Odnos između mokraćne kiseline, hiperglikemije i hipertrigliceridemije u općoj populaciji

Relationship between uric acid, hyperglycemia and hypertriglyceridemia in general population

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Sažetak

Uvod: Postoje oprečne informacije o odnosu između mokraćne kiseline i nekoliko sastavnica metaboličkog sindroma.

Materijali i metode: Retrospektivno smo analizirali rezultate pretraga mokraćne kiseline u serumu, glukoze u plazmi natašte te triglicerida, provedenih na čitavoj kohorti izvanbolničkih odraslih bolesnika, koji su bili uzastopno upućivani u naš laboratorij radi rutinskih krvnih pretraga tijekom protekle dvije godine.

Rezultati: Za ispitanike čije su koncentracije glukoze i triglicerida prelazile granične vrijednosti prema kriterijima ATP III postojala je veća vjerojatnost da su muškarci s izraženim porastom koncentracije mokraćne kiseline u serumu (355 µmol/L, 95% CI = 208–555 µmol/L prema 304 µmol/L, 95% CI = 172–494 µmol/L; P < 0,001). Gotovo istovjetni rezultati utvrđeni su nakon stratifikacije ispitivane populacije među muškarcima i ženama te prilagodbi za dob. Kod ispitanika s hiperurikemijom (mokraćna kiselina u serumu ≥ 506 µmol/L u muškaraca te ≥ 416 µmol/L u žena) također je uočena značajno viša prevalencija patoloških koncentracija glukoze i triglicerida (32% prema 11%; P < 0,001) u odnosu na ispitanike s normalnim vrijednostima mokraćne kiseline u serumu. Glukoza i trigliceridi su u linearnoj regresijskoj analizi s više varijabli bili neovisno povezani s koncentracijama mokraćne kiseline u serumu nakon prilagodbi za dob i spol.

Zaključak: Uzajaman biološki međuodnos zapažen između mokraćne kiseline u serumu, hipertrigliceridemije i hiperglikemije otvara mogućnost za potencijalno patogenetsko preklapanje među tim stanjima.

Ključne riječi: šećerna bolest, glukoza natašte, hiperglikemija, metabolički sindrom, hipertrigliceridemija, mokraćna kiselina

Abstract

Introduction: There is controversial information on the relationship between uric acid and several components of the metabolic syndrome.

Materials and methods: We retrospectively analyzed results of serum uric acid, fasting plasma glucose (FPG) and triglyceride tests performed on the whole cohort of outpatient adults consecutively referred to our laboratory for routine blood testing in the previous two years.

Results: Subjects with both FPG and triglyceride values exceeding the ATP III criteria thresholds were more likely to be male and had a marked increase in serum uric acid levels (355 µmol/L, 95% CI = 208–555 µmol/L versus 304 µmol/L, 95% CI = 172–494 µmol/L; P < 0.001). Nearly identical results were found after stratifying the study population between males and females and after adjustment for age. The study subjects with hyperuricemia (serum uric acid ≥ 506 µmol/L for males and ≥ 416 µmol/L for females) also had a significantly higher prevalence of abnormal values of both FPG and triglycerides (32% versus 11%; P < 0.001) as compared to subjects with normal serum uric acid values. In multivariable linear regression analysis, FPG and triglycerides were independently associated with serum uric acid levels after adjustment for age and gender.

Conclusion: The mutual biological interrelationship observed between serum uric acid, hypertriglyceridemia and hyperglycemia raises the possibility of a potential pathogenetic overlap between these conditions.

Key words: diabetes, fasting plasma glucose, hyperglycemia, metabolic syndrome, hypertriglyceridemia, uric acid.

