The Effect of Trandolapril on Insulin Resistance is Determined by the Degree of Baseline Resistance Level

Canan Ersoy[1], Alparslan Ersoy[2], Gulsah Elbuken[3], Ercan Tuncel[1]

[1] Division of Endocrinology and Metabolism, Uludag University Medical Faculty, Bursa, Turkey
[2] Division of Nephrology, Uludag University Medical Faculty, Bursa, Turkey
[3] Division of Endocrinology and Metabolism, Tekirdağ State Hospital, Tekirdağ, Turkey

Abstract

Insulin resistance (IR) is the core problem in type 2 diabetes mellitus that may lead to cardiovascular morbidity and mortality. Hypertension commonly accompanies type 2 diabetes. Antihypertensive agents improving IR may reduce the risk of cardiovascular diseases. This study was conducted to assess the effect of trandolapril on IR, glucose and lipid metabolisms in hypertensive subjects with different degrees of IR and investigate the importance of IR level in angiotensin converting enzyme inhibitor response. The subjects were nondiabetic and type 2 diabetic hypertensive patients treated with trandolapril for 12 weeks. Blood pressures (BP) and metabolic parameters were measured in all patients at baseline and after 12 weeks of trandolapril treatment and compared. Trandolapril reduced BP similarly in nondiabetic and diabetic patients. Homeostasis model assessment insulin resistance (HOMA-IR), serum glucose and hemoglobin A1C (A1C) in diabetic patients were higher than nondiabetics. HOMA-IR (from 9.0 □ 1.0 to 6.6 □ 0.7, $p<0.05$) values improved significantly after trandolapril in diabetics, while serum glucose, insulin and A1C remained unchanged. The posttreatment HOMA-IR values were comparable in both groups. Pretreatment HOMA-IR value was found to be associated with HOMA-IR response to trandolapril while changes in BMI, A1C and BPs were unrelated. The patients with a pretreatment HOMA-IR of >4.67 responded better. In conclusion, trandolapril improved insulin sensitivity better in type 2 diabetic hypertensive patients with higher degree of IR compared with the ones with low grade IR, being independent of its hemodynamic action.

Key Words: Trandolapril, insulin resistance, type 2 diabetes mellitus, glucose, lipid

(Rec.Date: Jul 25, 2013 Accept Date: Sep 04, 2013)

Corresponding Author: Canan Ersoy, Uludag University Medical School Department of Internal Medicine, Division of Endocrinology and Metabolism-16059, Görükle-Bursa, Turkey
Fax: +90 224 2951249, **Tel**: +90 224 2951113
E-mail: ecanan@uludag.edu.tr

Introduction

Insulin resistance (IR) syndrome is composed of risk factors for cardiovascular disease, including IR with hyperinsulinemia, atherogenic dyslipidemia, hypertension, abdominal obesity, and impaired hemostasis. Patients with type 2 diabetes mellitus (DM) in whom IR is the core problem frequently manifest multiple risk factors for cardiovascular morbidity and mortality. Hypertension is a common problem in diabetic patients [1-4]. Antihypertensive agents that can ameliorate IR may help to reduce the risk of cardiovascular disease [5]. Class differences in the effects of antihypertensives on metabolic indices may therefore be an important consideration when choosing treatment for patients who exhibit these characteristics. Experience from clinical trials suggests that drugs that target the renin-angiotensin system may have metabolic advantages over drugs such as beta-blockers and diuretics, but this conclusion has not been proved definitively [6].

Most of the clinical studies evaluating the effect of angiotensin converting enzyme inhibitors (ACEI) on insulin sensitivity reported enhanced insulin sensitivity. However a limited number of clinical investigations have demonstrated ACEIs to be metabolically neutral in healthy and in hypertensive nondiabetic or type 2 diabetic subjects [4,5]. One possible explanation for these neutral findings might be the fact that the baseline insulin sensitivity of the subjects in these investigations was either normal or slightly depressed [7,8]. It was shown that as the number of the components of the metabolic syndrome increases, the degree of IR increases [9].

Trandolapril is a long acting ACEI [10]. Although it was shown to improve IR in insulin resistant obese Zucker or spontaneously hypertensive rat studies [11,12], many clinical studies showed that trandolapril has a neutral effect on IR in hypertensive patients with type 2 DM [13-15]. As trandolapril is a lipophylic agent [10], by acting on adipose tissue, it might be more efficient in obese subjects by tissue ACE inhibition. Although the antihypertensive effectiveness of trandolapril has been detailly investigated, its' effects on IR, glucose and lipid metabolisms in humans are quite obscure. This study was aimed to compare these effects in type 2 diabetic and nondiabetic hypertensive patients with different degrees of IR and investigate the importance of IR level in ACEI response concerning glucose and lipid metabolisms.

