THE IMPORTANCE OF EVALUATING MICROALBUMINURIA IN HYPERTENSIVE PATIENTS: A SYSTEMATIC REVIEW

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Abstract

Microalbuminuria is a marker for generalized vascular endothelial dysfunction, that is considered an independent predictor of increased risk for cardiovascular morbidity and mortality in patients with hypertension. Numerous clinical studies in non-diabetic populations have shown an association between microalbuminuria and cardiovascular risk factors, target organ damage, and the presence of cardiovascular disease. Microalbuminuria occurs in approximately 11% to 40% of patients with essential hypertension. Treatment with an angiotensin converting enzyme inhibitors and angiotensin II receptor blockers has shown superiority over other antihypertensive drugs in reducing urine albumin excretion and may prove to be a more targeted approach to reducing cardiovascular risk. Microalbuminuria can be considered not only a risk factor for progressive renal damage, but also a provider of an integrated assessment of long-term damage to the cardiovascular system. That is why it is used in cardiovascular risk assessment clinics. Whether targeted treatment of microalbuminuria in the non-diabetic population reduces cardiovascular morbidity and mortality, remains to be proven. However, there is a general consensus recommending the identification and quantification of microalbuminuria as an important, cost-effective examination that helps evaluate overall cardiovascular risk and identify high-risk patients for whom additional preventive and therapeutic measures are advisable.
Keywords: microalbuminuria, albumin creatinine ratio, hypertension, cardiovascular risk.

RËNDËSIA E VLERËSIMIT TË MIKROALBUMINURISË NË PACIENTËT HIPERTENSIVË: RISHIKIM LITERATURE

Abstrakt

Mikroalbuminuria është një vlerësues i disfunksionit endotelial vaskular, që konsiderohet si një parashikues i pavarur i rrezikut të rritur për mortalitet dhe morbiditet kardiovaskular në pacientët me hipertension. Një numër i madh studimesh klinike në popullsinë jo-diabetike kanë treguar një lidhje midis mikroalbuminurisë dhe faktorëve të rrezikut kardiovaskular, dëmtimit të organeve target dhe pranisë së sëmundjeve kardiovaskulare. Mikroalbuminuria ndodh në rreth 11% deri në 40% të pacientëve me hipertension primar. Trajtimi me frenues të enzimës konvertuese të angiotenzinës (shkurtimi në Anglisht ACE-I) dhe një bllokues të receptorit të angiotenzinës (shkurtimi në Anglisht ARB) ka treguar epërsi mbi barna të tjerë antihypertensive, në reduktimin e ekskretimit të albuminës në urinë dhe mund të provohet të jetë një qasje më objektive për zvogëlimin e rrezikut kardiovaskular. Mikroalbuminuria mund të konsiderohet, jo vetëm si një faktor rreziku për dëmtimin progresiv renal, por edhe si një mundësues i një vlerësimi

gjithëpërfshirës të dëmtimit afatgjatë të sistemit kardiovaskular. Për këtë është përdorur në klinikat e vlerësimit të rrezikut kardiovaskular. Mbetet për t'u provuar, nëse trajtimi objektiv i mikroalbuminurisë në popullsinë jodiabetike zvogëlon morbiditetin dhe mortalitetin kardiovaskular. Megjithatë, ka një konsensus të përgjithshëm që rekomandon njohjen dhe vlerësimin e mikroalbuminurisë, si një ekzaminim të rëndësishëm dhe kosto-efektiv, që ndihmon në vlerësimin e përgjithshëm të rrezikut kardiovaskular dhe njohjen e pacientëve me rrezik të lartë, për të cilët janë të kështillueshme masat shtesë parandaluese dhe terapeutike.

Fjalë kyçe: Mikroalbuminuria, Raporti albuminë/kreatininë, Hipertensioni, Risku kardiovaskular.

