Effect of nebivolol and metoprolol treatments on serum asymmetric dimethylarginine levels in hypertensive patients with type 2 diabetes mellitus

Tip 2 diyabetes mellituslu hipertansif hastalarda nebivolol ve metoprolol tedavilerinin serum asimetrik dimetilarginin düzeyleri üzerine etkisi

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ABSTRACT

Objective: Elevated asymmetric dimethylarginine (ADMA) levels, an endogenous inhibitor of nitric oxide synthase, are an important cardiovascular risk factor. In patients with diabetes, increased ADMA levels have been reported, which may be associated with endothelial dysfunction. In this study, effect of nebivolol on serum ADMA levels in hypertensive patients with type 2 diabetes have been compared with metoprolol, an another beta-blocker.

Methods: A total of 54 patients (27 female, 27 male; mean age: 53.0±8.7 years) with type 2 diabetes and hypertension were included in this randomized, open-label, prospective study. Patients were randomized to receive either nebivolol 5 mg/day (n=28) or metoprolol 100 mg/day (n=26) for 12 weeks. When the patients could not reach target blood pressure levels at the end of week 4, indapamide (2.5 mg/day) was added. Enzyme Linked Immunosorbent Assay was used for serum ADMA measurements.

Results: Similar reductions in blood pressure values were observed in both groups (p>0.05). In nebivolol group, there were no significant changes in serum ADMA levels compared to baseline (0.6±0.2 µmol/l vs 0.6±0.1 µmol/l, p>0.05), whereas in metoprolol group a 35.6% increase in serum ADMA levels was observed (0.6±0.1 µmol/l vs 0.7±0.2 µmol/l, p<0.01).

Conclusions: We observed a significant increase in ADMA levels, a marker of endothelial dysfunction, during metoprolol treatment, whereas nebivolol had neutral effects on ADMA levels in patients with type 2 diabetes mellitus and hypertension. *(Anadolu Kardiyol Derg 2007; 7: 383-7)*

Key words: Asymmetric dimethylarginine, endothelial dysfunction, diabetes, hypertension, nebivolol, metoprolol

ÖZET

Amaç: Nitrik oksit sentazın endojen bir inhibitörü olan asimetrik dimetilarginin (ADMA) yüksek düzeyleri önemli bir kardiyovasküler risk faktörüdür. Diyabetli hastalarda ADMA düzeylerinin yüksek bulunduğu ve bunun endotel disfonksiyonu ile ilişkili olabileceği bildirilmektedir. Bu çalışmada tip 2 diyabeti ve hipertansiyonu olan hastalarda nebivololün serum ADMA düzeyleri üzerine etkisi bir başka beta-bloker metoprolol ile karşılaştırılmıştır.

Yöntemler: Bu prospektif, randomize açık-etiket araştırma çalışmasına tip 2 diyabeti ve hipertansiyonu olan toplam 54 hasta (27 kadın, 27 erkek, ortalama yaş: 53.0±8.7 yıl) alındı. Hastalar 12 hafta süreyle nebivolol 5 mg/gün (n=28) veya metoprolol 100 mg/gün (n=26) tedavilerinden birine randomize edildi. Dördüncü hafta sonunda hedeflenen kan basıncına ulaşılamadığında tedaviye indapamid (2.5 mg/gün) eklendi. Asimetrik dimetilarginin ölçümleri için "Enzyme-Linked Immunosorbent Assay" yöntemi kullanıldı.

Bulgular: Her iki grupta da kan basıncı değerlerinde benzer azalma gözlendi (p>0.05). Nebivolol grubunda başlangıca göre serum ADMA düzeylerinde anlamlı değişiklik yoktu (0.6±0.2 µmol/l'ye karşılık 0.6±0.1 µmol/l, p>0.05), buna karşılık metoprolol grubunda serum ADMA düzeylerinde %35.6 artış gözlendi (0.6±0.1 µmol/l'ye karşılık 0.7±0.2 µmol/l, p<0.01).