Material and Methods

Patient Selection and Study Design

A prospective, open-labelled observational study was conducted in consecutive hypertensive type 2 diabetic and nondiabetic outpatients who were followed up in our diabetes and hypertension outpatient clinics. Informed consent was obtained from all participants, and the study was performed in accordance with the Declaration of Helsinki and with the approval of the local ethics committee. The patients had mild to moderate hypertension according to World Health Organisation (WHO) criteria. Diabetic patients were on medical nutrition therapy (MNT) with or without gliclazide treatment and had stable glycemic control parameters three months and just before the enrollment of the study (7.59 ± 0.5 mmol/L vs 7.73 ± 0.5 mmol/L for glucose and 7.5 ± 0.3% vs 7.53 ± 0.3% for hemoglobin A1C (A1C), $p>0.05$). Same sulphonylurea; gliclazide which is thought to have no direct effect on IR was chosen in all patients to provide a standardization on oral hypoglycemic agent used. Patients having drug usage or illness except DM that may influence lipid and carbohydrate metabolism, pregnancy, nephrotic syndrome, renal artery stenosis, coronary artery disease, hyperkalemia (>5 mEq/L), hypersensitivity against ACEIs were excluded from the study. A fasting plasma glucose ≥7.0 mmol/L or a random plasma glucose ≥11.1 mmol/L measured at least twice in the presence of symptoms confirmed the diagnosis of DM. Late autoimmune diabetes of adults (LADA) was excluded by anti-islet cell antibody negativity and normal or high c-peptide levels (median 3.4 ng/ml). The study was carried out in accordance with the guidelines of the Helsinki Declaration of Human Studies. All the patients gave written informed consent before participation.

Twenty nine type 2 diabetic and 21 nondiabetic hypertensive outpatients were included in the study and underwent a complete physical examination, electrocardiographic, biochemical and hematological investigations. Starting from the first admission to our diabetes outpatient clinic each patient was guided to have a regular exercise programme as well as the nondiabetic group. Besides, a programme for MNT was given according to American Diabetes Association (ADA) guidelines for the diabetic group. Fifty five percent of the total calories was obtained from carbohydrates, 15% from protein and 30% from fat. Nine patients were under MNT only and not required oral hypoglycemic agent for blood glucose regulation.

The rest were under MNT and gliclazide treatment. After enrollment, treatment for diabetes remained unchanged throughout the study. All patients had a salt intake of 5 g/day or less.

Six diabetic patients under different antihypertensive treatment regimens other than ACEI on their first admissions had a washout period of 4 weeks. Later all patients received trandolapril 2 mgs once daily. Possible side effects of the drug were recorded during visits.

Measurements

Trandolapril was given once daily in the morning between 08:00 and 09:00 for 12 weeks. Blood Pressure (BP) measurements were obtained from each patient's right arm in seated position by using a standard mercury sphigmomanometer. Measurements were taken in the morning before daily drug intake (ie, 24 h after dosing, at trough) and after the subject rested for ten minutes in a quiet room. Two successive BP readings were obtained at 5-min interval and averaged. Body weight and height were measured in the fasting state with the subjects only wearing underclothes and body mass index (BMI) was computed as weight in kilograms divided by height in meters squared.

Baseline laboratory parameters including whole blood count (Sysmex 2000), serum glucose (enzymatic method), total cholesterol (T-chol), triglyceride (TG) (Technicon Dax System Methods Manual, Technicon Instruments Corp. Tarrytown, USA), high density lipoprotein cholesterol (HDL) (phosphotungustic acid precipitation method), lipoprotein (a) (Lp(a)), apolipoprotein A1 (Apo A1), apolipoprotein B (Apo B) (N Latex Lp(a), N Antisera to human Apolipoprotein A-I and Apolipoprotein B, Behring Diagnostics Inc. Westwood, USA), hemoglobin A1c (A1C, normal range: 4.4 to 6.4%) (high performance liquid chromotography, BIO RAD Diagnostics Group, California, USA) and insulin levels (radioimmunassay, Medical System DPC, Los Angeles, CA, USA) were measured after 12 hours of overnight fasting in both groups. Low density lipoprotein cholesterol (LDL) was calculated by Friedewald Formula [16].