Introduction

Microalbuminuria (MAU) is defined as an amount of urinary albumin excretion (UAE) between 30 to 300 mg in an overnight collection or a urinary albumin/creatinine ratio (UACR) of 30-300 mg/g (3.5–30 mg/mmol in women, 2.5–30 mg/mmol in men), in the absence of urinary tract infection and acute illness, including myocardial infarction. MAU is an established marker of early renal disease and usually develops in terms of glomerular basement membrane dysfunction (GBM), allowing albumin entrance into the urine (1, 2). Normal urinary albumin excretion varies between 1 and 22 mg/day and can be influenced by changes in posture, exercise, and blood pressure (2). MAU does not present with any specific symptoms and mainly occurs in the absence of any serious underlying renal disease. The most common causes include essential hypertension, glucose intolerance, type 1 or type 2 diabetes, and metabolic syndrome. Epidemiological studies of MAU reveal a close association between systemic endothelial dysfunction and vascular disease. Numerous studies have demonstrated that MAU serves as a powerful predictor of cardiovascular disease onset, progression and mortality in adults (3-5). Post-hoc analyses of major clinical trials indicate that UAE levels, even below the cut-off values used to define MAU, correlate with an increased rate of cardiovascular disease, irrespective of the presence of existing kidney disease or diabetes (6-9). However, the exact pathophysiology of this relationship is under investigation. These findings suggest that detecting MAU may be the most reliable indicator of an increased global cardiovascular risk in a given patient. Although reducing arterial pressure remains the gold standard for cardiovascular and renal protection (10), controlling it within strict values does not completely eliminate albuminuria and MAU in patients with hypertension, thus giving special importance to therapeutic strategies for the optimal reduction of microalbuminuria. The LIFE study demonstrated that reducing urinary protein excretion in both diabetic and non-diabetic patients during treatment translates to a reduction in cardiovascular events and a slower progression of renal disease (11). Screening for MAU is recommended by several expert committees and associations, providing clinicians with prognostic information concerning cardiovascular risk and assisting in guiding therapy. The European Society of Cardiology (ESC) guidelines recommend assessing the UACR in all hypertensive patients (12).

The aim of this article is to provide updated and comprehensive information about the relationship between MAU, hypertension, and cardiovascular disease, as well as the importance of evaluating MAU in hypertensive patients.

Microalbuminuria and hypertension

The prevalence of MAU ranges from 11% to 40% in patients with essential hypertension (13) and increases with age and severity of hypertension. The finding that MAU in hypertensive patients is an independent risk factor for cardiovascular disease, suggests a relationship between vascular leakage in the glomeruli and vascular damage. A significant increase in intracapillary pressure or structural damage of the glomerular membrane may lead to the leakage of protein from the plasma into Bowman's space, resulting in the development of microalbuminuria, which may vary with the severity of hypertension. Changes in hemodynamics that occur in hypertension (elevation in intraglomerular pressure and generalized angiopathy due to endothelial dysfunction that causes renal and systemic transvascular albumin leakage), are the most probable causes of MAU in hypertensive patients (14).

The presence of MAU in patients with essential hypertension serves as a marker of early intrarenal vascular dysfunction (7). A study published by Catena et al. revealed that elevated UACR was associated with significant and progressively higher blood pressure (BP), HDL-cholesterol, and plasma aldosterone levels, and with lower glomerular filtration. MAU was detected in 17% of 242 hypertensive patients, who had significantly higher BP and plasma aldosterone levels (178 ± 113 vs. 128 ± 84 pg/ml; P = 0.001), and lower glomerular filtration compared with patients without microalbuminuria. UACR was directly and independently correlated with BP and plasma aldosterone levels. In conclusion, the presence of low-grade albuminuria independently correlates with increased plasma aldosterone, suggesting a contribution of aldosterone to the early glomerular changes seen in hypertensive nephropathy (15). Numerous studies have provided evidence that hypertensive target organ damage is more common in microalbuminuric patients. MAU correlates with early signs of extra-renal organ damage, including left ventricular hypertrophy and dysfunction, carotid artery thickening and plaque formation, and a higher incidence of hypertensive retinopathy (16). A recent analysis of the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study was the first to address the issue of the prognostic value of UAE in a very large cohort (n= 8206) entirely composed by hypertensive subjects, demonstrating that both the frequency and severity of MAU were linked to greater LV mass and dysfunction. This correlation was independent of systolic BP, age, race, or coexisting diabetes (8). MAU has been identified as a predictor for silent myocardial ischemia. In a large nondiabetic population, patients with microalbuminuria and ST-T changes on their electrocardiograms had markedly increased risks for cardiovascular and all-cause mortality compared to patients with the same electrocardiographic changes but no microalbuminuria (17). Due to the significant association between microalbuminuria and carotid artery intima-media thickness observed in patients with hypertension, MAU may be a marker for early development of carotid artery atherosclerosis (16). The latest ESC hypertension guidelines advocate for the inclusion of hypertension-mediated organ damage (HMOD) assessment, notably focusing on the presence of MAU, left ventricular hypertrophy and arterial stiffness, in order to enhance the accuracy of cardiovascular risk evaluation during blood pressure management. Early screening of hypertensives for MAU and prompt treatment of positive cases might reduce the disease burden related to severe chronic kidney disease and cardiovascular events in the community. Given the substantial evidence highlighting the importance of MAU and hypertension in cardiovascular disease, both the American College of Cardiology/American Heart Association and the International Society of Hypertension recommend routine urine dipstick testing or UACR testing to assess MAU (12,18).