Sonuç: Tip 2 diyabeti ve hipertansiyonu olan hastalarda metoprolol tedavisi ile endotel disfonksiyonunun bir göstergesi olan ADMA düzeylerinde anlamlı bir artış gözlendi, buna karşılık nebivololün ADMA düzeyleri üzerinde nötral etkisi vardı. *(Anadolu Kardiyol Derg 2007; 7: 383-7)*

Anahtar kelimeler: Asimetrik dimetilarginin, endotel disfonksiyonu, diyabet, hipertansiyon, nebivolol, metoprolol

Introduction

Diabetes mellitus is associated with an increased risk of atherosclerotic cardiovascular disease (1). There is an evidence that endothelial dysfunction plays a significant role in the initiation of atherosclerotic vascular disease in patients with type 2 diabetes (2). Endothelium, the biggest endocrine organ with 1800 gr. weight in human body, releases the endothelium-derived vasoactive mediator, nitric oxide (NO), which maintains vascular integrity (3). Nitric oxide is a potent vasodilator produced from L-arginine in

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endothelial cells via endothelial nitric oxide synthase (eNOS) (4). It is involved in a wide variety of regulatory mechanisms of the cardiovascular system, including vascular tone and vascular structure (5). Decreased NO synthesis has been reported in several conditions associated with atherosclerosis, such as diabetes mellitus, hypertension, and hypercholesterolemia (6). Asymmetric dimethylarginine (ADMA), an endogenous L-arginine metabolite, inhibits cellular L-arginine uptake and eNOS activity competitively (7). It is known that increased levels of ADMA are associated with endothelial dysfunction and increased risk of cardiovascular disease (8, 9), besides Abbasi F et al (10) and Takiuchi S et al (11) indicate that the patients with type 2 diabetes and hypertension have high ADMA levels.

Nebivolol is a selective beta1-receptor blocker with vasodilating properties related to nitric oxide modulation. Metoprolol is also selective beta1-receptor blocker without known vasodilator properties (12-14).

In this study, effect of beta-blocker with vasodilating properties - nebivolol on serum ADMA levels, a marker of endothelial dysfunction, in hypertensive patients with type 2 diabetes have been compared with metoprolol, a beta-blocker without vasodilating features.

Methods

Overall 54 subjects between 40 and 70 years of age attending to Outpatient Clinics of the Department of Internal Medicine, Göztepe Training and Research Hospital (Istanbul, Turkey) were included in the study. Informed consent from the patients and local ethics committee approval (date and no. of approval: 02 February 2005/20) were obtained before the study procedures were commenced. The study was conducted in accordance with the Declaration of Helsinki.

Inclusion criteria: Diagnosis of type 2 diabetes and hypertension (systolic/diastolic blood pressure [SBP/DBP] ≥ 130/80 mmHg) (15); controlled blood glucose with diet and/or oral antidiabetics.

Exclusion criteria: Use of antihypertensives or insulin; blood pressure ≥180/100 mmHg; HbA1c ≥%7; presence of macro- or microvascular complications.

Diagnosis of type 2 diabetes mellitus was based on the criteria proposed by the American Diabetes Association (16).

Study design: This is an open-label randomized prospective study. Patients who met the inclusion criteria and gave informed consent were randomly assigned into two treatment groups (nebivolol or metoprolol) using a simple randomization method. Before treatment with nebivolol (p.o. 5 mg/day) or metoprolol (p.o. 100 mg/day) was started demographic data were collected, detailed physical examination was performed, 12-lead electrocardiogram recording was obtained, and fasting blood samples were taken for the biochemical tests in each patient. The treatment lasted for 12 weeks. In both arms, indapamide (2.5 mg) was added to the treatment for patients failing to reach target blood pressure values (≤130/80 mmHg) by the end of week 4. Patients were advised to continue their previously adopted diet and exercise program.

Anthropometric measurements: Blood pressure was measured in both arms after at least 10 minutes of at rest and while the patient was sitting. Korotkoff Phase I and IV sounds were used for the measurements. A second measurement was performed in the arm with the higher reading. Measurements were at least 3 minutes apart, and the average systolic (SBP) and diastolic (DBP) blood pressure values were calculated. Body-mass index (BMI) was estimated using Quetlet index (weight/height2 - kg/m^2) (17).

