Mikroalbuminurija i rizik od srčanožilnih bolesti u bolesnika s šećernom bolesti i hipertenzijom

Microalbuminuria and risk of cardiovascular diseases in patients with diabetes and hypertension

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Sažetak

Izlučivanje albumina mokraćom je pokazatelj rizika od srčanožilnih bolesti, poglavito u bolesnika s šećernom bolesti i hipertenzijom. Mikroalbuminurija se danas smatra biljegom opće endotelne disfunkcije. Ona odražava transvaskularno propuštanje albumina, što je danas prepoznato kao rani događaj u aterogenezi i kardiovaskularnim bolestima. Opservacijske studije i intervencijska ispitivanja utvrdila su kako su čak i niske razine albuminurije (mikroalbuminurija) udružene s povećanim rizikom od srčanožilnog pobola i smrtnosti u općoj populaciji, te osobito u populacijama s visokim rizikom kao što su oni sa šećernom bolešću, hipertenzijom ili bubrežnom bolešću. Cilj ovoga kratkog osvrta je prikazati današnje definicije albuminurije i metode za njezino mjerenje, te sažeto prikazati raspoložive dokaze koji naglašavaju snažan međusobni odnos mikroalbuminurije i drugih kardiovaskularnih čimbenika rizika.

Ključne riječi: mikroalbuminurija, endotelna disfunkcija, kardiovaskularni rizik, šećerna bolest, hipertenzija

Abstract

Urinary albumin excretion is an indicator of the cardiovascular risk, especially in patients with diabetes and hypertension. Microalbuminuria is currently regarded as a marker of generalized endothelial dysfunction. It reflects transvascular albumin leakage, now recognized as an early event in atherogenesis and cardiovascular diseases. Observational studies and intervention trials have established that even low levels of albuminuria (microalbuminuria) are associated with an increased risk of cardiovascular morbidity and mortality in general, and especially in high-risk populations such as those with diabetes mellitus, hypertension or kidney disease. The aim of this short review is to present actual definitions of albuminuria and methods for measurement, and to summarize available evidence emphasizing strong relationships between microalbuminuria and other cardiovascular risk factors.

Key words: microalbuminuria, endothelial dysfunction, cardiovascular risk, diabetes, hypertension

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Uvod

Mikroalbuminurija je neovisni predskazatelj kardiovaskularne smrtnosti i srčanožilnih bolesti poput srčane, cerebrovaskularne i periferne arterijske bolesti u bolesnika s šećernom bolesti ili hipertenzijom, ali i u općoj populaciji. Određivanje mikroalbuminurije danas se preporuča kao strategija za procjenu rizika u bolesnika s šećernom bolesti i hipertenzijom. U ovom osvrtu opisuju se metode za mjerenje mikroalbuminurije i izdavanje nalaza izlučivanja albumina u mokraći, te se postavlja pitanje njihove standardizacije. Kako udruženost mikroalbuminurije s endotelnom disfunkcijom i kardiovaskularnim bolestima

Introduction

Microalbuminuria is an independent predictor of cardiovascular mortality and cardiovascular diseases such as cardiac, cerebrovascular and peripheral arterial disease in patients with diabetes or hypertension, and in the general population. Determination of microalbuminuria is now recommended as a risk stratification strategy in diabetic and hypertensive patients. In this review, methods for the measurement of microalbuminuria and reporting of urinary albumin excretion are described and a question of their standardization is raised. As the association between microalbuminuria, endothelial dysfunction and cardiovascu-

u prisutnosti šećerne bolesti ili hipertenzije nije još u potpunosti razjašnjena, raspravlja se o nedavno objavljenim studijama o ovoj temi.

Definicija i mjerenje mikroalbuminurije

Definicija mikroalbuminurije

Izraz „mikroalbuminurija" u literaturi se prvi put pojavio 1981. godine, a opisivao je prisutnost albumina u mokraći ispod granice otkrivanja standardnim test trakom, no na razini koja u znatnoj mjeri ukazuje na buduću proteinuriju u bolesnika sa šećernom bolešću (1). Prema klasičnoj definiciji „normalno" izlučivanje albumina u mokraći može se definirati kao:

- UAE (engl. *urinary albumin excretion*) < 30 mg/24 h u 24-satnoj mokraći;
- stopa izlučivanja albumina u mokraći < 20 μg/min;
- omjer albumina i kreatinina u mokraći (engl. *albumin-to-creatinine ratio,* ACR) < 30 mg/g ili < 3,4 mg/mmol kod žena i < 20 mg/g ili < 2,5 mg/mmol kod muškaraca; te
- koncentracija albumina u mokraći < 20 mg/L u jednokratnom uzorku mokraće (2,3).

Nedavno su de Jong i Curhan preporučili uporabu izraza „visoko normalne" za gornje vrijednosti (4). Dijagnostički prag za normalnu albuminuriju snižen je na:

- UAE < 15 mg/24 h,
- ACR < 10 mg/g ili < 1,25 mg/mmol kod muškaraca i ACR < 15 mg/g ili < 1,75 mg/mmol kod žena; te
- < 10 mg/L albumina u mokraći (4-6).

Vrijednosti koje definiraju mikroalbuminuriju su:

- UAE 30 do 300 mg/24 h;
- UAE 20 do 200 μg/min;
- ACR 20 do 200 mg/g ili 2,4 do 25 mg/mmol kod muškaraca i 30 do 300 mg/g ili 3,5 do 35 mg/mmol kod žena; te
- 20 do 200 mg/L albumina u mokraći.

Više razine izlučivanja albumina u mokraći svrstavaju se kao makroalbuminurija (5).

