Microalbuminuria and estimated glomerular filtration rate

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Abstract

Hypertension and diabetes mellitus are the major causes of renal damage and cardiovascular events. The co-existence of these conditions further increases the risk of progressive renal disease, cardiovascular events, and mortality. Urinary excretion of albumin, even in small amounts, and a lowered glomerular filtration rate (GFR) are early markers of such a tendency. The importance of screening for microalbuminuria, and a lowered GFR in hypertensive and diabetic patients, lies in the early detection of preclinical kidney disease, and identification of individuals at increased risk of progressive renal disease, cardiovascular events, and mortality. Intensive therapy, directed at the optimal control of blood pressure, blood sugar, and cardiovascular risk factors, as well as interventions aimed at decreasing albuminuria and slowing the progression of renal disease, have demonstrable beneficial effects.

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What is microalbuminuria?

In the healthy kidney, over 99% of the filtered albumin is reabsorbed by the tubular cells. A small increase in glomerular vascular permeability results in an increase in albumin escape, because the reabsorption mechanism is close to saturation.[1] Excretion of albumin, even in small amounts, is pathological. The upper level of normal urinary albumin excretion is difficult to establish, because there is a continuous association between the level of urine albumin excretion and the risk of cardiovascular morbidity and mortality. For practical reasons, in a clinical setting, values for normo-, micro- and macroalbuminuria have been established. Microalbuminuria is defined as albumin excretion in the urine between 20-200 µg/minute, or 30-300 mg/24 hours.[2] Values below this range indicate normoalbuminuria, while those above are regarded as macroalbuminuria, which is indicative of overt nephropathy. However, it is noteworthy that even at levels below those for microalbuminuria, the continuous association with cardiovascular events still holds true.[3]

In a clinical setting, the concentration of albumin in the urine can be obtained in a timed urine collection, or the albumin:creatinine ratio in the first voided urine sample. Whilst the albumin excretion in a 24-hour urine collection is the gold standard, a timed urine collection and an early morning spot urine collection are convenient, practical, and correlate satisfactorily with the 24-hour collection.[1] Furthermore, to diagnose microalbuminuria, a single test is inadequate, and the test should be repeated over a period of three months. It needs to be emphasised that the diagnosis of microalbuminuria should not be made in the presence of an acute metabolic crisis,which is commonly observed after an intercurrent illness or exercise. Microalbuminuria may also be present in a number of chronic conditions, such as chronic kidney disease, diabetes mellitus, congestive cardiac failure, chronic obstructive airways disease, hypertension, and malignancy. Acute conditions with microalbuminuria include burns, urinary tract infections, acute pancreatitis, trauma, myocardial infarction, bacterial meningitis, and inflammatory bowel disease.

What is the significance of micro-albuminuria?

Diabetes mellitus and hypertension are the leading causes of end-stage renal disease.[4,5] In our setting of limited available resources to treat end-stage renal disease, it is imperative that renal damage is identified at an early stage, and that measures to prevent, or slow down, its progression are instituted. Although the clinical significance of microalbuminuria was initially established as an early

marker for progressive diabetic renal disease and vascular complications and mortality in diabetes, its association with primary hypertension appears to have a similar significance. Microalbuminuria is common in type 2 diabetes. In the United Kingdom Prospective Diabetes Study (UKPDS), 39% of patients had hypertension at diagnosis, and 24% of those with hypertension had microalbuminuria, as did 14% of those with normal blood pressure.[6] The true prevalence of microalbuminuria within the hypertensive population is variable, and ranges from as low as 8 to 23%.[7]

The vascular complications associated with microalbuminuria relate to generalised endothelial injury and endothelial dysfunction.[8] Markers of endothelial dysfunction have been demonstrated in individuals with microalbuminuria.[9] Endothelial dysfunction is an early step in the atherosclerotic process. The actual mechanism of microalbuminuria in diabetes and hypertension may be due to an increase in vascular permeability of glomerular vessels, as a consequence of this generalised endothelial dysfunction.

