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REVIEW ARTICLE

Early Renal Abnormalities as an Indicator of Cardiovascular Risk in Type 2 Diabetes

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Abstract Accurate assessment of cardiovascular (CV) risk is a prerequisite for devising effective therapeutic strategies in patients with type 2 diabetes (T2DM) as it allows to refine prognosis and treatment targets as well as the cost-benefit ratio for specific pharmacological interventions. The presence of subclinical vascular organ damage plays a well known role in determining overall risk and a wider use of low cost, easy to perform diagnostic tools to stratify CV risk is very much needed. Besides their well known prognostic value for progression to end stage renal disease (ESRD), subclinical renal abnormalities such as microalbuminuria and/or a slight reduction in estimation of glomerular filtration rate (eGFR), have been shown to be powerful, independent predictors of CV diseases in patients with T2DM. Through the combined evaluation of these two biomarkers of chronic kidney disease (CKD), clinicians can usefully and reliably get a perspective on global and CV outcome of their diabetic patients.

Keywords Diabetes · Cardiovascular risk · Microalbuminuria · Glomerular filtration rate · Chronic kidney disease

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1 Introduction

Accurate assessment of CV risk is a prerequisite for devising effective therapeutic strategies in patients with T2DM as it allows to refine prognosis and treatment targets as well as the cost-benefit ratio for specific pharmacological interventions. Thus, for example, according to almost all international guidelines, each patient's individual burden of risk may dictate blood pressure values for starting antihypertensive treatment or the preferred type of drug as well as the opportunity to start antiplatelet agents or lipid profile correction [1].

Besides previous history and risk factors that are traditionally associated with diabetes, such as hypertension and lipid abnormalities, the presence of subclinical vascular organ damage plays a well known role in determining global risk and therefore in tailoring therapeutic choices to the individual patient [2]. However, in the context of the ongoing epidemic of T2DM and because of population aging, both of which place a growing logistic and economic burden on public health systems, a broader use of low cost, easy to perform diagnostic tools to stratify CV risk is very much welcome.

CKD has traditionally been acknowledged as a devastating microvascular complication of long standing diabetes and a multiplier of vascular risk [3]. As a matter of fact, although the natural history of diabetic kidney disease is often characterized by progression toward ESRD, diabetic kidney disease patients are more likely to die prematurely due to CV events than to survive long enough to require renal replacement treatment [4].

More recently, the unfavorable predictive power of even mild, renal function abnormalities such as increased urine albumin excretion and/or a slight reduction in eGFR rate has been clearly demonstrated in patients with diabetes as

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well as in several other high and low risk subgroups [5, 6]. Following the recent publication of a series of landmark papers on this topic, a wider body of clinicians has been reminded that the kidney is a sensor of future CV events and may represent a useful diagnostic tool for low cost risk evaluation [7].

Another clinically useful lesson that we have learned in recent years is the substantial heterogeneity of diabetic kidney disease phenotypes [8]. While increased albuminuria, alone or in combination with GFR reduction is the most commonly found renal abnormality, up to 10–15 % of patients with T2DM actually show renal function impairment despite normal urine albumin excretion (Fig. 1) [9, 10].

The two components of kidney damage have been shown to bear independent prognostic value [11], thus, in any single patient the finding of albuminuria entails a worse outcome for any given level of eGFR reduction and vice versa [12]. Besides the obvious inference that the concomitance of reduced eGFR and an increase in albuminuria entail the worst renal and CV risk, albuminuria retains stronger prognostic power when compared to abnormal eGFR [6].

This narrative review will focus on available evidence that makes the two components of CKD, i.e. albuminuria and eGFR invaluable diagnostic and prognostic tools for clinicians wishing to assess CV risk in diabetic patients.

2 Albuminuria, from Risk Predictor to Treatment Target

Since the first report [13], more than 30 years ago showing that increased urine albumin excretion could be found in a significant percentage of patients with diabetes and normal urine dipstick for protein, the evidence linking microalbuminuria to increased CV and renal risk has been steadily accumulating in the literature [14]. Microalbuminuria was traditionally believed to reflect a generalized increase in vascular permeability possibly due to multiple pathogenetic mechanisms including abnormal hemodynamic load as well as endothelial changes which may foster the development of the atherosclerotic process. It is now considered an undisputed marker of subclinical vascular damage and a forerunner of cardiovascular as well as renal complications [1]. In fact, abnormal urine albumin excretion has been shown to cluster with several unfavorable risk factors such as metabolic syndrome and hyperuricemia [15], as well as left ventricular hypertrophy and extracardiac atherosclerosis [16]. Over the years, several large prospective studies have confirmed that microalbuminuria is a strong independent predictor of cerebrovascular and cardiac events and that it signals the presence of incipient nephropathy [17]. Most, although not all, patients with T2DM and microalbuminuria do show a tendency to progress toward ESRD over a period of time which ranges from 5–15 years [18]. Given the dual nature of albuminuria as a CV and renal risk factor, most of these patients have a greater chance of dying prematurely because of vascular events than of surviving on enough to reach ESRD [4]. Furthermore, the relationship between albuminuria and CV morbidity has been reported to hold even for values well within normal range, making this test even more useful in the context of overall risk assessment (Fig. 2) [19].

