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Originalni naučni rad
Original study
UDK 616.12-008.331.1:615.03:612.349.8:616-056

UTICAJ TERAPIJE RAMIPRILOM NA POJEDINE KOMPONENTE SINDROMA INSULINSKE REZISTENCIJE U BOLESNIKA SA ESENCIJALNOM HIPERTENZIJOM

EFFECTS OF RAMIPRIL THERAPY ON SOME COMPONENTS OF INSULIN RESISTANCE SYNDROME IN PATIENTS WITH ESSENTIAL HYPERTENSION

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Sažetak - Esencijalna hipertenzija predstavlja komponentu sindroma insulinske rezistencije. Insulinska rezistencija se definiše kao stanje u kome insulin ostvaruje manji odgovor od očekivanog, biološkog odgovora. Prospektivnom kliničkom studijom analizirano je 15 bolesnika (7 muškaraca i 8 žena), sa normalnom glikoznom tolerancijom prosečne starosti 53,24 ± 6,60 godina, sa BMI 26,97 ± 1,24 kg/m^2, sa blagom ili umerenom esencijalnom hipertenzijom pre i posle primene ramiprila u trajanju od 12 nedelja. Za procenu periferne insulinske senzitivnosti i glikozne efektivnosti izvođen je Bergmanov test minimalnog modela sa redukovanim brojem uzoraka. Indeks insulinske senzitivnosti u 12. nedelji povećan za 50%, ali nisu dostignute normalne vrednosti za referntni model (Si = 1,22 ± 0,66 vs 1,78 ± 0,8 x 10^{-4} min/μU/ml). Vrednosti glikozne efektivnosti, lipida i elektrolita plazme ostale su relativno nepromenjene, dok su vrednosti hemoglobina i broja trombocita značajno smanjene. Zbog metaboličke neutralnosti i antitrombotične aktivnosti, ramipril se preporučuje bolesnicima sa hipertenzijom i insulinskom rezistencijom, posebno sa dijabetesom.
Ključne reči: Ramipril; Hipertenzija; Insulinska rezistencija. Hematološki agensi; Elektroliti; Lipidi

Summary - *Essential hypertension presents a component of insulin resistance syndrome. Insulin resistance exists whenever normal concentration of hormone produces less than normal biologic response. This prospective clinical study included 15 patients (7 male and 8 female), with normal glucose tolerance, aged 53,24 ± 6,60 years, BMI 26,97 ± 1,24 kg/ m^2, with mild-to-moderate essential hypertension before and after ramipril treatment lasting 12 weeks. For assessment of peripheral insulin sensitivity and glucose effectiveness we used a reduced samples Bergman's Minimal Model method. At week 12, we noted a 50% elevation of mean insulin sensitivity index, but without achieving normal reference values (Si = 1,22 ± 0,66 vs 1,78 ± 0,8 x 10^{-4} min/μU/ml). Glucose effectiveness, plasma lipids and electrolytes were relatively unchanged. Haemoglobin and platelet count were significantly decreased. Being metabolically neutral, with antithrombotic activity, ramipril can be recommended for treatment of patients with hypertension and insulin resistance, especially for patients with accompanied diabetes mellitus.*
Key words: *Ramipril; Hypertension; Insulin Resistance. Hematologic Agents; Electrolytes, Lipids*

Uvod

Insulinska rezistencija je jedan od mogućih patofizioloških mehanizama odgovornih za nastanak esencijalne hipertenzije. Teoretski, postoji više objašnjenja za povezanost ova dva entiteta. Prvi mogući patofiziološki mehanizam kojim insulinska rezistencija dovodi do esencijalne hipertenzije jeste hiperinsulinemija, kao kompenzatorna pojava u insulinrezistentnim stanjima. Hiperinsulinemija do arterijske hipertenzije dovodi sledećim pretpostavljenim mehanizmima: povećanom renalnom reapsorpcijom natrijuma, aktivacijom simpatičkog sistema, stimulacijom faktora rasta ili/i dejstvom na transmembranski jonski transport (povećanom aktivnošću Na/H pumpe i smanjenom aktivnošću Na-K-ATP-aze) [1].