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Uvod

Epidemiološke su studije pokazale značajne povezanosti između povišenih koncentracija mokraćne kiseline u serumu i nekoliko sastavnica metaboličkog sindroma kao što su pretilost, šećerna bolest tipa 2 i hipertrigliceridemija (1,2). Značajno je da su te povezanosti prisutne već i u djece i mladih osoba (3,4). Nedavno je također naglašeno da, iako su povišene koncentracije mokraćne kiseline u serumu čvrsto povezane s metaboličkim sindromom, ipak ne predstavljaju neovisan čimbenik rizika za vaskularnu bolest u bolesnika s tim sindromom (5). Osim toga, Liou i suradnici su izvijestili da se prisutnost metaboličkog sindroma nije mogla dovesti u vezu s povišenim koncentracijama mokraćne kiseline (6), dok Lin i suradnici nisu zapazili nikakvu povezanost između koncentracije mokraćne kiseline u serumu, hiperglikemije i ostalih sastavnica metaboličkog sindroma (7). Ova je studija stoga osmišljena radi otkrivanja mogućih bioloških odnosa između koncentracija mokraćne kiseline, glukoze u plazmi natašte i triglicerida u općoj populaciji.

Materijali i metode

Ispitanici

Provedena je retrospektivna analiza baze podataka našeg laboratorijskog informacijskog sustava kako bi se ispitao odnos koncentracija mokraćne kiseline u serumu, glukoze natašte i triglicerida (dvije ključne biokemijske sastavnice metaboličkog sindroma prema definiciji ATP III (8), a koje su provedene na čitavoj kohorti izvanbolničkih odraslih pacijenata koje su liječnici opće prakse uzastopno upućivali radi rutinskih krvnih pretraga tijekom protekle dvije godine (lipanj 2005. – lipanj 2007.). Za stratifikaciju čitave populacije tih bolesnika nisu korišteni ni kriteriji za uključivanje niti za isključivanje u studiju.

Metode

Venska se krv rutinski prikupljala ujutro nakon gladovanja. Koncentracije glukoze, triglicerida i mokraćne kiseline određene su standardnim enzimskim postupcima na modularnom sustavu Roche/Hitachi (Roche Diagnostics GmbH, Milano, Italija). Gornja granica referentnog raspona za mokraćnu kiselinu bila je 506 µmol/L za muškarce i 416 µmol/L za žene.

Statistička analiza

Značajnost razlika i frekvencije razdioba vrijednosti bile su procijenjene Kruskal-Wallisovim testom za kvantitativne varijable te Chi-kvadrat-testom za kategoričke varijable. Načinjena je multipla linearna regresija, no najprije su varijable koje nisu pokazivale normalnu razdiobu logaritamski preoblikovane. U potpuno prilagođenom multiplom regresijskom modelu mokraćna kiselina je postavlje-

Introduction

Epidemiological studies have shown significant associations between increased serum uric acid concentrations and several components of the metabolic syndrome, such as obesity, type 2 diabetes and hypertriglyceridemia (1,2). Notably, these associations were already present in children and young adolescents (3,4). It was also recently emphasized that elevated serum uric acid levels are strongly associated with the metabolic syndrome, yet are not an independent risk factor for vascular disease in patients with this syndrome (5). Additionally, Liou et al. reported that the presence of metabolic syndrome was not associated with increased circulating uric acid levels (6), whereas Lin et al. did not observe any association between serum uric acid, hyperglycemia and other components of the metabolic syndrome (7). Thus, this study was designed to unveil potential biological relationships between uric acid, fasting plasma glucose (FPG) and triglycerides in the general population.

Materials and methods

Patients

We performed a retrospective analysis on the database of our Laboratory Information System to retrieve results of serum uric acid, FPG and triglyceride tests (the two key biochemical components of the metabolic syndrome according to the ATP III definition) (8), which had been performed on the whole cohort of outpatient adults consecutively referred by general practitioners for routine blood testing in the previous two years (June 2005 – June 2007). Neither inclusion nor exclusion criteria were applied to stratify the entire population of outpatients.

Methods

Venous blood was routinely collected in the morning on fasting subjects. FPG, triglycerides and uric acid concentrations were assayed by standard enzymatic procedures on Roche/Hitachi Modular System (Roche Diagnostics GmbH, Milan, Italy). The upper limit of the reference range for uric acid was 506 µmol/L for males and 416 µmol/L for females.