Klausen i sur. su ispitali 2762 osoba bez koronarne srčane bolesti u anamnezi i izvijestili kako je mikroalbuminurija snažna odrednica koronarne srčane bolesti i smrti (7). U općoj populaciji rizik od srčanožilnih bolesti raste kod razine albuminurije ispod praga za mikroalbuminuriju. Postoji stalan odnos između koncentracije albumina u mokraći i kardiovaskularnog rizika (1). Noćno izlučivanje albumina tek iznad 5 μg/min znatno je predskazivalo koronarnu srčanu bolest i smrt u općoj populaciji (7).

Podatci iz nekoliko velikih studija ukazuju na to da je izlučivanje albumina mokraćom iznad 2 mg/dan (oko 4 μg/min) značajno udruženo s kardiovaskularnim ispa-

lar diseases in the presence of diabetes or hypertension has not yet been fully explained, the authors discuss the recently published studies related to the topic.

Definition and measurement of microalbuminuria

Definition of microalbuminuria

The term "microalbuminuria" first appeared in the literature in 1981 to describe the presence of albumin in the urine below the detection limit of a standard test strip, but at a highly predictive level for future proteinuria in patients with diabetes mellitus (1). According to classic definition, "normal" urinary albumin excretion (UAE) may be defined as:

- UAE < 30 mg/24 h in 24-hour collection;
- urinary albumin excretion rate < 20 μg/min in timed urine sample;
- urinary albumin-to-creatinine ratio (ACR) < 30 mg/g or < 3.4 mg/mmol in women and < 20 mg/g or < 2.5 mg/mmol in men; and
- urinary albumin concentration < 20 mg/L in spot urine (2,3).

Recently, de Jong and Curhan have recommended the term "high normal" to be used for the values defined above (4). The diagnostic threshold for normal albuminuria has been decreased to

- UAE < 15 mg/24 h;
- ACR < 10 mg/g or < 1.25 mg/mmol in men and ACR < 15 mg/g or < 1.75 mg/mmol in women;
- and < 10 mg/L of urinary albumin (4-6).

The values defining microalbuminuria are:

- UAE 30 to 300 mg/24 h;
- 20 to 200 μg/min;
- ACR 20 to 200 mg/g or 2.5 to 25 mg/mmol in men and 30 to 300 mg/g or 3.5 to 35 mg/mmol in women; and
- 20 to 200 mg/L of urinary albumin.

Higher UAE levels are classified as macroalbuminuria (5). Klausen *et al*. examined 2,762 subjects without a history of coronary heart disease and report that microalbuminuria was a strong determinant of coronary heart disease and death (7). In the general population, the risk of cardiovascular diseases rises at albuminuria level below the threshold for microalbuminuria. A continuous relationship exists between the level of urinary albumin concentration and the cardiovascular risk (1). An overnight UAE above only 5 μg/min was strongly predictive of coronary heart disease and death in the general population (7).

Data from several large studies suggest that UAE over 2 mg/day (about 4 μg/min) was associated significantly with cardiovascular events even in subjects without diabetes (1). Assuming the normal range of UAE as 20 μg/min,

dima čak i u osoba bez šećerne bolesti (1). Uzimajući 20 mg/min kao normalan raspon izlučivanja albumina mokraćom, rizik od srčanožilnih bolesti ili smrti povećao se za 70% ili 50% u hipertenzivnih bolesnika s albuminurijom od samo 5-10 μg/min (8).
Prisutnost mikroalbuminurije definirane kao izlučivanje iznad 5 μg/min u osoba s kardiovaskularnom ili cerebrovaskularnom bolešću povećava rizik od smrti za 100% (9). Prema ovoj studiji, trebalo bi prihvatiti definiciju mikroalbuminurije kao izlučivanje albumina mokraćom iznad 5 μg/min.

Mjerenje mikroalbuminurije

Prema smjernicama zasnovanima na dokazima, testiranje albuminurije, općenito jedanput na godinu, preporuča se za bolesnike sa šećernom bolešću i hipertenzijom. U bolesnika s hipertenzijom albuminuriju treba provjeravati svakih 6 mjeseci u prvoj godini liječenja, kako bi se pratilo djelovanje antihipertenzivne terapije (10). Međutim, podatci za Sjedinjene Države iz 2004. godine otkrivaju kako se kod bolesnika s šećernom bolesti uglavnom ispituje status lipida (91%) i udio HbA1c (86%), a tek kod oko 50% mikroalbuminurija (11). Godine 2006. je AHA (engl. *American Heart Association*) objavila preporuke za pretrage radi otkrivanja bubrežne bolesti koje uključuju procijenjenu stopu glomerularne filtracije (engl. *glomerular filtration rate*, GFR) uz primjenu jednadžbe za Promjenu prehrane kod bubrežne bolesti (engl. *Modification of Diet in Renal Disease*, MDRD) i ispitivanje albuminurije radi otkrivanja kronične bubrežne bolesti (12). Ove preporuke znače velik napredak, jer povezuju kroničnu bubrežnu bolest i srčanožilne bolesti.
U primjeni je nekoliko metoda za mjerenje koncentracije albumina u mokraći uključujući imunološko otkrivanje (uz uporabu test traka, imunonefelometrija, imunoturbidimetrija, radioimuno test, ELISA, kemiluminescentni imuno test, fluorescentni imuno test), HPLC i spektrofotometriju. Najčešće se rabe imunološke metode koje su osjetljive, ali omogućavaju samo procjenu intaktnih molekula imunoreaktivnog albumina (13). Fragmenti albumina otkrivaju se spektrofotometrijom, a molekule neimunoreaktivnog albumina tekućinskom kromatografijom visoke djelotvornosti (HPLC) (14). Klinička značajnost neimunoreaktivnog albumina još nije potpuno razjašnjena, tek se očekuje objašnjenje. Nedavno je objavljeno kako se spektralni test raspršenja rezonance (engl. *resonance scattering spectral assay,* RSSA), koji se zasniva na imunoreakciji i njezinom učinku raspršenja rezonance, čini jednostavnom, brzom i osjetljivom pretragom za mjerenje mikroalbumina (15). Valja naglasiti kako niti tehnika HPLC niti RSSA ne mogu naći široku primjenu za procjenu koncentracije albumina u mokraći zbog visoke cijene i nedostupnosti tehnologije.

the risk of cardiovascular disease or death increased by 70% or 50% in hypertensive patients with albuminuria as low as 5–10 μg/min (8).
The presence of microalbuminuria defined as excretion above 5 μg/min in subjects with cardiovascular or cerebrovascular disease increases the risk of death by 100% (9). According to this study, the definition of microalbuminuria as UAE above 5 μg/min should be accepted.