Biochemical measurements: Venous blood samples were collected following 12 hours of overnight fasting and the serum were separated by centrifugation at 2500 rpm. Glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (Roche Diagnostics, Product Code: 20763020, 03039773, 04399803, 03038866, and 20767107, respectively) were measured by enzymatic methods in a Cobas Integra 800 device. Hemoglobin A1c (HbA1c, Primus Corporation, Product Code: 01040016) was measured by immunoturbidimetry method in a Primus Ultra 2. Insulin levels (Roche Diagnostics, Product Code: 120175479) were measured by electrochemiluminescence immunoassay (ECLIA) method in a Roche E170 device. Insulin sensitivity was assessed by HOMA-IR (Homeostasis Model Assessment Insulin Resistance) (18). Serum samples separated for ADMA measurement were stored at -20 °C for a short period of time, and the tests were performed by ELISA (Enzyme Linked Immunosorbent Assay) method using DLD Diagnostica GMBH kits (Cat. No: EA201/96). The analytic sensitivity of the test was 0.05 μmol/l, and the intra-assay variation coefficient (CV%) for the two separate concentrations were 7.5 (mean value: 0.81, SD: 0.06, n=36) and 4.5 (mean value: 1.76, SD: 0.08, n=36).

Statistical analyses

SPSS (Statistical Package for Social Sciences) 10.0 for Windows (Chicago, Il, USA) was used for the statistical analyses. Quantitative data were compared using paired and unpaired Student's t test and Mann-Whitney U test, and qualitative data were assessed by Chi-square and Fisher's Exact Chi-square tests. The results were evaluated at a significance level of 0.05 and 95% confidence intervals were given.

Results

A total of 54 patients (27 female, 27 male, mean age: 53.0±8.7 years) were included. Twenty-eight patients (14 female, 14 male) were randomized to receive nebivolol, and 26 (13 female, 13 male) metoprolol. Two groups were comparable with regard to age, gender, average duration of diabetes, medications, number of smokers and alcohol consumers (Table 1).

Anthropometric measurements (Table 2): After treatment there were no significant differences between the two groups with respect to SBP, DBP, BMI, body weight, and heart rate ($p>0.05$). Within group comparisons showed a decrease in SBP, DBP, and heart rate compared to baseline in both arms ($p<0.05$).

Biochemical parameters (Table 2): Following treatment serum ADMA, triglycerides and triglycerides/HDL cholesterol ratio increases were significantly higher in metoprolol group than in nebivolol group (percent changes were 35.6±46.8 vs. 0.3±31.4, $p=0.008$; 45.2±75.6 vs. 6.1±39.0, $p=0.023$; 40.4±69.8 vs. 6.8±42.8, $p=0.039$; respectively). No significant differences between groups were observed in fasting plasma glucose, total cholesterol, LDL cholesterol, HDL cholesterol, HbA1c, insulin, and HOMA-IR ($p>0.05$).

Treatment characteristics: All patients completed the 12-week treatment. No significant adverse events were observed. Indapamide (2.5 mg/day, per os) treatment was required in 3 and 2 patients in metoprolol and nebivolol groups, respectively, in order to reach target blood pressure.

Discussion

Our results show that nebivolol and metoprolol treatments had different effects on serum ADMA levels in hypertensive patients with type 2 diabetes, despite similar blood-pressure lowering efficacy: nebivolol did not significantly alter serum ADMA levels, while metoprolol resulted in increased serum ADMA levels.

The ADMA is an endogenous inhibitor of endothelial NO synthase (7) synthesized from arginine residues and is metabolized by dimethylarginine-dimethylaminohydrolase (DDAH) to citrulline (19). Elevated concentrations of ADMA are associated with endothelial dysfunction, impaired NO bioavailability and increased risk of cardiovascular events (20-22). It has been reported that patients with type 2 diabetes (10, 23) and subjects with hypertension (24, 25) have elevated serum ADMA levels, which are responsible for reduced NO bioactivity (7, 9, 26). Moreover, patients with hypertension and or diabetes mellitus have an increased oxidative stress (4, 27-29) and it has been demonstrated that reactive oxygen species (ROS) decrease the