Druga mogućnost je da insulinska rezistencija *per se*, za sada nepoznatim mehanizmima uzrokuje nastanak esencijalne hipertenzije [2]. Kako insulin u blagoj hiperinsulinemiji ne uzrokuje hipertenzivne efekte, pretpostavljena je veća verovatnoća povezanosti insulinske rezistencije i esencijalne hipertenzije, nego hiperinsulinemije i esencijane hipertenzije [3].

Nedavno je ustanovljena povezanost između insulinske rezistencije i hiperinsulinemije sa smanje-

Introduction

Insulin resistance is one of the possible pathophysiological mechanisms responsible for development of essential hypertension. There seem to be several theoretical explanations for the relationship between these two entities. Hyperinsulinemia persists in insulin resistance as a compensatory phenomenon. It may affect blood pressure by several possible mechanisms, such as: increased renal sodium reabsorption, sympathetic nervous system stimulation, enhanced growth factor activity and disturbed transmembrane cation transport activity (increased activity of Na/H pump and decreased activity of Na-K-ATP-ase) [1].

Another possibility is that insulin resistance *per se* causes development of essential hypertension by some unknown mechanisms [2]. Although insulin has no hypertensive effects in mild hyperinsulinemia, it was concluded that insulin resistance rather than hyperinsulinemia may be more closely associated with essential hypertension [3].

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Skraćenice

RAAS	- renin-angiotenzin-aldosteron sistem
BMI	- indeks telesne mase
GTT	- test tolerancije glikoze
NIDDM	- insulin nezavisni šećerni dijabet

nom funkcijom arterijskog baroreceptorskog mehanizma, koji je povezan sa povišenim krvnim pritiskom. Hiperinsulinemija kao aterogeni činilac smanjuje arterijsku komplijansu, čime smanjuje stimulaciju arterijskih baroreceptora. Na pomenute promene nadovezuje se endotelijalna disfunkcija, koja postoji u insulin rezistentnim stanjima, sa daljim pogoršanjem periferne vaskularne rezistencije i arterijske hipertenzije [4]

Dugotrajna inhibicija RAAS (renin-angiotenzin-aldosteron sistema), primenom strukturno različitih ACE inhibitora, različito utiče na perifernu insulinsku senzitivnost u insulinrezistentnim oblicima esencijalne hipertenzije. Poboljšanje periferne insulinske senzitivnosti predstvalja ključni činilac u primarnoj i sekundarnoj prevenciji kardiovaskularnih oboljenja [5].

Cilj našeg rada je ispitivanje uticaja ramiprila na insulinsku senzitivnost i glikoznu efektivnost, na lipide i elektrolite plazme, kao i na hematološke parametre u bolesnika sa blagom (hipertenzija I stepena) i umerenom (hipertenzija II stepena) pre i posle terapije ramiprilom u trajanju od 12 nedelja.

Materijal i metode

Prospektivnom kliničkom studijom analizirano je 15 bolesnika (7 muškaraca i 8 žena) sa normalnom glikoznom tolerancijom, uzrasta između 20 i 55 godina (prosečne starosti 53,24 ± 6,60 godina) sa vrednostima indeksa telesne mase (BMI) 26,97 ± 1,24 kg/m^2, sa blagom (hipertenzija I stepena) ili umerenom (hipertenzija II stepena) esencijalnom hipertenzijom pre i posle lečenja cilazaprilom u trajanju od 12 nedelja.

Za procenu periferne insulinske senzitivnosti korišćen je test minimalnog modela po Bergmanu sa redukovanim brojem uzoraka, koji zahteva izvođenje 3-časovnog iv.GTT. U 0. minutu daje se 300 mg/kg hipertone, 50% glikoze intravenski tokom 1-2 minuta. U 20. minutu se aplikuje intravenski 0.05 U/kg insulina u podlakticu suprotne ruke. U određenim vremenskim intervalima: 0, 2, 4, 8, 10, 22, 30, 40, 50, 70, 90, i 180. minutu sakupljaju se uzorci za određivanje koncentracije glikoze [6] (metoda glukozo oksidaze, mmol/l) i insulina (RIA, INEP, mU/l) u krvi. Za obradu dobijenih rezultata koristi se program MINMOD za izračunavanje indeksa insulinske senzitivnosti (Si) i glikozne efektivnosti (Sg). Intravenski GTT na opisani način je izvođen u 0. i 12. nedelji istraživanja.