Measurement of microalbuminuria

Testing for microalbuminuria, generally once a year, is recommended for patients with diabetes and hypertension according to the evidence-based guidelines. In patients with hypertension, albuminuria should be assessed every 6 months within the first year of treatment to monitor the impact of antihypertensive therapy (10). However, the US data from 2004 have disclosed that diabetic patients are mainly tested for their lipid profile (91%) and HbA1c levels (86%), and only about 50% for microalbuminuria (11). In 2006, the American Heart Association published recommendations for testing to detect kidney disease, that includes estimated glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease (MDRD) equation and a test for microalbuminuria for detection of chronic kidney disease (12). These recommendations are important developments because they link chronic kidney disease and cardiovascular diseases.
Several methods for urinary albumin measurement have been applied including immunologic detection (with the use of test strips, immunonephelometry, immunoturbidimetry, radioimmunoassay, ELISA, chemiluminescence immunoassay, fluorescence immunoassay), HPLC and spectrophotometry. The most frequently used are immunologic methods, which are sensitive but enable assessment of intact immunoreactive albumin molecules only (13). Albumin fragments are detected by spectrophotometry and non-immunoreactive albumin molecules by high-performance liquid chromatography (HPLC) (14). The clinical significance of non-immunoreactive albumin is not yet understood and remains to be explained. Recently, the resonance scattering spectral assay (RSSA) for microalbumin measurement, based on the immunoreaction and its resonance scattering effect, has been reported as being simple, rapid and sensitive (15). It should be noted that neither HPLC technique nor immunoresonance scatter spectral assay for assessment of urinary albumin can be widely used because of their high cost and technology inaccessibility.
There are few methods of urine sampling: complete 24-hour urine sample or timed urine sample (4 hours or overnight) used mostly in clinical settings, and random sample – spot urine collection used mainly in primary care (www.labstestonline.org). The validity of screening by albumin measurements in spot morning urine sample

Nekoliko je metoda prikupljanja mokraće: sveukupan 24-satni uzorak mokraće ili vremenski ograničen uzorak mokraće (4 sata ili preko noći) najčešće se rabe u kliničkim uvjetima, dok se slučajan uzorak – uzorak mokraće uzet pri pregledu uglavnom rabi u primarnoj skrbi (www.labstestonline.org). Valjanost probira pomoću mjerenja albumina u slučajnom jutarnjem uzorku mokraće ispitivala se ne samo kako bi se identificirale osobe s mikroalbuminurijom u općoj populaciji, nego i kod bolesnika s hipertenzijom (16,17). Utvrđeno je kako je dijagnostička uspješnost mjerenja koncentracije albumina u slučajnom uzorku mokraće usporediva s onom omjera albumina i kreatinina. Štoviše, mjerenje omjera albumina i kreatinina zahtijeva dodatno određivanje koncentracije kreatinina i primjenu graničnih vrijednosti specifičnih za spol (17). Stoga je mjerenje koncentracije albumina u slučajnom uzorku mokraće predloženo kao metoda probira koja je prikladnija za svakodnevnu kliničku praksu.

Treba voditi računa o promjenjivosti izlučivanja albumina u mokraći, što znatno ograničava točnost mjerenja. Nekoliko je čimbenika i stanja koji mogu privremeno povisiti izlučivanje albumina u mokraći, primjerice: groznica, tjelesna aktivnost, srčano zatajivanje, infekcije mokraćnog sustava i prehrana s visokim sadržajem bjelančevina (13,18). Izlučivanje albumina mokraćom smanjuje se noću i razlikuje se od dana do dana. Kako ova promjenjivost ovisi o vremenu kad se mokraća prikuplja, ponovljivost UAE je bolja kod uzoraka prikupljenih preko noći te u uzorcima prvog jutarnjeg mlaza mokraće. Individualna i dnevna promjenjivost također ovise o vrsti bolesti, a niže su u bolesnika s hipertenzijom nego u onih s šećernom bolesti (13). Ponovljivost mjerenja albumina može se poboljšati ako se mjerenje ponavlja tri puta u uzorcima mokraće prikupljenim na isti način, a prijeanalitičke pogreške su isključene.

Godine 2005. je IFCC (engl. *International Federation of Clinical Chemistry*) osnovao Radnu skupinu za standardizaciju testa za mikroalbumin u mokraći, kako bi se utvrdili referentni postupak i referentni materijali. Standardizacija još nije završena, međutim, upravo se provode projekti kojima je cilj kemijsko i imunokemijsko opisivanje različitih oblika albumina u mokraći (definicija analita) i odluka o optimalnom analitu za procjenu (mikro)albuminurije (19).

Standardiziranje izvješćivanja o izlučivanju albumina u mokraći ili omjeru albumina i kreatinina također je veoma važno, kao i iskazivanje triju pragova za albuminuriju u laboratorijskim nalazima. Ujednačen format izvješćivanja i u istim jedinicama omogućio bi usporedivost rezultata među različitim zemljama te bi se izbjegla mogućnost krivog tumačenja rezultata.