Table 1. Demographic characteristics

Variables	Nebivolol (n=28)	Metoprolol (n=26)	p*
Mean age, years	53.4±9.6	52.6±7.8	NS
Mean duration of diabetes, years	3.2±3.6	3.6±3.1	NS
Female gender, n (%)	14 (50)	13 (50)	NS
Smoking, n (%)	9 (32.1)	3 (11.5)	NS
Alcohol, n (%)	5 (17.9)	4 (15.4)	NS
Medications			
Only oral antidiabetics, n (%)	6 (21.4)	2 (7.6)	NS
Only diet, n (%)	3 (10.7)	4 (15.3)	NS
Oral antidiabetics plus diet, n (%)	19 (67.8)	20 (76.9)	NS

* - Chi-square and Fisher exact tests
NS- nonsignificant

Table 2. Comparison of anthropometric and biochemical data

Variables	Nebivolol (n=28)			Metoprolol (n=26)			Nebivolol vs Metoprolol % changes p**
	Baseline	After Treatment	Change (%)	Baseline	After Treatment	Change (%)	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
BMI, kg/m^2	32.6±4.8	31.5±4.8	-3.2±3.4	30.9±4.3	30.4±4.1	-1.5±2.8	NS
Weight, kg	87.9±10.3	85.1±10.6	-3.2±3.4	82.6±12.8	81.3±12.4	-1.5±2.8	NS
HR, beats/min	94.0±12.6	80.9±7.1*	-13.0±9.8	91.7±9.0	83±8.1*	-9.2±7.6	NS
SBP, mmHg	148.2±15.5	113.5±20.1*	-23.1±13.0	143.7±16.3	110.0±15.6*	-23.2±9.7	NS
DBP, mmHg	96.3±6.2	71.2±12.9*	-25.8±13.3	94.2±7.4	69.8±10.9*	-25.6±12.4	NS
FPG, mg/dl	147.0±21.1	139.8±30.3	-4±21	146±28.6	136.8±24.4	-4.3±17.6	NS
Total-C, mg/dl	191.3±28.2	186.7±32.1	-2.1±11.4	205.5±44.9	209.4±49.3	2.7±17.6	NS
LDL-C, mg/dl	115.5±30.1	113.2±27.1	2.4±35.4	137.2±38.9	127.5±37.1	-6.2±17.4	NS
HDL-C, mg/dl	42.6±10.7	42.3±8.2	1.2±12.1	44.3±14.9	44.8±11.4	4.5±20.1	NS
TG, mg/dl	153.3±79.5	152.6±100.6	6.1±39.0	128.7±55.4	185.5±128.6	45.2±75.6	0.023
TG/HDL-C	4.0±2.5	3.8±2.6	6.8±42.8	3.3±1.7	4.4±3.3	40.4±69.8	0.039
HbA1c, %	6.2±1.0	6.4±0.8	5.1±10.6	6.4±0.4	6.4±0.7	0.7±8.2	NS
HOMA-IR	4.6±1.7	4.1±2.2	-7.4±40.7	4.7±4.8	3.9±2.9	-2.7±48.4	NS
Insulin, µU/ml	12.7±4.7	11.7±50	-3.9±32.8	12.4±9.3	11.6±7.6	1.5±47.0	NS
ADMA, µmol/l	0.6±0.2	0.6±0.1	0.3±31.4	0.6±0.1	0.7±0.2	35.6±46.8	0.008

• $p<0.05$ for paired Student's t test intragroup comparisons,
• ** - unpaired Student's t test of Mann-Whitney U test for comparisons between groups
ADMA- asymmetric dimethylarginine, BMI- body mass index, DBP- diastolic blood pressure, FPG- fasting plasma glucose, HC- cholesterol, HOMA-IR- homeostasis model assessment-insulin resistance, NS- nonsignificant, HR- heart rate, SBP- systolic blood pressure, TG- triglycerides

activity of DDAH (29, 30), which is involved in ADMA metabolism, contributing to increase plasma concentration (31). Therefore, two mechanisms are responsible for NO reduction: the eNOS inhibition by ADMA and the NO breakdown to form peroxynitrite by superoxides.