Serum glucose and insulin levels were measured 3 times with 5 minute intervals after 12 hours of fasting in all patients just before trandolapril administration. The arithmetical means of the 3 values were obtained. Insulin sensitivity was calculated using the homeostasis model assessment-insulin resistance (HOMA-IR) index [formula: (fasting glucose (mmol/L) x fasting insulin (μIU m/L))/22.5] [17]. Creatinine clearance was studied in 24 hour urine

collection. It was corrected according to body surface area. Microalbuminuria was determined with enzyme immunoassay method using Immulite 2000 albumin kit (Diagnostic Products Corporation, Los Angeles CA). All these measurements were repeated after 12 weeks of trandolapril treatment.

Statistical Analysis

Clinical and laboratory data were expressed as mean ± SEM. By taking variability skewness (a3) and curtosis (a4) values into account the non-parametric and parametric test options were evaluated. The numerical variables were compared with paired student t test or Wilcoxon signed rank test in intragroup comparisons and with unpaired student t test or Mann-Whitney U test in intergroup comparisons. In groups percentage changes of numerical variables was also calculated. Comparisons of ratios in both groups were performed with chi-squared test. To evaluate the correlation between percentage changes and numeric variables Pearson r correlation test was used. Nonparametric Spearman's rho correlation test was used in the case of the presence of extreme values and non-homogenous distribution of variables. The variables were studied with Binary logistic regression analysis to determine whether they directly decrease in HOMA-IR after trandolapril treatment or not. The ROC curve was used to determine the threshold for predicting trandolapril treatment outcome. All statistical analysis was done with statistical programme of SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). *P* values ≤0.05 were considered significant.

Results

All patients enrolled in the trial completed the trandolapril treatment except two female patients -one from each group- who could not tolerate the drug due to severe headache and symptomatic hypotension. The characteristic features of both groups were similar (p>0.05, Table 1). Obese ratios (BMI ≥30 kg/m2) were also indifferent (30% vs 53.9%, p>0.05).

Table 1. Comparison of the Characteristics of Nondiabetic and Diabetic Groups*

	Nondiabetic group (n=20)	Diabetic group (n=28)
Age (years)	50.5 ± 1.2	53.2 ± 1.6
Gender (F/M)	10/11	20/9
BMI (kg/m^2)	28.5 ± 0.6	30.6 ± 0.7
Duration of diabetes (years)		3.3 ± 0.8
Duration of hypertension (years)	2.0 ± 0.6	3.7 ± 0.6
Hemoglobin (g/dL)	14.5 ± 0.2	13.2 ± 0.2
Creatinine (mg/dL)	0.82 ± 0.04	0.82 ± 0.03
Creatinine clearance (ml/min)	112.8 ± 7.2	99.7 ± 9.2
Microalbuminuria (µg/min)	19.4 ± 7.1	13.8 ± 2.6

*p>0.05 vs other group.
F: Female; M: Male; BMI: Body mass index.

The baseline serum glucose, A1C and HOMA-IR values of the diabetic group were significantly higher than the nondiabetic group. BMI, serum insulin, systolic and diastolic BPs were indifferent. Mean systolic and diastolic BPs decreased in both groups after trandolapril treatment. Percentage changes of systolic and diastolic BPs in nondiabetic and diabetic patients were comparable (-11% and -10% vs -6.6% and -15%, respectively). BMI and HOMA-IR values decreased significantly in the diabetic group after 12 weeks of trandolapril treatment. Decrements in serum glucose, insulin and A1C levels were statistically insignificant. There was no significant change in these parameters in the nondiabetic group after trandolapril treatment. The posttreatment HOMA-IR values were similar in both groups (Table 2). While percentage changes of BMI (0.2% vs -1.4%), serum glucose (3.1% vs -5.7%), insulin (-9.1% vs -18.4%) and HOMA-IR (-10.9% vs -13.8%) in nondiabetic and diabetic patients were comparable, percentage changes of A1C (3.6% vs -5.5%, $p<0.01$) were significant.