Statistical analysis

Significance of differences and frequency distribution of values were assessed by the Kruskal-Wallis test (for continuous variables) and the chi-squared test (for categorical variables), respectively. Multivariable linear regression analysis was also preformed but skewed variables were first logarithmically transformed to improve normality. In the fully adjusted multivariable regression model, uric acid was entered as a dependent variable, whereas age, gender, FPG and triglycerides were included as covaria-

na kao ovisna varijabla, dok su dob, spol, glukoza u plazmi natašte i trigliceridi uključeni kao kovarijable. Statističke su analize provedene primjenom statističkog paketa SPSS, verzija 12.0 (SPSS, Chicago, SAD), a razina statističke značajnosti je trajno određena na < 0,05. Podatci su prikazani kao srednje vrijednosti (± 95% interval pouzdanosti) ili postotci. Studiju je odobrio etički odbor naše klinike.

Rezultati

Zbirni rezultati za koncentracije mokraćne kiseline u serumu, glukoze u plazmi natašte i triglicerida dobiveni su za 10.181 ambulantnih bolesnika starijih od 35 godina tijekom dvogodišnjeg razdoblja. Kao što je pokazano u tablici 1, za osobe s koncentracijama glukoze i triglicerida koje su prelazile granične vrijednosti definirane kriterijima ATP III, postojala je veća vjerojatnost da su muškarci i da imaju istaknut porast koncentracija mokraćne kiseline u serumu. Gotovo su istovjetni rezultati utvrđeni nakon stratifikacije istraživane populacije u muškaraca (367 µmol/L, 95% CI = 226–579 µmol/L prema 338 µmol/L, 95% CI = 208–512 µmol/L; P < 0,001) i žena (334 µmol/L, 95% CI = 201–525 µmol/L prema 270 µmol/L, 95% CI = 155–458 µmol/L; P < 0,001). Razlike u koncentracijama mokraćne kiseline u serumu ostale su statistički značajne čak i nakon prilagodbe za dob (podatci nisu prikazani). Sukladno tome, učestalost patoloških vrijednosti mokraćne kiseline bila je veća među ispitanicima s visokim koncentracijama glukoze u plazmi nakon gladovanja i triglicerida i navodila na dijagnozu metaboličkog sindroma, nego među ispitanicima s normalnim vrijednostima glukoze i triglicerida (Tablica 1). Za ispitanike s hiperurikemijom bila je također karakteristična značajno viša prevalencija patoloških vrijednosti kako glukoze, tako i triglicerida (32% prema 11%; P < 0,001) u usporedbi s ispitanicima čije su vrijednosti mokraćne kiseline u serumu bile unutar referentnog raspona. U multiploj linearnoj regresijskoj analizi glukoza (standardizirani beta-koeficijent = 0,520; P < 0,001) i triglyceridi (standardizirani beta-koeficijent = 0,293; P < 0,001) bili su neovisno povezani s koncentracijama mokraćne kiseline u serumu nakon prilagodbe za dob i spol.

Rasprava

Raspravlja se o tome je li mokraćna kiselina jednostavno biljeg kardiovaskularne bolesti ili može imati aterogeni učinak neovisno o drugim poznatim čimbenicima kardiovaskularnog rizika. Povišene koncentracije mokraćne kiseline koreliraju sa starijom dobi, muškim spolom, hiperlipidemijom, pretilošću, inzulinskom rezistencijom i šećernom bolesti tipa 2 (1,2) te ubrzavaju napredovanje ozljede krajnjeg organa izazvane hipertenzijom (9). Mokraćna kiselina također aktivira sustav komplementa izazivanjem razvoja oksidacijskog stresa i oksidacije LDL-a (10), te ima

tes. Statistical analyses were performed using the statistical package SPSS version 12.0 (SPSS, Chicago, IL) and the level of statistical significance was always set at P < 0.05. Data are presented as means (± 95% confidence intervals) or percentages. The study was approved by our departmental ethics committee.