Iz uzoraka venske krvi uzete natašte određivane su vrednosti bazne insulinemije, bazne glikemije, triglicerida, ukupnog holesterola, HDL- i LDL-ho-

Abbreviations

RAAS	- renin-angiotensin-aldosterone system
BMI	- body mass index
GTT	- glucose tolerance test
NIDDM	- non-insulin dependent diabetes mellitus

It has been established recently that insulin resistance and hyperinsulinemia may be associated with an attenuation of the arterial baroreceptor-cardiac refelex, with arterial hypertension as consequence. Hyperinsulinemia is recognized to be atherogenic, and there is an association with a stiffening of the arterial wall and attenuation of arterial baroreceptor sensitivity. In addition, it is possible to speculate that abnormal endothelial function, as has been documented in insulin resistance, may impair the response of the arterial baroreceptors, with further deterioration of peripheral vascular resistance and arterial hypertension [4].

Long-term inhibition of renin-angiotensin-aldosterone system (RAAS) is thought to produce either improvement or unchanged values of peripheral insulin sensitivity in patients with essential hypertension, most probably according to structural differences of various angiotensin-converting enzyme (ACE) inhibitors. Improvement of insulin resistance is crucial for primary and secondary prevention of cardiovascular diseases [5]. The aim of the current study was to investigate the effects of ramipril on insulin sensitivity and glucose effectiveness, on plasma lipids and electrolytes, as well as on haematological parameters in patients with mild-to-moderate essential hypertension before and after treatment, during 12 weeks.

Material and methods

This prospective clinical study included 15 patients (7 male and 8 female) with normal glucose tolerance, aged 20 to 55 years (average age 53.24 ± 6.60 years), with body mass index (BMI) 26.97 ± 1.24 kg/m^2, with mild (hypertension stage I) or moderate (hypertension stage II) essential hypertension, before and after ramipril therapy, during 12 weeks.

For assessment of peripheral insulin sensitivity we used Bergman's minimal model method with reduced samples. This model requires 3-hour intravenous glucose tolerance test (ivGTT). At 0. min 300 mg/kg 50% glucose was infused intravenously over 1-2 minutes into the antecubital fossa vein. After 20 minutes bolus intravenous injection of 0.05 U/kg human insulin was infused in contralateral antecubital fossa vein. At definite intervals - 0, 2, 4, 8, 10, 22, 30, 40, 50, 70, 90 and 180 minute sampling for glucose (glucoso oxidaze method, mmol/l) [6] and insulin (RIA, INEP, mU/l) took place. Using software package MINMOD we calculated insulin sensitivity (Si) and glucose effectiveness (Sg) based on obtained insulinemia and glycemia values. Intravenous GTT was performed at 0 and 12th week of the study.

lesterola, natrijuma, kalijuma, bikarbonata, hlora, određivan je broj eritrocita, leukocita i trombocita, vrednosti hematokrita i hemoglobina. Navedeni parametri su određivani svake 4 nedelje.

Krvni pritisak je meren konvencionalnim sfingomanometrom u sedećem položaju svake druge nedelje. Blaga i umerena hipertenzija su definisane za vrednosti sistolnog pritiska: 140-159 vs. 160-179 mmHg i vrednosti dijastolnog pritiska: 90-99 vs. 100-109 mmHg.

Telesna težina i vrednosti indeksa telesne mase (BMI; kg/m^2) određivani su u 0. i 12. nedelji. BMI predstavlja količnik telesne težine izražene u kilogramima i kvadrata telesne visine izražene u metrima. U studiju su bile uključene normalno uhranjene osobe (BMI do 24,9 kg/m^2) ili sa gojaznošću I stepena (BMI < 28 kg/m^2).