Učestalost mikroalbuminurije

Mikroalbuminurija je utvrđeni čimbenik rizika za kardiovaskularni pobol i smrtnost, te za bubrežnu bolest zavr-

has been investigated not only to identify subjects with microalbuminuria in the general population but also in patients with hypertension (16,17). Diagnostic performance of albumin concentration measurement in spot urine sample was found to be comparable to that of the albumin-to-creatinine ratio. Moreover, the measurement of the albumin-to-creatinine ratio requires an additional determination of creatinine and the use of gender-specific cut-off values (17). Measuring albumin concentration in the spot morning urine sample has therefore been proposed as a screening method that is more convenient in daily clinical practice.

One should also be aware of the variability of UAE, which is an important limitation of the measurement accuracy. There are several factors and conditions that may temporary rise UAE, such as fever, exercise, heart failure, urinary tract infection and high-protein diet (13,18). UAE decreases at night and varies between days. Because the variability depends on the time of urine collection, the reproducibility of UAE is better for samples collected during the nighttime and for the first morning samples. The individual variability and circadian variability also depend on the type of the disease, being lower in patients with hypertension than in diabetics (13). The reproducibility of albumin measurement can be increased if the measurement is repeated three times in the urine samples collected in the same fashion and if preanalytical errors are excluded.

In the year 2005, the International Federation of Clinical Chemistry founded the Working Group for the Standardization of Microalbumin Assay in Urine, with the aim to establish a reference procedure and reference materials. The standardization has not yet been completed, however, projects on chemical and immunochemical characterization of the various forms of albumin in urine (definition of the analyte) and on the decision on the optimum analyte for the assessment of (micro)albuminuria have just been under way (19).

The standardization for reporting UAE or urine albumin-to-creatinine ratio is also of primary importance as well as indicating the three thresholds for albuminuria on the lab report. The uniform reporting format in the same units would allow for comparability of the results across different countries and avoidance of misinterpretation of the results.

Prevalence of microalbuminuria

Microalbuminuria represents an established risk factor for cardiovascular morbidity and mortality and for end-stage renal disease in individuals with an adverse cardiovascular risk profile. It is common in the general population, particularly in patients with diabetes mellitus or hypertension. Data from large population-based studies in the United States, Europe and Australia show that the prevalen-

šnog stadija u osoba s nepovoljnim profilom kardiovaskularnog rizika. Mikroalbuminurija je česta u općoj populaciji, poglavito u bolesnika sa šećernom bolešću ili hipertenzijom. Podatci velikih populacijskih studija provedenih u Sjedinjenim Državama, Europi i Australiji pokazuju učestalost mikroalbuminurije u općoj populaciji od 5-15%, među dijabetičarima 20-30% te u bolesnika s hipertenzijom 11-17% (20-23).

U ranijim studijama zabilježena je udruženost albuminurije/proteinurije i kardiovaskularne smrtnosti u bolesnika bez šećerne bolesti (24,25). Izvješće ispitivanja naslovljenog Prevention and Vascular End-Stage Disease Study pokazalo je kako je u 7% od 40.856 ispitanika mikroalbuminurija bila neovisno udružena s prethodnim infarktom miokarda i moždanim udarom. Zaključeno je kako je UAE predskazatelj smrtnosti od svih uzroka u općoj populaciji (26,27).

Endotelna disfunkcija i kardiovaskularni rizik u bolesnika sa šećernom bolesti

Patogeneza endotelne disfunkcije

Mikroalbuminurija može biti uzrok ili posljedica vaskularne bolesti. Endotelna disfunkcija može izravno doprinijeti patogenezi albuminurije uzrokujući povećani glomerularni tlak te sintezu glomerularne bazalne membrane neprimjerenog ustroja, što dovodi do transvaskularnog propuštanja albumina. S druge strane, endotelna disfunkcija može parakrinim putem utjecati na funkciju glomerularnih mezangijalnih i epitelnih stanica (28). Udruženost mikroalbuminurije i srčanožilnih bolesti nije jasna, međutim, postoji hipoteza o endotelnoj disfunkciji i kroničnoj upali kao mogućim čimbenicima koji bi objasnili osnovni mehanizam (29). Poznato je kako upala niskog stupnja može biti uzrokom ili posljedicom endotelne disfunkcije te može biti povezana s pojavom i progresijom mikroalbuminurije i povećanim kardiovaskularnim rizikom (30). Usprkos postojećoj vezi između endotelne disfunkcije, upale niskog stupnja i mikroalbuminurije, one su neovisni čimbenici rizika za kardiovaskularnu smrt (31). Opisana je udruženost mikroalbuminurije s povećanom sintezom vaskularnog endotelnog čimbenika rasta i s C-reaktivnim proteinom, proteinom akutne faze i biljegom kronične upale, što pokazuje kako su višestruki mehanizmi upleteni u razvoj i progresiju kardiovaskularnih komplikacija kod dijabetičara s albuminurijom (32). Endotelna disfunkcija je generalizirana u oba tipa šećerne bolesti kompliciranih mikro- ili makroalbuminurijom i ona utječe na mnoge vidove endotelne funkcije. U oba tipa šećerne bolesti mikroalbuminurija je praćena raznovrsnim biljezima endotelne disfunkcije. U bolesnika sa šećernom bolesti tipa 2 zabilježena je značajna i neovisna korelacija između mikroalbuminurije i povišenih plazmatskih koncentracija von Willebrandova faktora (vWF), endotelina, trombomodulina, aktivatora tkivnog plazminogena (t-PA), inhibitora aktivatora plazmince of microalbuminuria is 5%–15% in the general population, 20%–30% in diabetics and 11%–17% in patients with hypertension (20–23).

In earlier studies, an association was found between albuminuria/proteinuria and cardiovascular mortality in patients without diabetes (24,25). Report from the Prevention and Vascular End-Stage Disease Study shows that in 7% out of 40,856 examined subjects, microalbuminuria was associated independently with previous myocardial infarction and stroke. It was concluded that UAE was a predictor of all-cause mortality in the general population (26,27).