Enthusiasm about recommending screening for microalbuminuria in primary hypertension has not been as pronounced as that for diabetes mellitus, and the clinical significance of microalbuminuria in nondiabetic hypertensives has been a subject of debate. However, there is growing evidence of the importance of screening for microalbuminuria in primary hypertension.[10] Available data do suggest that microalbuminuria is a marker for cardiovascular risk and an early marker for renal impairment in hypertension.[10] The issue of whether a reduction in urinary albumin excretion has a beneficial effect, in decreasing both cardiovascular and renal risk in primary hypertension, has not been convincingly resolved. However, the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study has demonstrated a decrease in cardiovascular events associated with a decrease in microalbuminuria in primary hypertension.[11]

Renal damage in diabetes mellitus and primary hypertension is associated with, as well as being an independent marker for, cardiovascular diseases.[12] Preclinical renal disease in these conditions can be detected by the combination of microalbuminuria and a lowered GFR. Instead of the more complex methods of measuring the GFR, formulae are now available which can provide an estimate of the GFR. Both the Cockcroft-Gault and the Modification of Diet in Renal Disease (MDRD) formulae provide a relatively accurate estimate of the estimated GFR (eGFR). The eGFR values, determined by means of these formulae, are useful in the staging of chronic kidney disease. A persistent eGFR below 60 ml/minute/1.73m^2 is indicative of the presence of chronic kidney disease. The burden of chronic kidney disease is huge, and a lowered eGFR is a risk factor for progression of renal disease, and also for future cardiovascular events.[12] However, the combination of a lowered eGFR and microalbuminuria is a more efficient indicator of kidney damage.[13] It is likely that both parameters represent the spectrum of renal vascular malfunction from systemic endothelial dysfunction.

The importance of screening for microalbuminuria in diabetic patients relates to its prognostic value, and to the beneficial effects resulting from the positive outcomes of therapeutic strategies using agents that block the renin angiotensin system (RAS). Intervention trials in patients with type 2 diabetes and hypertension have clearly and consistently demonstrated the efficacy of angiotensin-receptor antagonists in limiting the progression of renal disease.[14,15] Screening for microalbuminuria is recommended. In type 1 diabetes and can be initiated after five years of diabetes. In type 2 diabetes, screening should commence at the time of diagnosis, and annually thereafter.

Therapeutic considerations

Diabetic patients with established microalbuminuria, a lowered eGFR or macroalbuminuria require an intensive multifactorial interventional approach. The essential goal of therapy is cardiovascular and renal protection. This is achieved through attainment of optimal blood pressure and tight glycaemic control, initiating lipid-lowering therapy, and decreasing urinary albumin excretion.[16]

Suppression of the RAS in diabetic patients with microalbuminuria seems to convey specific benefit in terms of renal and cardiovascular protection. In addition to the blood pressure-lowering effect of these agents, RAS suppression decreases albuminuria, which possibly contributes to both renal and cardiovascular protection.[17]

The recommended target blood pressure in diabetic patients is a level below 130/80 mmHg. In order to achieve this, combination antihypertensive therapy may be necessary.[18] The glycaemic target in these patients is glycated haemoglobin (HbA_{1c}) < 7%, total cholesterol level < 4.5 mmol/l, low-density cholesterol < 4.5 mmol/l, and triglycerides < 1.7 mmol/l.[19]

The association between microalbuminuria and renal disease progression in nondiabetic hypertensive patients is still under debate, as is the specific benefit to be derived from RAS suppression.[20] The presence of microalbuminuria is viewed as a marker of inflammation, and although associated with a higher risk of cardiovascular events, does not imply the presence of kidney disease. Despite these considerations, in such instances, it is still prudent to lower the blood pressure, using agents with a proven cardiovascular protective effect such as angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. It is noteworthy that although these agents can lower urinary protein excretion, microalbuminuria may still develop in hypertensive patients treated with maximal doses.[21] This is particularly so in patients with a high burden of cardiovascular complications.

In all patients with hypertension, whether diabetic or not, specific attention to the management of all the other cardiovascular risk factors is essential.