Table 2. Comparison of the Changes after 12 weeks of Trandolapril Treatment in BP and Metabolic Indices in Nondiabetic and Diabetic Groups

	Nondiabetic group (n=20)		Diabetic group (n=28)	
	Baseline	After 12 week	Baseline	After 12 week
BMI (kg/m^2)	28.5 ± 0.6	28.5 ± 0.7	30.6 ± 0.7	30.0 ± 0.7*
Systolic BP (mmHg)	158.5 ± 3.7	140.2 ± 2.5*	158.2 ± 2.3	142.3 ± 2.7*
Diastolic BP (mmHg)	97.5 ± 1.2	87.5 ± 1.2*	100.1 ± 1.1	85.0 ± 1.1*
Glucose (mmol/L)	5.7 ± 0.2	5.9 ± 0.2	7.7 ± 0.5**	6.9 ± 0.4
A1C (%)	5.5 ± 0.1	5.7 ± 0.09	7.5 ± 0.3**	6.9 ± 0.3†
Insulin (μIU/mL)	20.6 ± 2.8	16.9 ± 1.9	25.6 ± 3.1	21.7 ± 2.3
HOMA-IR	5.6 ± 1.0	4.6 ± 0.6	9.0 ± 1.0‡	6.6 ± 0.7§

*p<0.001 vs baseline values of same group, ** p<0.01 vs baseline of other group, † p<0.01 vs after 12 weeks of other group, ‡ p<0.05 vs baseline of other group, § p<0.05 vs baseline of same group.
BP: Blood pressure; BMI: Body mass index; A1C: Hemoglobin A1c; HOMA-IR: Homeostasis model assessment-insulin resistance.

A subgroup analysis was performed concerning the changes in HOMA-IR values. The population was divided into two as having a decrement in HOMA-IR (Group 1, n: 26, n diabetics: 15) and no decrement in HOMA-IR (Group 2, n. 22, n diabetics: 13) after trandolapril treatment. There was no difference between the baseline characteristics among two groups. Pretreatment insulin (29.0 ± 3.4 vs 17.0 ± 1.6) and HOMA-IR (9.8 ± 1.2 vs 5.0 ± 0.7) values of Group 1 were higher than those of Group 2 (p<0.01). Changes in serum insulin and HOMA-IR after the treatment were also significant (-39.6% vs 25.7% and -51.3% vs 48.5%, respectively, p<0.01) but not A1C, BMIs and BPs.

The changes that had occurred in HOMA-IR in all patients after trandolapril treatment and variables that might influence IR were evaluated. The changes in HOMA-IR after 12 weeks of trandolapril treatment were negatively correlated with pretreatment glucose (r=-0.289,

p<0.05), pretreatment insulin (r=-0.391, p=0.006) and pretreatment HOMA-IR (r=-0.419, p=0.003) but not age, diabetes and hypertension durations, baseline A1C, T-chol and TG levels, the changes in weight, BMI, A1C and BPs. When Logistic regression model was applied for all factors related to IR except glucose and insulin, which were included in the HOMA-IR equation, pretreatment HOMA-IR value was found to be associated with a decreament in HOMA-IR after trandolapril treatment (OR: 0.754, p<0.01, 95% CI: 0.612 to 0.928). Age, gender, hypertension duration, being diabetic, changes in variables such as BMI, A1C and BPs were found to be unrelated with the response. The ROC curve for the pretreatment HOMA-IR showed that all patients with a resistance of > 4.67 responded better to the trandolapril treatment with a sensitivity of 75% and a specificity of 65% (area under the ROC curve= 0.700, Fig. 1), but not for the pretreatment insulin level.

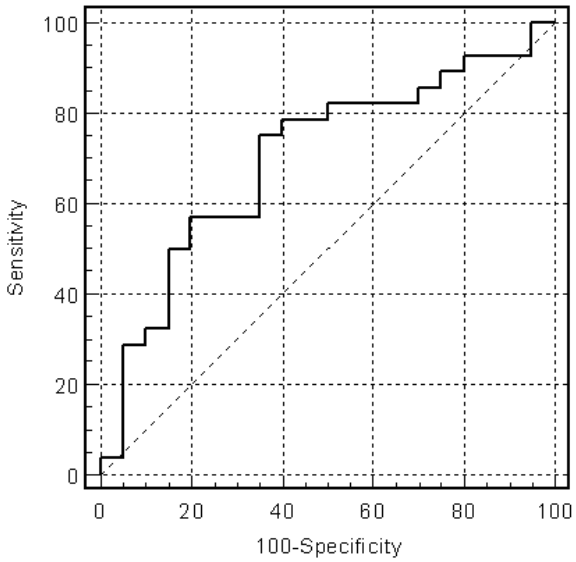

Figure 1. The ROC curve of the pretreatment HOMA-IR for predicting the outcome of the trandolapril treatment in 48 patients (area under the ROC curve= 0.700, standard error= 0.075, p=0.019, 95% confidence interval= 0.551 to 0.824).