Endothelial dysfunction and cardiovascular risk in patients with diabetes

Pathogenesis of endothelial dysfunction

Microalbuminuria can be a cause or a consequence of vascular disease. Endothelial dysfunction could contribute to the pathogenesis of albuminuria directly, by causing increased glomerular pressure and the synthesis of glomerular basement membrane of improper structure leading to transvascular albumin leakage. On the other hand, endothelial dysfunction, in a paracrine fashion, could influence glomerular mesangial and epithelial cell function (28). The association between microalbuminuria and cardiovascular diseases is not clear, however, the endothelial function and chronic inflammation have been suggested as the possible factors to explain the underlying mechanism (29). It is known that low-grade inflammation may be a cause and a consequence of endothelial dysfunction and can be related to the occurrence and progression of microalbuminuria and a higher cardiovascular risk (30). In spite of the existing link between endothelial dysfunction, low-grade inflammation and microalbuminuria, they are independent risk factors for cardiovascular death (31).

The association of microalbuminuria with the increased synthesis of vascular endothelial growth factor and with C-reactive protein, an acute phase protein and a marker of chronic inflammation, has been described showing that multiple mechanisms are involved in the development and progression of cardiovascular complications in diabetic patients with albuminuria (32). Endothelial dysfunction in both types of diabetes complicated by micro- or macroalbuminuria is generalized and affects many aspects of endothelial function. In both types of diabetes, microalbuminuria is accompanied by a variety of markers of endothelial dysfunction. A significant and independent correlation between microalbuminuria and increased levels of plasma von Willebrand factor (vWF), endothelin, thrombomodulin, tissue plasminogen activator (t-PA), inhibitor of plasminogen activator 1 (PAI-1), soluble adhesion molecules and soluble E-selectin was found in type 2 diabetics (6,29,33).

nogena 1 (PAI-1), topljivih adhezijskih molekula i topljivog E-selektina (6,29,33).

Najnoviji podatci pokazuju kako su mikroalbuminurija i koronarne vazomotorne nenormalnosti predskazatelji srčanih ispada u bolesnika s šećernom bolesti tipa 2. Ovi bolesnici su imali teže poremećenu koronarnu vazodilataciju ovisnu o endotelu u prisutnosti mikroalbuminurije (34). Cao i sur. su pokazali kako je u odsutnosti hipertenzije ili šećerne bolesti mikroalbuminurija udružena s kliničkom kardiovaskularnom bolešću, ali ne sa subkliničkom aterosklerozom. Autori su pretpostavili kako mehanizam udruženosti mikroalbuminurije s kliničkom vaskularnom bolešću uključuje destabilizaciju krvožilja, što dovodi do kliničke bolesti (35).

Veza između mikroalbuminurije i srčanožilnih ispada samo se djelomice objašnjava čimbenicima dobi, spola, šećerne bolesti, hipertenzije, pretilosti, dislipidemije i pušenja. Weir je pretpostavio da bi ona mogla proizlaziti iz neprimjerenih mjera endotelne funkcije i upale uz primjenu biokemijskih procjena (5).

Drugo objašnjenje nudi de Zeeuw, a povezuje individualnu sklonost ka organskom oštećenju sa svojstvenom varijabilnošću vaskularnog statusa određenog prema izlučivanju albumina (36). Prema ovoj hipotezi mikroalbuminurija bi mogla biti predskazatelj srčanožilnih bolesti, kao i novo nastale hipertenzije i šećerne bolesti (5). Bez obzira na njezin mehanizam, mikroalbuminurija ukazuje na rani stadij s povećanim rizikom za razvoj bubrežnih i srčanožilnih komplikacija u slučajevima sa šećernom bolešću, hipertenzijom i dislipidemijom.

Hiperhomocisteinemija i endotelna disfunkcija u bolesnika s mikroalbuminurijom

Utvrđeno je kako je povišena koncentracija homocisteina udružena s mikroalbuminurijom i retinopatijom u oba tipa šećerne bolesti. Čini se da je hiperhomocisteinemija jedan od glavnih uzroka povišene smrtnosti u bolesnika sa šećernom bolešću tipa 2. Hiperhomocisteinemija izravno je i značajno korelirala s jačinom mikroalbuminurije. Ovi rezultati ukazuju na to da bi u bolesnika s šećernom bolesti tipa 2 hiperhomocisteinemija mogla imati ulogu u razvoju vaskularnih komplikacija (37,38).

Osnovni mehanizam koji povezuje homocistein i endotelnu disfunkciju kod dijabetičara s mikroalbuminurijom nije jasan. Preostaje utvrditi je li hiperhomocisteinemijom posredovani oksidativni stres koji dovodi poremećene endotelne funkcije povezan s povećanim kardiovaskularnim rizikom u bolesnika s šećernom bolesti i mikroalbuminurijom. Novija studija u bolesnika s šećernom bolesti tipa 1 i mikroalbuminurijom pokazala je prisutnost blage hiperhomocisteinemije i smanjenu antioksidantnu obranu u ovih bolesnika u usporedbi s normoalbuminuričnim bolesnicima i nedijabetičnim ispitanicima (39).

Latest findings show that microalbuminuria and coronary vasomotor abnormalities are both predictors for cardiac events in type 2 diabetics. These patients had a more severely impaired coronary endothelium-dependent vasodilation in the presence of microalbuminuria (34). Cao *et al.* showed that in the absence of hypertension or diabetes, microalbuminuria was associated with clinical cardiovascular disease but not with subclinical atherosclerosis. They postulated that the mechanism of association of microalbuminuria with clinical vascular disease involved destabilization of the vasculature, leading to clinical disease (35).