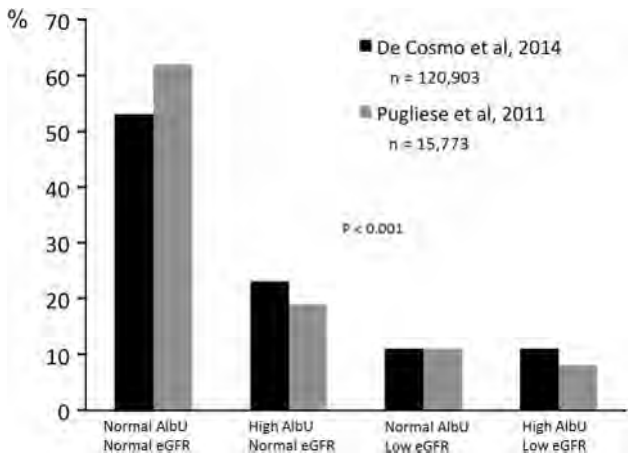

Fig. 1 Prevalence of albuminuria or low eGFR in patients with type 2 diabetes. *AlbU* Albuminuria, *eGFR* estimated glomerular filtration rate. Modified from References [9] and [10]

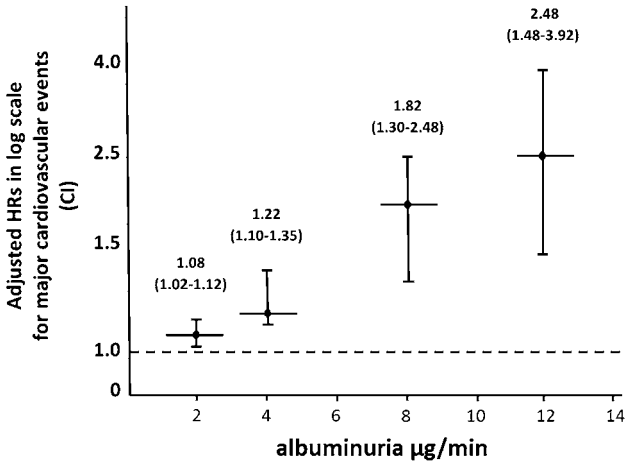

Fig. 2 Albumin predicts cardiovascular risk among normoalbuminuric patients with type 2 diabetes. The reference value (HR = 1) is set at UAE = 1 µg/min. The HRs are adjusted for age, sex, duration of diabetes, history of cardiovascular events, smoking habit, body mass index, mean BP, logarithms of HbA1c, LDL to- HDL cholesterol ratio, triglyceride and serum creatinine levels, and whether the patient was allocated to ACEI therapy. *HR* Hazard ratio, *CI* confidence intervals 95 %. Modified from Reference [19]

More recently, on the basis of retrospective analysis of some large trials [20, 21] the interesting possibility that changes in albuminuria overtime may parallel similar variations in vascular risk has been raised. Reducing microalbuminuria may thus become an intermediate target for treatment in patients with diabetes and or hypertension [22].

3 Impaired Kidney Function, a Useful Tool for Risk Assessment

Up to 20 % of diabetic patients with renal involvement show a reduction in eGFR in the absence of albuminuria or, looking at it from a different angle, up to half of the patients with low eGFR are normoalbuminuric [3]. This condition, also referred to as "non albuminuric renal impairment" has recently been shown to entail an increased risk of CV morbidity and mortality [9, 23], although probably to a lesser extent as compared to albuminuric renal involvement. Isolated reduction of eGFR has been related to a specific risk phenotype which might suggest underlying pathogenetic mechanisms at least in part different from the albuminuric phenotype. Thus, for example, in the Italian Association of Clinical Diabetologists (AMD) and in the Renal Insufficiency and Cardiovascular Events (RIACE) cohorts nonalbuminuric renal impairment was not associated with HbA1c and correlated less strongly with retinopathy and hypertension than did albuminuria [9, 23]. However, this very same subgroup of diabetic patients showed a prevalence of CV disease greater than those with albuminuria alone, but lower than what was observed in the presence of albuminuric renal impairment. More studies are certainly needed to clarify whether different phenotypes of diabetic renal involvement relate to specific pathogenetic mechanisms which might account for different outcome. Regardless of the above mentioned points, systematic evaluation of eGFR together with albuminuria, allows to reclassify a significant number of patients [24] and may be regarded as a useful, cost-effective tool for risk assessment in clinical practice.