Baseline and after 12 weeks treatment, lipid parameters were similar in both groups. Mean HDL, Apo A1 and Lp(a) values were increased and Apo B decreased in the nondiabetic group after trandolapril treatment. There were increments in apo A1 and decrements in Lp(a) levels in the diabetic group (Table 3). There was only a significant difference between percentage changes of Lp(a) in nondiabetic and diabetic patients (5.8% vs -11.5%, p>0.01). There was no

correlation between changes of Lp(a) levels and HOMA-IR in diabetics. Whole blood counts, serum urea, creatinine and electrolyte levels, creatinine clearances and microalbuminurias of these patients did not change significantly after the treatment ($p>0.05$). No side effect due to trandolapril was observed except dry cough in three nondiabetic hypertensive patients.

Table 3. Comparison of the Changes after 12 weeks of Trandolapril Treatment in Lipid Parameters in Nondiabetic and Diabetic Groups

	Nondiabetic group (n=20)		Diabetic group (n=28)	
	Baseline	After 12 week	Baseline	After 12 week
T-chol (mg/dL)	186.1 ± 8	197.7 ± 8.2	192.5 ± 6	196.7 ± 6.4
HDL (mg/dL)	44.1 ± 1.8	48.2 ± 2.0*	45.6 ± 1.6	46.6 ± 1.6
TG (mg/dL)	116.5 ± 13.7	121.9 ± 18.3	199.1 ± 23.3	185.1 ± 21.2
LDL (mg/dL)	118.7 ± 5.9	125 ± 6.1	107.0 ± 4.4	113.0 ± 6.2
Apo A1(mg/dL)	150.8 ± 5.7	161.9 ± 5.5**	148.7 ± 4.9	165.1 ± 5.1*
Apo B (mg/dL)	109.5 ± 6.0	97.5 ± 4.4*	124.2 ± 5.3	127.1 ± 4.0
Lp(a) (mg/dL)	14.9 ± 3	16.6 ± 3.2**	28.0 ± 3.8	17.5 ± 2.0*

*$p<0.01$ vs baseline values of same group, ** $p<0.05$ vs baseline of other group.
T-chol: Total cholesterol; TG: Triglyceride; HDL: High density lipoprotein cholesterol; LDL: Low density lipoprotein cholesterol; Apo A1: Apolipoprotein A1; Apo B: Apolipoprotein B; Lp(a): Lipoprotein (a).

Discussion

In the present study, after 12 weeks of treatment, trandolapril was found to be improving insulin sensitivity in type 2 diabetic hypertensive patients, despite no effect on IR in nondiabetic ones and lowers BP significantly in both groups.

In a hospital-based study performed in our country, mean value for HOMA-IR was found to be 2.24 in healthy subjects, 3.13 for hypertensives and 5.51 for diabetic patients [18]. Mean

HOMA-IR level of our diabetic patients were higher than those of nondiabetics (9.0 vs 5.6) and both higher than those of the groups mentioned above.

The potential mechanisms of metabolic actions of ACEIs appear to represent a class effect, which are inhibition of angiotensin II formation that may have glycogenolytic and gluconeogenic properties, inhibition of bradykinin degradation, vasodilatation of insulin-sensitive tissues or decrease in circulating catecholamines [5,14]. However, no increase in insulin sensitivity was found in healthy volunteers or in hypertensive subjects with essentially normal insulin sensitivity following administration of the ACEIs, lisinopril [7] or enalapril [8] for 4 weeks. These negative findings might be due to either normal [7] or only slightly depressed [8] baseline insulin sensitivity of the subjects in these investigations. Another potential explanation may be the design of the studies in which the action of the ACEI was measured 24 h after the last administration [5].