The link between microalbuminuria and cardiovascular events is only partly explained by age, gender, diabetes, hypertension, obesity, dyslipidemia and smoking. Weir suggests that it may result from inadequate measures of endothelial function and inflammation using biochemical estimates (5).

Another explanation has been proposed by de Zeeuw, relating the individual susceptibility to organ damage to inherent variability of the vascular state as determined by albumin excretion (36). According to this hypothesis, microalbuminuria may be a predictor of cardiovascular diseases as well as of new-onset hypertension and diabetes (5). Whatever the mechanism, microalbuminuria identifies an early stage with an increased risk of developing renal and cardiovascular complications in cases with diabetes, hypertension and dyslipidemia.

Hyperhomocysteinemia and endothelial dysfunction in patients with microalbuminuria

Elevated homocysteine was found to be associated with microalbuminuria and retinopathy in both types of diabetes. Hyperhomocysteinemia seems to be one of the main causes of increased mortality in type 2 diabetic patients. Increased homocysteine correlated directly and significantly with the level of microalbuminuria. These results suggest that hyperhomocysteinemia in patients with type 2 diabetes may play a role in the development of vascular complications (37,38).

The underlying mechanism linking homocysteine with endothelial dysfunction in diabetic patients with microalbuminuria is not clear. Whether hyperhomocysteinemia-mediated oxidative stress leading to impaired endothelial function is related to increased cardiovascular risk in patients with diabetes and microalbuminuria remains to be established. A recent study in patients with type 1 diabetes and microalbuminuria has shown the presence of mild hyperhomocysteinemia and reduced antioxidant defense in these patients as compared with normoalbuminuric patients and nondiabetic subjects (39).

Mikroalbuminurija i metabolički sindrom

Udruženost sa srčanožilnim bolestima opisuje se i za mikroalbuminuriju i za metabolički sindrom. Nedavno je u jednoj velikoj populacijskoj studiji dokazan snažna povezanost mikroalbuminurije definirane kao omjer albumina i kreatinina u mokraći s metaboličkim sindromom (40). Pokazano je kako je mikroalbuminurija povezana s pojedinačnim sastavnicama metaboličkog sindroma kao što su hiperglikemija i inzulinska rezistencija, koje su značajni predskazatelji endotelne disfunkcije (6).

Pretilost je važna sastavnica metaboličkog sindroma. Suvišak nakupljene masti i promjene u sintezi i lučenju adipokina mogli bi biti uzročni čimbenici koji doprinose razvoju šećerne bolesti tipa 2, hipertenzije i kardiovaskularnih bolesti (41). Adiponektin što ga sintetiziraju masne stanice ima protuupalni i protudijabetični učinak, ali je snižen kod pretilosti i šećerne bolesti s inzulinskom rezistencijom (42). Smanjeno lučenje adiponektina u pretilosti moglo bi doprinositi upalnim odgovorima i endotelnoj disfunkciji, dovodeći do aterosklerotskih promjena u krvnim žilama (43). U bolesnika s hipertenzijom mikroalbuminurija negativno je korelirala s koncentracijom adiponektina, odražavajući progredirajuću aterosklerozu (44). Usprkos sve većem broju dokaza, potrebno je još studija kako bi se objasnila uloga adipokina u fiziologiji i u bolesti.

Nedavno je popularnim postao izraz „kardiometabolički sindrom", koji opisuje konstelaciju inzulinske rezistencije/hiperinzulinemije, pretilosti i dislipidemije, hipertenzije i mikroalbuminurije, upale niskog stupnja i oksidativnog stresa (45). Hayden i sur. su predočili važne opservacijske nalaze o remodeliranju mikroresica proksimalnog tubula i oksidativnom stresu, što bi moglo pomoći u razjašnjavanju mikroalbuminurije kod kardiometaboličkog sindroma. Pretpostavlja se da je albuminurija udružena s oštećenjem proksimalnog tubula, kao i s gubitkom cjelovitosti glomerularne filtracijske barijere, zajedno s pretilošću i inzulinskom rezistencijom (46).

Dislipidemija i mikroalbuminurija

Odnos dislipidemije i mikroalbuminurije nije dosljedan. Aterosklerotska vaskularna bolest je udružena s povećanom endotelnom propusnošću koja pak dovodi do transvaskularnog propuštanja albumina i povećanog nakupljanja lipida u stijenci krvne žile (21). Povećana UAE usporedno s dislipidemijom nađena je kod dijabetičara (28). Dislipidemija i niska koncentracija HDL-kolesterola mogu poremetiti endotelnu funkciju u oba tipa šećerne bolesti. Dokazana je udruženost hipertrigliceridemije i niskog HDL-kolesterola s mikroalbuminurijom (39,47). Molitch i sur. su pokušali utvrditi je li visoka koncentracija HDL-kolesterola praćena nižom učestalošću albuminurije (48).

Microalbuminuria and the metabolic syndrome

Both microalbuminuria and metabolic syndrome have been associated to cardiovascular diseases. Recently, strong relationship between microalbuminuria, defined as urinary albumin-to-creatinine ratio, and metabolic syndrome was demonstrated in a large population-based study (40). Microalbuminuria was shown to be linked to particular components of the metabolic syndrome such as hyperglycemia and insulin resistance, which are significant predictors of endothelial dysfunction (6).

Obesity is an important component of metabolic syndrome. Excessive fat accumulation and changes in the synthesis and secretion of adipokines may be the causative factors contributing to the development of type 2 diabetes, hypertension and cardiovascular diseases (41). Adiponectin synthesized by fat cells has anti-inflammatory and antidiabetic effects but is decreased in obesity and diabetes with insulin resistance (42). The diminished adiponectin secretion in obesity may contribute to inflammatory response and endothelial dysfunction leading to atherosclerotic changes in the vessels (43). In patients with hypertension, microalbuminuria negatively correlated with adiponectin levels, reflecting progressing atherosclerosis (44). In spite of the increasing evidence, the explanation of the role of adipokines in physiology and disease requires much more studies.