Pre uvođenja ramipriła svi bolesnici su prošli kroz period obustave ("*wash out*" period) antihipertenzivne terapije, ako su prethodno lečeni, u trajanju od dve nedelje. Tokom posmatranog perioda bolesnici nisu uzimali lekove koji utiču na glikoznu toleranciju i metabolizam lipida. Početna doza ramipriła bila je najmanja preporučena antihipertenzivna doza od 2,5 mg, zbog prevencije hipotenzivnog efekta prve doze. Kod bolesnika kod kojih je prosečna vrednost dijastolnog pritiska u sedećem položaju iznosila 90-115 mmHg posle 4 nedelje primene prodoze, primenjivana je dupla doza leka tokom preostalih 8 nedelja lečenja.

Studija je bila otvorenog tipa. Pre uključivanja u studiju svakom bolesniku je bila objašnjena svrha studije, pri čemu je svaki bolesnik dao usmeni dobrovoljni pristanak za učešće u studiji.

Statistička analiza dobijenih rezultata je obrađena softverskim paketom SPSS. Podaci su dati kao srednje vrednosti sa standardnom devijacijom. Značajnost razlike endokrinoloških parametara pre i posle primene ramiprila testirana je Studentskim t-testom za vezane uzorke. Značajnost razlika vrednosti lipida, elektolita plazme, hematoloških parametara, testirana je dvofaktorskom analizom varijanse za ponovljena merenja.

Rezultati

Prosečna vrednost indeksa insulinske senzitivnosti u periodu pre terapije ramiprilom jako je niska, što ukazuje na postojanje smanjene insulinske senzitivnosti u ispitivanoj grupi. Analizom indeksa insulinske senzitivnosti u 12. nedelji lečenja uočava se povećanje datog indeksa za 50%, ali time nisu dostignute normalne vrednosti za referentni model i razlika nije statistički značajna (grafikon 1 i tabela 1).

Vrednosti glikozne efektivnosti, bazne insulinemije i bazne glikemije nisu se značajno promenile pre i posle terapije ramiprilom (tabela 1).

Vrednosti lipida i elektrolita plazme pre i posle primene ramiprila značajno se ne razlikuju (tabele 2 i 3).

Venous blood was obtained after an overnight fast for determination of fasting plasma glucose, fasting insulin, triglyceride, total cholesterol, LDL- and HDL-cholesterol, sodium, potassium, bicarbonate, chlorine, erythrocyte, leukocyte and platelet count, haemoglobin and haematocrit. These parameters were measured every 4 weeks.

Blood pressure was measured every second week, in sitting position, using a conventional mercury sphygmomanometer. Mild and moderate hypertension are defined for systolic blood pressure: 140-159 vs. 160-179 mmHg and for diastolic blood pressure: 90-99 vs. 100-109 mmHg.

Body weight and body mass inex (BMI; kg/m^2) were calculated at 0 and 12th week. BMI presents the equation among body weigt expressed in kilograms and the square of body heigh expressed in meters. We included either non-obese patients with BMI 24.9 kg/m^2 or with stage one obesity (BMI = 28 kg/m^2).

Before ramipril therapy all patients passed through wash out period, duration of 2 weeks, if they were treated before. During the study period patients did nit receive drugs known to affect glucose tolerance or lipid metabolism. The initial dose was 2.5 mg, minimal recommended therapeutic dose, with the purpose to avoid hypotensive effect of the first dose. Patients whose mean diastolic blood pressure in sitting position on pro-dose was 90-115 mmHg after 4 weeks of therapy, received a double dose in the remaining 8 weeks.

The study had an open-label design. All patients were informed about the purpose and the character of the research and provided oral consent before the study started.

Statistical analysis was performed using the software package SPSS. Data are given as mean and standard deviation. For paired comparison between two endocrinological measurements we used Student's t-test. A two-way analysis of covariance for repeated measurements was used to compare the means of plasma lipids, electrolytes and haematological parameters.

Results

The average initial value of insulin sensitivity index before ramipril treatment was too low, indicating a decreased insulin sensitivity. Analyzing insulin sensitivity in 12th week of ramipril treatment, we noted a 50% elevation of mean index. Established index value was not in normal range for refe' rential model, and differences were considered nonsignificant (Fig. 1 and Table 1).