Trandolapril is a new generation nonsulphydryl, lipophylic ACEI with high tissue penetration and long elimination half life [10]. In experimental studies, acute and/or chronic administration of trandolapril improved insulin stimulated glucose transport in skeletal muscle in IR obese Zucker or spontaneously hypertensive rats compared to lean and normotensive controls [11,12]. Trandolapril was shown to enhance skeletal muscle insulin action and GLUT-4 protein levels in insulin resistant obese rats and it had no effect in insulin sensitive lean rat muscle [19]. In contrast to experimental studies most of the clinical studies conducted indicated that trandolapril has a neutral effect on IR [13-15, 20]. Only in one clinical study conducted in overweight hypertensive patients with low grade IR trandolapril improved insulin sensitivity moderately compared to nifedipine in the absence of severely obese and diabetic individuals [21]. Despite these conflicting results, we observed a significant decrement in IR in diabetic patients, but not in nondiabetic hypertensives. This interesting result may be due to the fact that IR was more prominent in our diabetic hypertensive patients. The mean levels of HOMA-IR and fasting insulin were significantly higher in this group. A high HOMA-IR (≥2.56) and fasting insulin concentration (≥9.98 μIU/mL) were found to be independent risk factors of the metabolic syndrome by multiple regression analysis after adjusting for age, gender and BMI [9]. A ≥4.67 pretreatment HOMA-IR value was the main determinant of the IR decrement effect of trandolapril in our study, there was no such a value for pretreatment insulin level (Figure 1).

The changes in BP and BMI after trandolapril treatment could affect IR in our study population. MNT and exercise programmes could be considered in part a reason for the differences in weight change and IR. Infact, same programmes were given to both groups with similar percentages of carbohydrates, proteins and lipids in total daily calories except MNT without pure glucose for diabetics. No correlation was found between changes in BP and insulin sensitivity and a significant decrement was obtained in the BMI only in the diabetic patients. Multivariate model showed that changes in BP and BMI did not affect the decrease in HOMA-IR in all patients. ACEIs may affect insulin sensitivity, in part, by modulating some cytokines and inflammatory markers [22-24]. Adiponectin is a cytokine that has protective effect against cardiovascular diseases. It's level decreases in the presence of IR, hypertension and type 2 diabetes. Trandolapril was found to be increasing adiponectin levels alone or in combination with verapamil [22]. Resistin is another cytokine that has strong positive correlation with IR and vascular inflammation. Type 2 diabetic and hypertensive subjects are known to have higher plasma resistin levels. Trandolapril was found to be decreasing resistin levels alone or in combination with verapamil [23]. TNF-alpha levels were reported to be higher in obese type 2 diabetic patients with IR compared to ones without IR and controls [25]. It's known that TNF-alpha increases resistin production and has inverse relation with adiponectin [23]. Lipophylicity of trandolapril could improve insulin mediated glucose utilization in adipose tissue via changes in adiponectin, resistin and/ or TNF-alpha, which are known to be a involved in obesity related IR.

Some authors demonstrated no change in insulin sensitivity after 18 weeks or 3 months of treatment with captopril in hypertensive nondiabetic or type 2 diabetic patients, despite a reduction in patients' weight of 1.5 or 1.1 kg, respectively [26,27]. Obese ratios and baseline BMI values of nondiabetic and diabetic patients were comparable. We found no significant correlation between the changes in HOMA-IR and weight at the end of 12 weeks of trandolapril treatment in the diabetic patients.

ACEIs might have an effect on glycemic control. CAPPP and HOPE are two large intervention trials that have pointed out the fact that long-term ACEI treatment result in a lower risk of developing type 2 DM in subjects with different risks of cardiovascular disease [28,29]. Besides, it was reported that patients with metabolic syndrome may be at lower risk of diabetes when using ACEI containing fixed dose combination antihypertensive treatments [30]. The results of UKPDS showed that captopril provided a more favourable A1C profile

and a lesser reliance on antidiabetic drugs in type 2 diabetic patients compared to treatment with atenolol [31]. Contrary to these favourable effects on glucose metabolism, verapamil SR plus trandolapril was shown to lack an effect on glycemic control in a different study [32]. In our study, change of A1C in diabetic patients was significant when compared with nondiabetics after trandolapril treatment. But, decrements in serum glucose and A1C levels in diabetics were insignificant although HOMA-IR improved. Furthermore, multivariate model showed that changes in A1C did not affect the decrease in HOMA-IR in all patients.