It has been reported that angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may decrease serum ADMA levels. For example, Chen et al. (32), in their study in patients with syndrome X, observed a decrease in plasma ADMA levels after 8 weeks of treatment with enalapril, in addition to improvements in endothelial nitric oxide bioavailability and coronary microvascular function. Delles et al. (33) found that enalapril, eprosartan or their combination was more effective than placebo in reducing serum ADMA levels, independent of the decrease in blood pressure. In the study by Ito et al. (34), 4 weeks of treatment with perindopril or losartan was significantly more effective in lowering serum ADMA than bisoprolol treatment in patients with essential hypertension.

In our study, findings on increased ADMA levels in the metoprolol arm are in agreement with the previous reports suggesting a superior efficacy for ACE inhibitors and ARBs in improving endothelial function compared to beta-blockers. On the other hand, it is believed that nebivolol improves endothelial functions via increased endothelial nitric oxide synthase activity (35). In the present study, in contrary to metoprolol, which has no vasodilatory effects, nebivolol did not increase serum ADMA levels.

The favorable effect of nebivolol on endothelial dysfunction has been demonstrated in experimental models (36, 37), in healthy volunteers and in patients with hypertension or cardiovascular disease (38-41). The activity of nebivolol on L-arginine/NO pathway seems to be mediated by the endothelial beta-3 receptors (42) and related to eNOS activation (43). Moreover, nebivolol posses antioxidant activity demonstrated in vitro and in vivo in different studies (36, 43). In these studies, nebivolol significantly decreased plasma and LDL hydroperoxides, plasma oxidized LDL, reactive oxygen species in endothelial cells exposed to oxidative stress, plasma 8-isoprostanes and malondialdehyde, in hypertensive patients.

Metoprolol is a beta-1 selective beta-blocker devoid of pharmacological effect on endothelial function and antioxidant activity (44) and in comparative studies nebivolol, but not metoprolol, inhibited superoxide formation (37). These different pharmacological properties of nebivolol and metoprolol might explain the results on ADMA concentration in our patients, despite the same blood pressure and shear stress reduction. We cannot exclude that the persistence of oxidative stress in patients treated with metoprolol has stimulated ADMA accumulation, whereas nebivolol possibly prevented the increase through its endothelial-NO effect and the antioxidant activity. The effect of nebivolol on DDHA has not been investigated, however considering its antioxidant activity it is conceivable that the reduction of DDHA inhibition has contributed to the lack of ADMA increase.

Many factors including hypertension, hyperglycemia, dyslipidemia, hormone replacement therapy, cigarette smoking, and alcohol use have been shown to be associated with altered serum ADMA levels (45-47). In our study, two groups were comparable with respect to pre- and post-treatment blood pressure, fasting plasma glucose and HbA1c values. There were no patients receiving hormone replacement therapy. Furthermore, the number of smokers and alcohol consumers were also similar in both groups at baseline and after the treatment. There is evidence that antidiabetics and lipid lowering agents have effect on serum ADMA concentrations (8, 48, 49). In this study, antidiabetic and lipid lowering treatment rates were similar in both groups. Thus, the present results may be interpreted as an indication of different effects of nebivolol and metoprolol on endothelial function. Besides, serum ADMA levels have been reported to be associated with high triglycerides levels (50). In this study, the significant increase in triglycerides concentrations in patients receiving metoprolol might have played a role in the increased ADMA levels.

Limitations of the study

Undoubtedly, absence of a placebo group is a major drawback of our study. Although our study is comparable to several other studies with respect to the number of participants and duration of treatment, it is clear that longer follow up with a larger sample size would yield firmer conclusions.

Conclusion

In conclusion, our results show that in patients with type 2 diabetes mellitus and hypertension nebivolol and metoprolol had different effects on serum ADMA and triglycerides levels, despite similar blood-pressure lowering activity. Metoprolol increased ADMA and triglycerides significantly, whereas nebivolol, stabilized ADMA concentration and had neutral effects on plasma triglycerides. The exact mechanism of nebivolol activity on ADMA still remains to be elucidated.

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