Effect of various antihypertensive drugs on microalbuminuria.

Although numerous studies have demonstrated the impact of MAU on cardiovascular risk, it remains unclear whether the reduction of MAU leads to a corresponding reduction in this risk. Multiple clinical trials have shown the efficacy of several antihypertensive drugs in reducing MAU. Among available antihypertensive drugs, angiotensin converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) seem to be superior to other antihypertensive drugs in reducing UAE (19-23). In a large study conducted in African American subjects (AASK study) with primary hypertension, ramipril was more effective than amlodipine in reducing UAE (20). Furthermore, the LIFE trial revealed that subjects with the lowest CV event rates exhibited the most significant reduction in UAE when treated with losartan-based regimen, compared to baseline. Treatment with losartan resulted in a greater reduction in albuminuria compared with beta-blocker therapy, despite equivalent decreases in blood pressure (24). The Prevention of Renal and Vascular End-Stage Disease Intervention Trial (PREVEND IT) enrolled patients with baseline MAU and randomized them to the angiotensin-converting enzyme inhibitor fosinopril or a matching placebo. The study noted that the fosinopril-treated subjects had a 26% reduction in albumin excretion, which was less than that observed in the LIFE trial. However, this reduction did not correlate with a decrease in CV mortality or hospitalization (25). A study on the reduction of MAU among hypertensive patients using triple combination therapy (perindopril 4 mg, amlodipine 5 mg and indapamide 1.25 mg) (26) demonstrated a significant reduction in blood pressure with the use of triple combination therapy. Additionally, MAU reverted to normal albumin excretion in urine, which was statistically significant ($p < 0.01$). This was the most significant and convincing finding. Dihydropyridine calcium antagonists have failed to reduce proteinuria in patients with type 2 diabetes. On the other hand, non-dihydropyridine calcium channel blockers (CCBs) have been proven to have a therapeutic effect on MAU in type 2 diabetes (27).

Conclusion

By demonstrating a strong association between MAU and hypertension, evaluating the presence of MAU becomes a simple and accurate method to detect hypertensive patients at high risk for cardiovascular and potential renal damage. Early detection of microalbuminuria has been extensively studied and observed to aid in halting the progression of the underlying disease. An interprofessional team is crucial for early screening and management of microalbuminuria. Healthy lifestyle changes and effective antihypertensive management can be implemented through more aggressive BP controls. Additionally, MAU can indirectly assist in reducing CVD risk in patients, serving not only as a predictor for CVD, but also as a target for therapy.

Conflicts of Interest: No conflict of interest

References

1. Microalbuminuria. Rohan M. Prasad; Atul Bali; Richa Tikaria. Last Update: May 30, 2023.
2. Totto R. Microalbuminuria: Definition, Detection, and Clinical Significance. J Clin Hypertens (Greenwich). 2004; 6:2-7.

3. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073-81. doi: 10.1016/S0140-6736(10)60674-5.
4. Hillege HL, Fidler V, Diercks GF, Gilst WH, Zeeuw D, Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, Jong PE. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation. 2002;106:1777–1782. doi: 10.1161/01.CIR.0000031732.78052.81.
5. Volpe M. Microalbuminuria screening in patients with hypertension: recommendations for clinical practice. Int J Clin Pract. 2008;62:97-108.
6. Matsushita K, Velde M, Astor BC, Woodward M, Levey AS, Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–2081. doi: 10.1016/S0140-6736(10)60674-5.
7. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001;286:421–426. doi: 10.1001/jama.286.4.421.
8. Wachtell K, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlof B, Devereux RB, Beevers G, Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Okin PM, Omvik P, Oparil S, Wedel H, Snapinn SM, Aurup P. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. Ann Intern Med. 2003;139:901–906.
9. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, Appleyard M, Jensen JS. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. Circulation. 2004;110:32–35. doi: 10.1161/01.CIR.0000133312.96477.48.
10. Chobanian, G.L. Bakris, H.R. Black, et al.The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. JAMA, 289 (2003), pp. 2560-2572
11. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux R, de Faire U, Fyhrquist F, Julius S, Kjeldsen S, Lederballe-Pedersen O, Nieminen M, Omvik P, Oparil S, Wan Y. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. Hypertension. 2005;45:198-202.
12. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, et al. 2020 International Society of Hypertension Global Hypertension practice guidelines.Hypertension. 2020; 75:1334–1357. doi: 10.1161/HYPERTENSIONAHA.120.15026.
13. Rossa TT, Palatini P: Clinical value of microalbuminuria in hypertension. J Hypertens 2000;18:645–654.
14. Microalbuminuria and cardiovascular risk. Janaka Karalliedde, Giancarlo Viberti. American Journal of Hypertension, Volume 17, Issue 10, October 2004, Pages 986–993, https://doi.org/10.1016/j.amjhyper.2004.08.010.

15. Microalbuminuria and plasma aldosterone levels in nondiabetic treatment-naïve patients with hypertension. Cristiana Catena 1, GianLuca Colussi, Flavia Martinis, Marileda Novello, Leonardo A Sechi. 2017 Dec;35(12):2510-2516. doi: 10.1097/HJH.0000000000001476.
16. Evaluation of subclinical organ damage for risk assessment and treatment in the hypertensive patient: role of microalbuminuria. Roberto Pontremoli 1, Giovanna Leoncini, Francesca Viazzi, Elena Ratto, Valentina Vaccaro, Valeria Falqui, Angelica Parodi, Novella Conti, Cinzia Tomolillo, Giacomo Deferrari. 2006 Apr;17(4 Suppl 2):S112-4. doi: 10.1681/ASN.2005121327.
17. Diercks GF, van Boven AJ, Hillege HL, Janssen WM, Kors JA, de Jong PE, Grobbee DE, Crijns HJ, van Gilst WH: Microalbuminuria is independently associated with ischaemic electrocardiographic abnormalities in a large non-diabetic population: the PREVEND (Prevention of REnal and Vascular ENdstage Disease) study. Eur Heart J 2000;21:1922–1927.
18. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71:e13–e115. doi: 10.1161/HYP.0000000000000065.
19. Ruilope LM, Alcazar JM, Hernandez E, Praga M, LaheraV, Rodicio JL. Long-term influences of antihypertensivetherapy on microalbuminuria in essential hypertension.Kidney Int Suppl 1994; 45: S171–3.94.
20. Agodoa LY, Appel L, Bakris GL,et al. African AmericanStudy of Kidney Disease and Hypertension (AASK) StudyGroup. Effect of ramipril versus amlodipine on renaloutcomes in hypertensive nephrosclerosis. JAMA 2001;285: 2719–28.95.
21. Monster TB, Janssen WM, de Jong PE, de Jong-van denBerg LT PREVEND Study Group. The impact of anti-hypertensive drug group on urinary albumin excretion in a non-diabetic population. Br J Clin Pharm 2002; 53: 31–6.96.
22. Garg J, Bakris GL. Angiotensin converting enzyme inhibi-tors or angiotensin receptor blockers in nephropathy from type 2 diabetes. Curr Hypertens Rep 2002; 4: 185–90.97.
23. Pisoni R, Ruggenenti P, Remuzzi G. Renoprotectivetherapy in patients with non-diabetic nephropathies. Drugs2001; 61: 733–45.98.
24. Ibsen H, Wachtell K, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux RB, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wan Y; LIFE substudy. Does albuminuria predict cardiovascular outcome on treatment with losartan versus atenolol in hypertension with left ventricular hypertrophy? A LIFE substudy. J Hypertens. 2004;22:1805-11.
25. Asselbergs FW, Diercks GF, Hillege HL, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004;110:2809–2816.
26. Arun, Abhishek, Study on reduction of microalbuminuria amongst hypertensive patients with use of triple combination therapy (triplixam). Journal of Hypertension 39: pp e31, April 2021. | DOI: 10.1097/01.hjh.0000744680.94912.ce

27. Bakris GL, Copley JB, Vicknair N, Sadler R, Leurgans S. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. Kidney Int. 1996;50:1641-50.