Hyperinsulinemia becomes a risk factor for macrovascular complications and coronary artery disease by increasing VLDL, IDL and LDL levels and decreasing HDL level. ACEIs are generally known to be neutral when lipid metabolism is considered [33]. Fosinopril was shown to decrease Lp(a) levels 23% compared to the basal level while the decrement in the placebo group was 12% [13]. On the other hand, trandolapril was shown to be neutral concerning lipid metabolism [34]. In our study trandolapril increased apo A1 in both groups and decreased Lp(a) only in the diabetic patients. Lp(a) is a cardiovascular risk factor genetically committed, but several nongenetic factors may affect it's plasma concentration. The improvement of IR may modify Lp(a) levels in our diabetic patients. But, our data was limited to clarify this observation.

In conclusion, trandolapril improved insulin sensitivity better in type 2 diabetic hypertensive patients with moderate degree of IR in comparison with the ones with low grade IR, being independent of its hemodynamic action. ACEIs can have some theoretical clinical advantages beyond BP lowering in the antihypertensive treatment of the subjects at greater risk for complications due to IR. Prospective clinical studies with longer follow-up and larger sample sizes are warranted to evaluate the use of trandolapril to predict the IR response in patients with high IR.

References

1. Ruderman NB, Carling D, Prentki M, Cacicedo JM. AMPK, insulin resistance, and the metabolic syndrome. J Clin Invest. 2013;123(7):2764-72.
2. Garcia-Touza M, Sowers JR. Evidence-based hypertension treatment in patients with diabetes. J Clin Hypertens (Greenwich). 2012;14(2):97-102.
3. Miller JL. Insulin resistance syndrome. Description, pathogenesis, and management. Postgrad Med. 2003; Spec No: 27-34.

4. Sharma SK, Ruggenenti P, Remuzzi G. Managing hypertension in diabetic patients-focus on trandolapril/verapamil combination. Vasc Health Risk Manag. 2007;3(4):453-65.
5. Henriksen EJ, Jacob S. Angiotensin converting enzyme inhibitors and modulation of skeletal muscle insulin resistance. Diabetes Obes Metab. 2003;5(4):214-22.
6. Rayner B. Selective imidazoline agonist moxonidine plus the ACE inhibitor ramipril in hypertensive patients with impaired insulin sensitivity: partners in a successful marriage? Curr Med Res Opin. 2004;20(3):359-67.
7. Heinemann L, Heise T, Ampudia J, Sawicki P, Sindelka G, Brunner G, Starke AA. Four week administration of an ACE inhibitor and a cardioselective beta-blocker in healthy volunteers: no influence on insulin sensitivity. Eur J Clin Invest. 1995;25(8):595-600.
8. Heise T, Heinemann L, Kristahn K, Berger M, Sawicki PT. Insulin sensitivity in patients with essential hypertension: no influence of the ACE inhibitor enalapril. Horm Metab Res. 1999;31(7):418-23.
9. Park SH, Lee WY, Rhee EJ, Jeon WK, Kim BI, Ryu SH, Kim SW. Relative risks of the metabolic syndrome according to the degree of insulin resistance in apparently healthy Korean adults. Clin Sci (Lond). 2005;108(6):553-9.
10. Guay DR. Trandolapril: a newer angiotensin-converting enzyme inhibitor. Clin Ther. 2003;25(3):713-75.
11. Leighton B, Sanderson AL, Young ME, Radda GK, Boehm EA, Clark JF. Effects of treatment of spontaneously hypertensive rats with the angiotensin-converting enzyme inhibitor trandolapril and the calcium antagonist verapamil on the sensitivity of glucose metabolism to insulin in rat soleus muscle in vitro. Diabetes. 1996;45(Suppl.1):S120-4.
12. Jacob S, Henriksen EJ, Fogt DL, Dietze GJ. Effects of trandolapril and verapamil on glucose transport in insulin-resistant rat skeletal muscle. Metabolism. 1996;45(5):535-41.
13. New JP, Bilous RW, Walker M. Insulin sensitivity in hypertensive Type 2 diabetic patients after 1 and 19 days' treatment with trandolapril. Diabet Med. 2000;17(2):134-40.
14. Petrie JR, Morris AD, Ueda S, Small M, Donnelly R, Connell JM, Elliott HL. Trandolapril does not improve insulin sensitivity in patients with hypertension and type 2 diabetes: a double-blind, placebo-controlled crossover trial. J Clin Endocrinol Metab. 2000;85(5):1882-9.
15. Schneider M, Lerch M, Papiri M, Buechel P, Boehlen L, Shaw S, Risen W, Weidmann P. Metabolic neutrality of combined verapamil-trandolapril treatment in contrast to beta-blocker-low-dose chlortalidone treatment in hypertensive type 2 diabetes. J Hypertens. 1996;14(5):669-77.
16. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499-502.