Table 1. Endokrinološki parametri pre i posle primene ramiprila

Table 1 *Endocrinological parameters before and after ramipril treatment*

Parametri/*Parameters*	Pre lečenja *Before treatment*	Posle lečenja *After treatment*	p
Insulinska senzitivnost *Insulin sensitivity*	1,22±0,66	1,78±0,81	ns
Glikozna efektivnost *Glucose efficacy*	0,27±0,15	0,37±0,27	ns
Bazni insulin *Fasting insulin*	12,75±4,33	11,73±5,05	ns
Bazna glikemija *Fasting glucose*	4,61±0,73	4,56±0,80	ns

ns - razlika nije značajna/*ns - difference is not significant*

Tabela 2. Vrednosti lipida plazme tokom primene ramiprila

Table 2. *Values of plasma lipids during ramipril therapy*

	0.nedelja 0.week	4.nedelja 4th week	8.nedelja 8th week	12.nedelja 12th week	p
Holesterol *Cholesterol*	6,117±0,16	6,08±0,18	6,10±0,21	6,12±0,15	ns
HDL-HDL-CC	1,26±0,07	1,22±0,06	1,16±0,04	1,22±0,07	ns
LDL-C	4,13±0,22	4,12±0,18	4,09±0,22	4,08±0,17	ns
LDL/HDL	3,53±0,20	3,46±0,24	3,70±0,22	3,52±0,20	ns
Triglyceridi *Triglycerides*	2,04±0,15	2,15±0,19	2,08±0,20	2,13±0,17	ns

ns - razlika nije značajna, *ns - difference is not significant*

Tabela 3. Vrednosti elektrolita plazme tokom primene ramiprila

Table 3. *Values of plasma elektrolytes during ramipril therapy*

	0.nedelja 0.week	4.nedelja 4th week	8.nedelja 8th week	12.nedelja 12th week	p
Natrijum *Sodium*	140,04±0,47	140,71±0,45	139,75±0,27	139,52±0,43	ns
Kalijum *Potassium*	3,94±0,06	4,02±0,09	3,93±0,07	4,00±0,06	ns
Hlor *Chloride*	101,16±0,15	100,66±0,45	101,08±0,45	101,04±0,51	ns
Bikarbonati *Bicarbonate*	27,42±0,51	28,41±0,24	27,6±0,22	27,91±0,57	ns

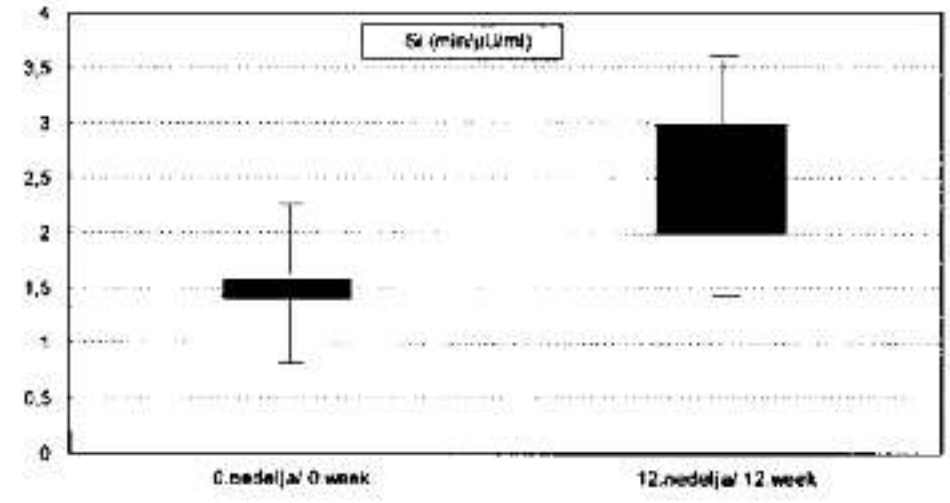
ns - razlika nije značajna; *ns - difference is not significant*

Tokom primene ramiprila registrovano je značajno smanjenje vrednosti hemoglobina i broja trombocita. Ostali hematološki parametri su relativno nepromenjeni (tabela 4).