Results

Cumulative results for serum uric acid, FPG and triglyceride levels were retrieved for 10,181 outpatients > 35 years old over the 2-year period. As shown in Table 1, subjects with both FPG and triglyceride values exceeding the thresholds defined by the ATP III criteria were more likely to be male and had a marked increase in serum uric acid levels. Almost identical results were found after stratifying the study population between males (367 µmol/L, 95% CI = 226–579 µmol/L *vs* 338 µmol/L, 95% CI = 208–512 µmol/L; P < 0.001) and females (334 µmol/L. 95% CI = 201–525 µmol/L *vs* 270 µmol/L, 95% CI = 155–458 µmol/L; P < 0.001). The differences in serum uric acid levels remained statistically significant even after adjustment for age (data not shown). Accordingly, the frequency of abnormal values of uric acid was higher among subjects with high FPG and triglyceride values, suggestive for diagnosing the metabolic syndrome, than among those with normal FPG and triglyceride values (Table 1). The study subjects with hyperuricemia were also characterized by a significantly higher prevalence of abnormal values of both FPG and triglycerides (32% versus 11%; P < 0.001) as compared to subjects with serum uric acid values within the reference range. In multivariable linear regression analysis, FPG (standardized beta coefficient = 0.520; P < 0.001) and triglycerides (standardized beta coefficient = 0.293; P < 0.001) were independently associated with serum uric acid levels, after adjustment for age and gender.

Discussion

There is debate whether uric acid is simply a marker of cardiovascular disease or it may exert an atherogenic effect independently of other known cardiovascular risk factors. Elevated levels of uric acid correlate with older age, male gender, hyperlipidemia, obesity, insulin resistance and type 2 diabetes (1,2) and accelerate the progression of hypertension-induced end-organ injury (9). Uric acid also activates the complement system inducing the development of oxidative stress and LDL oxidation (10), and exerts proinflammatory effects stimulating human mononuclear cells to produce inflammatory cytokines (9). Finally, uric acid induces systemic endothelial dysfunction, a pathogenetic mechanism in mediating hypertension (11).
The major finding of this study is that hypertriglyceridemic and hyperglycemic adults have increased prevalence rate of elevated serum uric acid levels, and that hypertrig-

Tablica 1. Osnovna obilježja sudionika studije (N = 10.181) grupirana prema prevalenciji patoloških vrijednosti glukoze i triglicerida (definiranih prema kriterijima ATP III) (9).

Table 1. Baseline characteristics of the study participants (N = 10,181) grouped according to the prevalence of abnormal glucose and triglyceride values (as defined by the ATP III criteria) (9).

	FPG < 6.1 mmol/L TG < 1.7 mmol/L	FPG > 6.1 mmol/L TG > 1.7 mmol/L	P
N	9112	1069	
Age	60 (37-83)	61 (40-80)	0.131
Sex (% females)	4375 (48%)	395 (37%)	0.022
Serum Uric Acid			
Mean and 95% CI (μmol/L)	304 (172-494)	355 (208-555)	< 0.001
% patients with abnormal values	3%	11%	0.018

FPG = fasting plasma glucose; TG = triglycerides
Abnormal values of uric acid were defined as ≥ 506 μmol/L for males and ≥ 416 μmol/L for females.

proupalne učinke koji potiču mononuklearne stanice na stvaranje upalnih citokina (9). Konačno, mokraćna kiselina izaziva sustavnu endotelnu disfunkciju koja predstavlja patogeni mehanizam u posredovanju hipertenzije (11).