Recently, the term "cardiometabolic syndrome" has become popular defining a constellation of insulin resistance/hyperinsulinemia, obesity and dyslipidemia, hypertension and microalbuminuria, low-grade inflammation and oxidative stress (45). Hayden *et al*. have presented important observational findings regarding proximal tubule microvilli remodeling and oxidative stress, which may help explain microalbuminuria in the cardiometabolic syndrome. It has been suggested that albuminuria is associated with proximal tubule injury and loss of integrity of the glomerular filtration barrier in association with obesity and insulin resistance (46).

Dyslipidemia and microalbuminuria

The relationship between dyslipidemia and microalbuminuria is inconsistent. Atherosclerotic vascular disease is associated with increased endothelial permeability that leads to transvascular albumin leakage and enhanced lipid accumulation in the vessel wall (21). Increased UAE in parallel with dyslipidemia was found in diabetic patients (28). In both types of diabetes, dyslipidemia and low HDL-cholesterol levels may impair endothelial function. It was demonstrated that hypertriglyceridemia and low HDL-cholesterol were associated with microalbuminuria (39,47). Molitch *et al*. tried to determine whether high le-

Našli su da je prisutnost albuminurije znatno manje vjerojatna u bolesnika sa šećernom bolešću tipa 1 koji imaju visoke koncentracije HDL-kolesterola. U drugoj studiji je zabilježena značajna udruženost albuminurije s trajanjem šećerne bolesti, hipertenzijom i koncentracijom HDL-kolesterola (49). Još valja razjasniti zaštitnu ulogu više koncentracije HDL-kolesterola protiv razvoja albuminurije u bolesnika s šećernom bolesti tipa 1 (48).

Mikroalbuminurija i hipertenzija

Udruženost mikroalbuminurije i hipertenzije već je dugo poznata (1,34,48,50-52). Učestalost mikroalbuminurije u bolesnika s esencijalnom hipertenzijom kreće se od 4% do 46%, što se može objasniti razlikama u dobi i etničkoj pripadnosti ispitivanih populacija, interindividualnim razlikama, te u mjernim metodama i primijenjenoj definiciji. Izlučivanje albumina mokraćom udruženo je s lijevom ventrikularnom dijastoličnom disfunkcijom i lijevom ventrikularnom hipertrofijom u bolesnika s hipertenzijom (53,54).

Pretpostavlja se kako je glomerularna endotelna disfunkcija rano obilježje esencijalne hipertenzije koje može dovesti do povišenja krvnog tlaka, a albuminurija odražava sistemsku disfunkciju vaskularnog endotela. Utvrđeno je da prisutnost mikroalbuminurije omogućava prepoznavanje osoba kod kojih je razvoj hipertenzije najvjerojatniji (52). Mikroalbuminurija bi mogla biti pokazatelj ranih vaskularnih komplikacija hipertenzije, predskazatelj kardiovaskularnih bolesti u bolesnika s esencijalnom hipertenzijom (55). Međutim, ona isto tako može predvidjeti kardiovaskularne bolesti neovisno o stupnju krvnog tlaka u hipertenzivnim slučajevima bez prethodnih vaskularnih komplikacija (56).

Reninsko-angiotenzinski sustav i albuminurija

Poremećena endotelna funkcija i narušeno vaskularno remodeliranje moglo bi biti povezano s aktiviranjem reninsko-angiotenzinskog sustava (RAS), što nastupa kod bubrežne bolesti. Djelovanje angiotenzina II na receptor tipa 1 angiotenzina II, što dovodi do sinteze i otpuštanja upalnog interleukina 6, povećanog stvaranja reaktivnih kisikovih spojeva, induciranja receptora za oksidirani LDL i induciranja adhezijskih molekula, ima ključnu ulogu u razvoju endotelnog oštećenja i ateroskleroze (57). Nedavno je predstavljeno više podataka o učinku lijekova koji utječu na RAS. Snižavanjem arterijskog krvnog tlaka smanjuje se albuminurija, ali su lijekovi koji blokiraju RAS mogli sniziti izlučivanje albumina mokraćom u većoj mjeri negoli se to moglo očekivati samo od snižavanja krvnog tlaka (58). To bi moglo značiti da je RAS upleten u patogenezu albuminurije i da igra važnu ulogu kao kardiovaskularni

vels of HDL-cholesterol accompanied lower prevalence of albuminuria (48). They found that type 1 diabetic patients with higher HDL-cholesterol concentrations were much less likely to have albuminuria. In another study, a significant association was found between albuminuria and duration of diabetes, hypertension and HDL-cholesterol concentration (49). The protective role of higher HDL-cholesterol level against the development of albuminuria in patients with type 1 diabetes still needs explanation (48).

Microalbuminuria and hypertension

Microalbuminuria has long been associated with hypertension (1,34,48,50-52). The prevalence of microalbuminuria in patients with essential hypertension varies from 4% to 46%, which may be explained by differences in age and ethnicity of study populations, intra-individual variability, measurement method and definition used. UAE has been associated with left ventricular diastolic dysfunction and left ventricular hypertrophy in patients with hypertension (53,54).

Glomerular endothelial dysfunction has been postulated as an early feature of essential hypertension that may lead to elevation of blood pressure, and albuminuria reflects systemic dysfunction of vascular endothelium. It has been found that the presence of microalbuminuria allows for identification of individuals most likely to develop hypertension (52). Microalbuminuria may be an indicator of early vascular complications of hypertension, a predictor of cardiovascular diseases in patients with essential hypertension (55). However, it can also predict cardiovascular diseases independently of the degree of blood pressure in hypertensive cases without previous vascular complications (56).