Diskusija

Strukturno različiti ACE inhibitori imaju isti hipotenzivni efekat, ali su njihovi efekti na insulinsku senzitivnost različiti i doznozavisni [7]. Metabolički efekti nisu zajednička karakteristika farmakološke grupe lekova, već zavise od strukture svakog pojedinačnog leka iz iste grupe [8].

Slično našim rezultatima, Ludvik je pokazao da kratkotrajna primena ramiprila (14 dana) ne menja



Grafikon 1. Insulinska senzitivnost pre i posle primene ramiprila

Graph. 1. *Insulin sensitivity before and after ramipril administration*

Tabela 4. Vrednosti hematoloških parametara tokom primene ramiprila

Table 4. *Values of haematological parameters during ramipril therapy*

	0.nedelja 0.week	4 nedelja 4th week	8.nedelja 8th week	12.nedelja 12th week	p
Eritrociti *Erythrocytes*	4,56±0,08	4,50±0,09	4,50±0,08	4,54±0,11	ns
Hemoglobin *Haemoglobin*	140,71±3,01	140,12±2,22	137,92±2,65	137,25±2,54	s
Hematokrit *Haematocrit*	0,41±0,01	0,42±0,01	0,40±0,01	0,40±0,01	ns
Leukociti *Leukocytes*	6,56±0,27	5,79±0,28	6,05±0,29	5,95±0,26	ns
Trombociti *Thrombocytes*	313,80±22,4	300,06±21,7	282,87±16,8	277,87±22,1	s

s- razlika je značajna, ns - razlika nije značajna

s - difference is significant, ns-difference is not significant

Comparison of data at the start and at the end of study period showed no significant differences in glucose effectiveness, fasting insulinemia and fasting glycemia (Table 1).

Values of lipids and electrolytes did not significantly differ before and after ramipril treatment (Tables 2 and 3).

During use of ramipril, we observed statistical decrease of haemoglobin and platelet count. Values of other haematological parameters did not significantly change (Table 4).

Discussion

Currently used structurally different ACE inhibitors effectively decrease blood pressure, but differ in their ability to improve insulin resistance [7]. Metabolic effects are not true class effects, but are linked to specific charactersitics of each drug from the same group [8].

značajno perifernu insulinsku senzitivnost pre početka terapije procenjivanu euglikemijskim klampom [9]. Primenjujući minimalni model za procenu periferne insulinske senzitivnosti, Sidani je ustanovio relativno nepromenjenu vrednost posmatranog parametra posle 8 nedelja lečenja kod starijih hipertoničara, dok je dugotrajna primena (6 meseci) pokazala trend pogoršanja insulinske senzitivnosti [10].

S druge strane, pokazano je da čak i male doze ramiprila (1,25 mg dnevno) posle 10 dana primene značajno poboljšavaju perifernu insulinsku senzitivnost u grupi od 5 normotenzivnih, nedijabetičnih, gojaznih žena [11]. A u grupi od 21 hipertoničara sa normalnom glikoznom tolerancijom primena 5 mg ramiprila dnevno tokom perioda od 6 meseci uzrokovala je značajno poboljšanje insulinske senzitivnosti, procenjivane insulin tolerance testom [12].

Različiti rezultati se mogu tumačiti na više načina: upotrebom različitih metoda za procenu periferene insulinske senzitivnosti, različitom dužinom trajanja hipertenzije (da li su u studiju uključeni novodijagnostikovani bolesnici ili oni sa već postojećim komplikacijama na ciljnim organima), nedovoljan broj ispitivanih bolesnika za izvođenje relevantnog zaključka o dejstvu primenjenog leka na insulinsku senzitivnost ili varijacija uticaja lekova iz iste farmakološke grupe na posmatrani parametar.