Glavni je nalaz ove studije da odrasle osobe s hipertrigliceridemijom i hiperglikemijom imaju veći postotak prevalencije povišenih koncentracija mokraćne kiseline u serumu, te da su ta dva poremećaja najjači pretkazatelji hiperurikemije u velikom uzorku opće populacije. Na prvi se pogled ta otkrića ne moraju činiti iznenađujućima s obzirom na snažnu vezu između koncentracija mokraćne kiseline u serumu i inzulinske rezistencije te prethodnih zapažanja o pozitivnoj povezanosti koncentracija mokraćne kiseline u serumu i hiperglikemije i dislipidemije (4). Međutim, temeljni patofiziološki mehanizmi koji povezuju hiperglikemiju, hipertrigliceridemiju i hiperurikemiju trenutno nisu poznati. Moguće je da su uključeni čimbenici koji pojačavaju sintezu mokraćne kiseline u serumu (npr. povećana aktivnost sporednog puta heksoza-monofosfata, a time i biosinteze purina), kao i oni koji smanju brzinu izlučivanja mokraćne kiseline iz mokraće (npr. pojačana tubularna reapsorpcija i/ili smanjeno tubularno lučenje). Zaista, kod bolesnika s inzulinskom rezistencijom ili oštećenim podnošenjem glukoze dokazano je da imaju snižene vrijednosti uklanjanja (klirensa) mokraćne kiseline iz mokraće (12) te kronično povišene koncentracije izvanstaničnog adenozina, što sve doprinosi povećanoj sintezi mokraćne kiseline (13).

Jače strane, ali i ograničenja ove studije zaslužuju komentar. Biokemijske varijable (hiperglikemija, hipertrigliceridemija) koje su obično okupljene u metaboličkom sindromu dobivene su iz opsežne baze podataka o rezultatima pret-

lyceridemia and hyperglycemia are the strongest predictors of hyperuricemia in a large sample of the general population. At first glance, these findings could appear unsurprising, given the strong association between serum uric acid levels and insulin resistance and the previous observations of a positive association of serum uric acid levels with hyperglycemia and dyslipidemia (4). However, the underlying pathophysiological mechanisms linking hyperglycemia, hypertriglyceridemia and hyperuricemia are currently unknown. Both the factors that increase serum uric acid synthesis (e.g., an increased activity of the hexose monophosphate shunt and thereby purine biosynthesis) or those that decrease urinary uric acid excretion rate (e.g., an increased tubular reasorption and/or diminished tubular secretion) might be involved. Indeed, it has been shown that patients with insulin resistance or impaired glucose tolerance have reduced values of urinary uric acid clearance (12) and chronically increased extracellular adenosine concentrations, thereby contributing to increasing uric acid synthesis (13).

The strengths and limitations of the present study deserve comment. The biochemical variables (hyperglycemia, hypertriglyceridemia) that typically cluster in the metabolic syndrome were retrieved from a large database of outpatient test results and confirm the previous observation that FPG was significantly and positively associated with the uric acid level (14). However, the cross-sectional design of the study precludes the establishment of causal or temporal relations among these variables, and prospective studies will be required to sort out the time sequence of events. Further, the study population of outpatient adults from laboratory may not be a representa-

raga ambulantnih bolesnika i potvrdile su prethodno zapažanje da je koncentracija glukoze značajno i pozitivno povezana s koncentracijom mokraćne kiseline (14). Međutim, presječni dizajn studije ne opravdava postavljanje uzročnih ili vremenskih veza među tim varijablama tako da su radi definiranja vremenskog slijeda događaja potrebne prospektivne studije. Nadalje, ispitivana populacija koju su činili ambulantni odrasli pacijenti laboratorija ne mora biti reprezentativan uzorak opće populacije. Također, nikakve dodatne informacije nisu, na žalost, bile dostupne o toj velikoj skupini ambulantnih bolesnika, kao ni o stvarnoj prevalenciji metaboličkog sindroma definiranog prema cjelovitim kriterijima ATP III. Ipak, biološki međuodnosi uočeni u ovoj velikoj ispitivanoj populaciji otvaraju mogućnost potencijalnog patogenetskog preklapanja (ili začaranog kruga) između hiperurikemije, hipertrigliceridemije i hiperglikemije.

tive sample of general population and, unfortunately, neither additional clinical information is available on this large cohort of outpatients, nor the effective prevalence of metabolic syndrome as defined by the complete ATP III criteria. Nevertheless, the biological interrelationships observed in this large study population raise the possibility of a potential pathogenetic overlap (or a vicious circle) between hyperuricemia, hypertriglyceridemia and hyperglycemia.

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