Conclusion

Hypertensive and diabetic patients with microalbuminuria are at an increased risk of renal disease progression and cardiovascular events. Screening for microalbuminuria and subclinical renal disease is important in identifying patients at risk of these morbid events. Multifactorial therapeutic interventions, including the use of agents which suppress the RAS, are relatively protective.

References

1. Rosa TT, Palatini P. Clinical value of microalbuminuria in hypertension. J Hypertens. 2000;18(6):645-654.
2. American Diabetic Association Consensus Development Conference on the diagnosis and management of nephropathy in patients with diabetes mellitus. Diabetes Care. 1994;17(11):1357-1361.
3. Scrader J, Luders S, Kulschewski, et al. Microalbuminuria and tubular proteinuria are risk predictors of cardiovascular morbidity and mortality in essential hypertension: final results of prospective long term study (MARPLE Study). J Hypertens. 2006;24(3):541-548.
4. Veriava Y, du Toit E, Milne FJ, et al. Hypertension as a cause of end-stage renal failure in South Africa. J Hum Hypertens. 1990;4(4):379-383.
5. The United States Renal Data System: USRDS Annual Data Report. 2001.
6. UK Prospective Diabetes Study (UKPDS). IX: Relationship of urinary albumin and N-acetylglucosaminidase to glycaemia and hypertension at diagnosis of type 2 diabetes mellitus and after 3 months diet therapy. Diabetologia. 1993;36(9):835-842.
7. Menne J, Chatzikyrkou, Haller H. Microalbuminuria as a risk factor: the influence of the rennin angiotensin system blockade. J Hypertens. 2010;28(10):1983-1993.
8. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, et al. Albuminuria reflects widespread vascular damage. The Steno hypothesis. Diabetologia. 1989;32(4):219-226.
9. Stehouwer CD, Smulders YM. Microalbuminuria and risk for cardiovascular disease: analysis of potential mechanisms. J Am Soc Nephrol. 2006;17(8):2106-2111.
10. Volpe M, Cosentino F, Ruilope LM. Is it time to measure microalbuminuria in hypertension? J Hypertens. 2003;21(7):1213-1220.
11. Isben H, Olsen MH, Wachtell K, et al. Reduction in albuminuria translates to reduction for endpoint reduction in Hypertension study. Hypertens. 2005;45(2):198-202.
12. Sciarretta S, Valenti V, Tocci G, et al. Association of renal damage with cardiovascular diseases is independent of individual risk profile in hypertension: data from the Italy – Developing Education and Awareness on Microalbuminuria in patients with Hypertensive Disease Study. J Hypertens. 2010;28(2):251- 258.
13. Gambaro G, Bonfante L, Gemelli A, et al. High chronic nephropathy detection yield in CKD subjects identified by the combination of albuminuria and estimated GFR. Nephrol Dial Transplant. 2011. [Epub ahead of print].
14. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of angiotensin receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851-860.
15. Brenner BM, Cooper ME, de Zeeu D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861-869.
16. Gaede P, Lund-Andersen H, Parving HH, et al. Effect of multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358(6):580-591.
17. Kunz R, Friedrich C, Wolberg M, et al. Meta-analysis effects of monotherapy and combination therapy with inhibitors of renin angiotensin system on proteinuria in renal disease. Ann Intern Med. 2008;148(1):30-48.
18. Seedat YK, Rayner B, Veriava Y, et al. South African Hypertension Society Guideline 2006. S Afr Med J. 2006;96(4 Pt 2):335-362.
19. Revised SEMDSA guidelines for diagnosis and management of type 2 diabetes mellitus for primary health care 2012. Society for Endicrinology Metablolism and Diabetes of South Africa [homepage on the Internet]. Available from: www.semdsa.org.za
20. Sarafidis PA, Bakris G. A reappraisal of rennin-angiotensin blockade on microalbuminuria development: do they offer anything unique? J Hypertens. 2012;30(1):48-50.
21. Cerezo C, Ruilope LM, Segura J, et al. Microalbuminuria break through under chronic rennin-angiotensin-aldosterone system suppression. J Hypertens, 2012:30(1):204-209.