Mogući mehanizmi kojima ACE inhibitori poboljšavaju perifernu insulinsku senzitivnost su potenciranje vazodilatatornog dejstva bradikinina, povećanje protoka krvi u skeletnim mišićima, povećanje aktivnosti Na-K-ATP-aze i/ili redukcija simpatičkog tonusa [13]. Eksperimentalna studija na spontano hipertenzivnim pacovima pokazala je da bi ramipril povećanjem defosforilacije insulinskog receptora i povećanjem aktivnosti protein-tirozin-fosfataze (PTP-aze) moglo da bude jedno od mehanizama kojima ACE inhibitori povećavaju perifernu insulinsku senzitivnost [14].

Insulinska rezistencija predstavlja komponentu metaboličkog sindroma X ili sindroma insulinske rezistencije, koju sačinjavaju arterijska hipertenzija, dislipidemija (povišene koncentracije LDL-C i triglicerida, a smanjene HDL-C), insulinska rezistencija sa hiperinsulinemijom, centralni tip gojaznosti, povišene koncentracije PAI-1 i fibrinogena, hiperuricemija i mikroalbuminurija. Bolesnici sa metaboličkim sindromom X imaju značajno veći rizik za nastanak aterosklerotičnog vaskularnog oboljenja od osoba sa normalnom insulinskom senzitivnošću [15].

Metaboličku neutralnost ramiprila pokazala je HOPE studija, čime se objašnjava smanjenje kardiovaskularnog morbiditeta tokom njegove primene. Tokom 4-5-godišnjeg praćenja HOPE, MICRO-HOPE i SECURE studije su pokazale veliku terapijsku efikasnost ramiprila kod hipertoničara preko 55 godina starosti (zbog čestih pridruženih vaskularnih komplikacija), dijabetičara i mlađih hipertoničara kod kojih postoji bar jedan dodatni faktor rizika

Similar to our results, Ludvik showed that short-term (14 days) treatment with ramipril has no influence on insulin secretion and insulin sensitivity, assessed with euglycemic clamp technique [9]. Using minimal model method, Sidani also found no significant increase of peripheral insulin sensitivity after 8 weeks of ramipril therapy in eldely hypertensive patients, while other studies have shown a declining trend in insulin sensitivity value after long-term (6 months) therapy with ramipril [10].

On the other side, short-term treatment with ramipril with low doses (1,25 mg daily), duration 10 days, induced improvement of insulin sensitivity in the group of five normotensive, non-diabetic, obese women [11]. Treatment with ramipril, dose of 5mg/day, lasting 6 months, significantly improved insulin sensitivity in 21 hypertensive subjects with normal glucose tolerance, assessed by insulin tolerance test [12].

Possible explanations for such differences might be: different methodologies used to calculate the index of insulin sensitivity, different duration of arterial hypertension (recent onset of disease or already sustained hypertension with complications on target organs), insufficient number of patients for relevant conclusion about the action of used drugs on insulin sensitivity and glucose kinetics or variation in action of different drugs from the same pharmacological group on abovementioned parameters.

Possible mechanisms which improved insulin sensitivity after ACE inhibition are: emphasized bradykinin action through its vasodilatative impact, increased blood flow in sceletal muscles, increased activity of Na-K-ATP pump and/or decrease in sympathetic nervous system activity [13]. Experimental study on spontaneously hypertensive rats has shown that increased phosphorylation of insulin receptor and protein tyrosine phosphatase (PTPase) activity might be possible mechanisms for improvement of insulin sensitivity after ramipril therapy [14].

Insulin resiastance is a part of metabolic syndrome X (or insulin resistance syndrome) which is a component of arterial hypertension, dyslipidemia (increased LDL-C and triglycerides, decreased HDL-C), insulin resistance with hyperinsulinemia, central obesity, higher PAI-1 and fibrinogen level, hyperuricemia and microalbuminuria. Patients with metabolic syndrome X have a markedly increased risk for development of atherothrombotic cardiovascular disease [15].

HOPE study has showed metabolic neutrality of ramipril. However, this is an explanation for decreased cardiovascular morbidity during ramipril treatment. During 4,5 years of follow-up period, HOPE, MICRO-HOPE and SECURE studies showed great therapeutic efficacy of ramipril in patients over 55 years (often associated with vascular complications), diabetic patients and younger hypertensive patients with at least one additional risk factor [16].

