamma stimulating effect at therapeutic dose plasma concentrations. Other ARBs and losartan do not have PPAR-gamma activity at therapeutic concentrations (17,18). In studies, significant structural similarities were found between pioglitazone (synthetic PPAR-gamma agonist) and telmisartan and telmisartan is thought to act as a synthetic PPAR-gamma ligand (18). However the molecular studies of telmisartan showed that telmisartan binds to the same ligand as full PPAR-gamma agonists, but provides 70%-75% less activation compared to these molecules (18). In addition, telmisartan has been shown to reduce diet-induced weight gain regardless of energy intake (18,26). This results from termisan's adipocyte differentiation and its being a weak stimulus on adipogenesis (18). Telmisartan has been shown to increase fatty acid catabolism in tissues where it activates PPAR-gamma-dependent lipolytic pathways (27). This positive effect of on the body weight provided by telmisartan was absent in Losartan, therefore it has been reported that this effect was independent from the inhibition of RAS (28). In the literature, three experimental and clinical studies are available comparing metabolic activities of losartan and telmisartan. In Benson and colleagues' study including high-carbohydrate diet taking rats, at the end of five weeks of treatment, telmisartan groups' glucose, insulin and triglyceride levels have dropped significantly compared to losartan and control groups. Also in this study, telmisartan caused a 10% reduction in the body weight of rats compared to losartan and control group (18). In Vitale and colleagues' study, in patients with newly diagnosed hypertension and metabolic syndrome, fasting glucose, insulin and HOMA scores dropped significantly in the telmisartan group compared to losartan (29). In Bahadir et al. study; in hypertensive patients with metabolic syndrome, telmisartan and losartan had neutral effects on insulin resistance calculated by HOMA-IR (30). Our study's results are interestingly different from these comparing studies. This could be due to several reasons. First of all, subjects used in these studies were not diabetic and also interpretations were made through HOMA-IR calculations that were determined only with blood glucose and insulin levels. Because of insulin having a pulsatile secretion kinetic

Table 1. Group 1 (telmisartan to losartan swithching group) patients' characteristics at the beginning and end of the study and change between the beginning and end of the study

Parameter	Study beginning	End of study	P value*
Body Weight (kg)	91,7±17,4	90,71±16,53	0,034
BMI (kg/m^2)	33,41±5,30	33,1±5,04	0,023
SBP (mm/Hg)	124±15	125,1±13,25	0,67
DBP (mm/Hg)	80±3,0	77± 8,7	0,28
Fasting plasma glucose (mg/dl)	129,4±46,1	127,8±27,69	0,12
Fasting insulin (uIU/ml)	16,5±9,6	14,86±10,69	0,072
HOMA-IR	5,1±2,9	4,62±3,16	0,091
HbA1C (%)	7,1±1,1	7,06±0,83	0,37
Adiponectin (mcg/ml)	7,4±2,2	8,44±3,41	0,27
M value	3,1±1,3	4,37±2,54	0,16

* P value limit for the statistical sifnificance was determined as <0.05

Table 2. Group 2 (losartan to telmisartan swithching group) patients' characteristics at the beginning and end of the study and change between the beginning and end of the study

Parameter	Study Beginning	End of Study	P value*
Body weight (kg)	89,8±11,7	90,6±13,7	0,27
BMI (kg/m^2)	31,57±4,29	31,84±4,86	0,34
SBP (mm/Hg)	124±15	124,1±8,85	0,62
DBP (mm/Hg)	74±6,0	79,9±7,7	0,87
Fasting plasma glucose (mg/dl)	130,9±31,7	121,75±25,74	0,29
Fasting insulin (uIU/ml)	13,2±7,1	10,81±5,54	0,37
HOMA-IR	4,2±2,6	3,42±2,32	0,63
HbA1C (%)	5,9±0,5	6,27±0,95	0,35
Adiponectin (mcg/ml)	7,7±2,8	7,84±2,86	0,087
M value	2,3±1,1	4,26±1,956	0,028

* P value limit for the statistical sifnificance was determined as <0.05

in normal physiology (31) and in routine measurements proinsulin and insulin are tested together (32), this method does not seem very useful due to the error it may cause at the determination of insulin sensitivity. Unlike this study; in our study, diabetic patients were included and insulin sensitivity was determined by HECT that is still regarded as the primary standard tool in the whole world for insülin sensitivity calculation (21). Therefore, although the results appear to be different from previous studies, our study is still reliable. Similar to Bahadir et als' study (30), we found no significant change in fasting plasma insulin levels, fasting plasma glucose and calculated HOMA-IR values at the end of the study compared to initial vaules. However, in telmisartan to losartan switching group there was a significant improvement in terms of insulin sensitivity calculated by HECT. Accuracy and reliability of HECT results and calculation of HOMA-IR obtained from these results are indisputable. Different results obtained from this method especially reveal the importance of the method chosen for studies with a limited number of patients.

In our study, we measured serum adiponectin concentration to compare both drugs' effects on adipocyte differentiation. At the beginning, there was no significant difference between two groups in terms of adiponectin levels. Also, in both groups, at the end of the study, we did not detect a significant change in adiponectin levels compared to initial values. In the literature, we found one study that compared losartan and telmisartans' effect on adiponectin levels published by Erba et al. Their results were similar to ours and both drugs did not show a significant effect on adiponectin levels (17). In studies, it has been shown that an increase in adipocyte differentiation and adiponectin synthesis occurs with AT1 blockade (12). This approach may explain why there was no difference between two drugs in terms of their effect on adiponectin levels. During the study, there was no change made in patients' nutrition, physical activity habits and antidiabetic treatment. Altough this eliminates complex results, in losartan to telmisartan switching group we observed statistically significant weight loss and BMI reduction compared to initial values (p=0.034 and p=0.023). These results are consistent with the literature (18,26). Telmisartan's weight loss effect was not observed in losartan. Hence this effect is thought to be independent from RAS inhibition (18). Weight loss is known to enhance insulin sensitivity. Even though losartan does not provide weight loss like telmisartan, it is more effective on insulin resistance. This makes us think that losartan is more effective on insulin sensitivity than telmisartan. Our explanation of this condition is: RAS inhibition has more effect on insulin sensitiviy than partial PPAR-gamma activity and in tissues; losartan is more potent in RAS inhibition than telmisartan. For this hypothesis to be valid, more in-vitro experimental comparative studies are needed.

In conclusion, in metabolically controlled type 2 diabetic patients, telmisartan (an ARB with a partial PPAR-gamma agonist effect) has more positive effect on body weight than losartan (which do not have PPAR-gamma agonist effect) but losartan reduces insulin sensitivity more than telmisartan. We argue that considering the positive metabolic effects, losartan is an antihypertensive agent that can be used for hypertensive patients with type 2 diabetes.

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