17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.
18. Gokcel A, Baltali M, Tarim E, Bagis T, Gumurdulu Y, Karakose H, Yalcin F, Akbaba M, Guvener N. Detection of insulin resistance in Turkish adults: a hospital-based study. Diabetes Obes Metab. 2003;5(2):126-30.
19. Foianini KR, Steen MS, Kinnick TR, Schmit MB, Youngblood EB, Henriksen EJ. Effects of exercise training and ACE inhibition on insulin action in rat skeletal muscle. J Appl Physiol. 2000;89(2):687-94.
20. Reneland R, Alvarez E, Andersson PE, Haenni A, Byberg L, Lithell H. Induction of insulin resistance by beta-blockade but not ACE-inhibition: long-term treatment with atenolol or trandolapril. J Hum Hypertens. 2000;14(3):175-80.
21. Galletti F, Strazzullo P, Capaldo B, Carretta R, Fabris F, Ferrara LA, Glorioso N, Semplicini A, Mancini M. Controlled study of the effect of angiotensin converting enzyme inhibition versus calcium-entry blockade on insulin sensitivity in overweight hypertensive patients: Trandolapril Italian Study (TRIS). J Hypertens. 1999;17(3):439-45.
22. Rubio-Guerra AF, Vargas-Robles H, Lozano Nuevo JJ, Elizalde-Barrera CI, Huerta-Ramirez S, Escalante-Acosta BA. Beneficial effect of combination therapy using an angiotensin-converting enzyme inhibitor plus verapamil on circulating resistin levels in hypertensive patients with type 2 diabetes. Exp Clin Cardiol. 2012;17(4):202-4.
23. Rubio-Guerra AF, Vargas-Robles H, Vargas-Ayala G, Rodríguez-Lopez L, Castro-Serna D, Escalante-Acosta BA. Impact of trandolapril therapy and its combination with a calcium channel blocker on plasma adiponectin levels in patients with type 2 diabetes and hypertension. Ther Adv Cardiovasc Dis. 2011;5(4):193-7.
24. Fukuzawa M, Satoh J, Sagara M, Muto G, Muto Y, Nishimura S, Miyaguchi S, Qiang XL, Sakata Y, Nakazawa T, Ikehata F, Ohta S, Toyota T. Angiotensin converting enzyme inhibitors suppress production of tumor necrosis factor-□ in vitro and in vivo. Immunopharmacology. 1997;36(1):49-55.
25. Mishima Y, Kuyama A, Tada A, Takahashi K, Ishioka T, Kibata M. Relationship between serum tumor necrosis factor-□ and insulin resistance in obese men with Type 2 diabetes mellitus. Diabetes Res Clin Pract. 2001; 52(2): 119-23.
26. Seghieri G, Yin W, Boni C, Sanna G, Anichini R, Bartolomei G, Ferrannini E. Effect of chronic ACE inhibition on glucose tolerance and insulin sensitivity in hypertensive type 2 diabetic patients. Diabet Med. 1992;9(8):732-8.
27. Pollare T, Lithell H, Berne C. A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. N Engl J Med. 1989;321(13):868-73.
28. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmäki K, Dahlöf B, de Faire U, Mörlin C, Karlberg BE, Wester PO, Björck JE. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet. 1999;353(9153):611-6.

29. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000;342(3):145-53.
30. Bakris G, Stockert J, Molitch M, Zhou Q, Champion A, Bacher P, Sowers J; STAR Investigators. Risk factor assesment for new onset diabetes: Literature review. Diabetes Obes Metab. 2009;11(3):177-87.
31. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. United Kingdom Prospective Diabetes Study Group. BMJ. 1998;317(7160):713-20.
32. Holzgreve H, Nakov R, Beck K, Janka HU. Antihypertensive therapy with verapamil SR plus trandolapril versus atenolol plus chlorthalidone on glycemic control. Am J Hypertens. 2003;16(5 Pt 1):381-6.
33. Gavras HP. Issues in Hypertension: drug tolerability and special populations. Am J Hypertens. 2001;14(7 Pt 2):231S-6S.
34. O'Keefe JH, Wetzel M, Moe RR, Bronsnahan K, Lavie CJ. Should an angiotensin-converting enzyme inhibitor be standard therapy for patients with atherosclerotic disease? J Am Coll Cardiol. 2001;37(1):1-8.