[16]. Doggrell je pokazao da ramipril snižava nivo LDL-C, ali i HDL-C tokom dugotrajne primene [17], dok je kod hipertoničara sa koronarnom bolešću pokazano sniženje LDL-C tokom dugotrajne primene ramiprila, čime se delom objašnjava smanjenje kardiovaskularnog morbiditeta [18].

Insulin je bitan faktor regulacije eritropoeze. Povećan broj eritocita može se smatrati novom komponentom sindroma insulinske rezistencije, koji povećava rizik za nastanak kardiovaskularnih komplikacija. Barbieri je pronašao korelaciju između insulinske rezistencije, broja eritrocita i koncentracija hemoglobina, hematokrita i gvožđa u plazmi. Kod osoba sa insulinskom rezistencijom registrovana je korelacija izmedu eritrocitoze, povišene koncentracije LDL-C i snižene koncentracije HDL-C [19]. U smislu antiaterogenog dejstva ramiprila, a u vezi sa njegovim dejstvom na hematološke parametre, rezultati nedavno sprovedene pilot studije pokazali su da ramipril značajno smanjuje agregaciju trombocita (za 26%). Antitrombotični efekat ACE inhibitora bitan je činilac njihovog vaskulotektivnog dejstva, jer su ruptura plaka i tromboza koja sledi iza toga ključni procesi u progresiji i nastanku komplikacija aterosklerotične bolesti [20].

Zaključak

Ramipril ne poboljšava značajno perifernu insulinsku senzitivnost posle 12 nedelja lečenja ($p>0,05$).

Posle 12 nedelja lečenja ramiprilom glikozna efektivnost, bazna insulinemija i glikemija, elektroliti i lipidi plazme relativno su nepromenjeni ($p > 0,05$).

Ramipril, ACE inhibitor nove generacije, pokazuje metaboličku neutralnost u odnosu na perifernu insulinsku senzitivnost i glikoznu kinetiku i kao takav može se preporučiti bolesnicima kod kojih uz arterijsku hipertenziju postoji insulinska rezistencija i hiperinsulinemija, gde spadaju gojazni hipertoničari i osobe sa insulin nezavisnim šećernim dijabetom.

Doggrell demonstrated that ramipril induced decrease of LDL-C, but also HDL-C during long-term therapy [17], while long-term ramipril use in patients with coronary disease induces only decrease of LDL-C. This is an explanation, at least partly, for decreased risk for development of cardiovacular disease [18].

Insulin has an important role in regulation of erythropoiesis. Increased erythrocyte count could be considered as a new component of insulin resistance syndrome which could contribute to increased risk from developing cardiovascular complications. Barbieri found a correlation between insulin resistance, erythrocyte count, plasma haemoglobin, haematocrit and plasma iron concentrations. Subjects with insulin resistance presented with higher erythrocyte count and LDL-C concentration, and lower HDL-C concentrations [19]. Concerning antiatherogenic action of ramipril, and its influence on haematological parameters, results of a pilot study showed significant decrease of platelet aggregation (by 26%). Antithrom- botic effect of ACE inhibitors is important for their vasculoprotective action, although plaque rupture and subsequent thrombosis are key events in complications and progression of atherosclerotic diseases [20].

Conclusion

Ramipril does not improve insulin sensitivity significantly after a 12-week therapy ($p>0.05$).

Ramipril has no significant influence on glucose effectiveness, fasting insulinemia and glycemia, electrolytes and plasma lipids after a 12-week therapy ($p > 0.05$).

Ramipril, an ACE inhibitor of new generation, as a metabolic neutral drug concerning peripheral insulin sensitivity and glucose kinetics, can be recommended for treatment of arterial hypertension accompanied with insulin resistance, especially in obese hypertensive patients and hypertensives with non-insulin dependent diabetes mellitus (NIDDM).

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Rad je primljen 1. IV 2002.
Prihvaćen za štampu 12. IV 2002.
BIBLID.0025-8105:(2002):LV:7-8:286-292.