Renin-angiotensin system and albuminuria

Impaired endothelial function and disturbed vascular remodeling may be related to activation of the renin-angiotensin system (RAS) occurring in kidney disease. The action of angiotensin II on the angiotensin II type 1 receptor, which leads to the synthesis and release of inflammatory interleukin 6, increased the generation of reactive oxygen species, induction of receptors for oxidized LDL and induction of adhesion molecules, has an essential role in the development of endothelial damage and atherosclerosis (57). Recently, several series of data have been presented on the effect of drugs influencing RAS. Reduction of arterial blood pressure diminishes albuminuria but RAS-blocking drugs were able to reduce UAE more than could be expected from lowering blood pressure alone (58). It may be suggested that RAS is involved in the pathogenesis of albuminuria and plays an important role as

čimbenik rizika. Takozvana dvojna blokada RAS pomoću inhibitora ACE i antagonista receptora angiotenzina II, čime se smanjuje albuminurija, odvojena je od učinka snižavanja krvnog tlaka (10). Međutim, zaštitni učinak ove vrste lijekova zahtijeva daljnje objašnjenje (59).

Zaključak

Prospektivne opservacijske studije nude dokaze o tome da je mikroalbuminurija niskog stupnja, znatno ispod sadašnjega praga, udružena s porastom kardiovaskularnih ispada i smrtnosti od svih uzroka. Kako su na tržištu dostupne osjetljive i pouzdane metode za procjenu izlučivanja albumina mokraćom, probir na mikroalbuminuriju mogao bi biti klinički važan i usporediv sa značenjem kontrole krvnog tlaka i probira na lipide u preventivnim strategijama.

a cardiovascular risk factor. The so-called dual blockade of the RAS, with ACE inhibitor and angiotensin II receptor antagonist, reducing albuminuria is dissociated from the blood pressure lowering effect (10). However, the protective effect of this type of medication needs further explanation (59).

Conclusion

The prospective observation trials provide evidence that low-grade microalbuminuria, well below the current threshold, is associated with an increase in cardiovascular events and all-cause mortality. As sensitive and reliable methods for assessment of UAE are commercially available, the screening for microalbuminuria may be of clinical importance comparable to that of blood pressure control and lipid screening in the preventive strategies.

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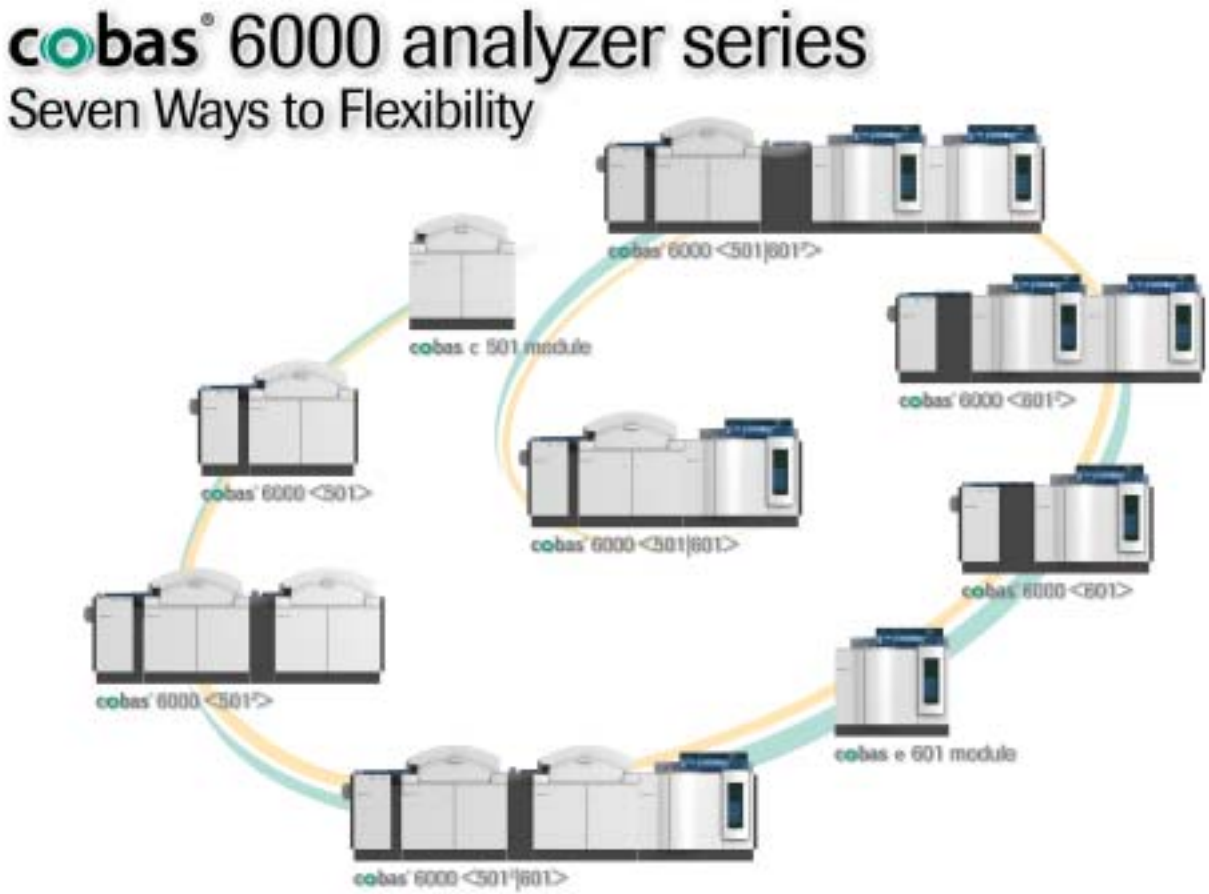

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