4 Conclusions

While the coexistence of microalbuminuria and a reduction in eGFR is known to entail a worse outcome, each of these two renal biomarkers retains independent prognostic value [11, 17], that is, each test adds information to what is conveyed by the other. Thus, they should be evaluated together to maximize the sensitivity and cost-effectiveness of the diagnostic process. Furthermore, both of these diagnostic biomarkers are particularly suitable in clinical practice because they are easily available and inexpensive. Nonetheless, a recent European survey carried out among general practitioners and specialists, suggests that only 30–50 % of high risk patients are routinely screened for albuminuria and that the clinician's awareness of the CV prognostic power of this abnormality is disappointingly low [25, 26]. Incorporating CKD markers such as eGFR and albuminuria into risk equations might provide better CV disease risk identification. Future studies should develop CV disease risk equations that account for the comorbidities particularly associated with CKD in addition to the traditional CV disease risk factors. Better identification of high risk subgroups through a more widespread use of renal biomarkers might lead to addressing more aggressive therapeutic measures to those who need them the most and might improve the currently disappointing rate of diabetic patients who fail to reach the recommended therapeutic targets.

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References

1. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens. 2013;2013(31):1925–38.
2. Viazzi F, Leoncini G, Parodi D, Ratto E, Vettoretti S, Vaccaro V, Parodi A, Falqui V, Tomolillo C, Deferrari G, Pontremoli R. Impact of target organ damage assessment in the evaluation of global risk in patients with essential hypertension. J Am Soc Nephrol. 2005;16(Suppl 1):S89–91.
3. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. UKPDS Group Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003;63:225–32.
4. Haynes R, Staplin N, Emberson J, Herrington GW, Tomson C, Agodoa L, Tesar V, Levin A, Lewis D, Reith C, Baigent C, Landray MJ, SHARP Collaborative Group. Evaluating the Contribution of the Cause of Kidney Disease to Prognosis in CKD: Results From the Study of Heart and Renal Protection (SHARP). Am J Kidney Dis. 2014;64:40–8.
5. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, Lee BJ, Perkins RM, Rossing P, Sairenchi T, Tonelli M, Vassalotti JA, Yamagishi K, Coresh J, de Jong PE, Wen CP, Nelson RG, Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet. 2012;380(9854):1662–73.
6. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int. 2011;80:17–28.

7. Leoncini G, Viazzi F, Pontremoli R. Overall health assessment: a renal perspective. Lancet. 2010;375(9731):2053–4.
8. Ekinci EI, Jerums G, Skene A, Crammer P, Power D, Cheong KY, Panagiotopoulos S, McNeil K, Baker ST, Fioretto P. Macisaac RJ Renal structure in normoalbuminuric and albuminuric patients with type 2 diabetes and impaired renal function. Diabetes Care. 2013;36:3620–6.
9. De Cosmo S, Rossi MC, Pellegrini F, Lucisano G, Bacci S, Gentile S, Ceriello A, Russo G, Nicolucci A, Giorda C, Viazzi F, Pontremoli R, AMD-Annals Study Group. Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes. Nephrol Dial Transplant. 2014;29:657–62.
10. Pugliese G, Solini A, Fondelli C, Trevisan R, Vedovato M, Nicolucci A, Penno G, Renal Insufficiency and Cardiovascular Events (RIACE) Study Group. Reproducibility of albuminuria in type 2 diabetic subjects. Findings from the Renal Insufficiency and Cardiovascular Events (RIACE) study. Nephrol Dial Transplant. 2011;26:3950–4.
11. Solini A, Penno G, Bonora E, Fondelli C, Orsi E, Arosio M, Trevisan R, Vedovato M, Cignarelli M, Andreozzi F, Nicolucci A, Pugliese G, Renal Insufficiency and Cardiovascular Events (RIACE) Study Group. Diverging association of reduced glomerular filtration rate and albuminuria with coronary and noncoronary events in patients with type 2 diabetes: the renal insufficiency and cardiovascular events (RIACE) Italian multicenter study. Diabetes Care. 2012;35:143–9.
12. Tonelli M, Muntner P, Lloyd A, Manns BJ, James MT, Klarenbach S, Quinn RR, Wiebe N, Hemmelgarn BR, Alberta Kidney Disease Network. Using proteinuria and estimated glomerular filtration rate to classify risk in patients with chronic kidney disease. A cohort study. Ann Intern Med. 2011;154:12–21.
13. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet. 1982;1(8287):1430–2.
14. De Zeeuw D, Parving HH, Henning RH. Microalbuminuria as an early marker for cardiovascular disease. J Am Soc Nephrol. 2006;17:2100–5.
15. Viazzi F, Garneri D, Leoncini G, Gonnella A, Muiesan ML, Ambrosioni E, Costa FV, Leonetti G, Pessina AC, Trimarco B, Volpe M, Agabiti Rosei E, Deferrari G, Pontremoli R. Serum uric acid and its relationship with metabolic syndrome and cardiovascular risk profile in patients with hypertension: insights from the I-DEMAND study. Nutr Metab Cardiovasc Dis. 2014. doi:10.1016/j.numecd.2014.01.018. [Epub ahead of print].
16. Leoncini G, Viazzi F, Parodi D, Vettoretti S, Ratto E, Ravera M, Tomolillo C, Del Sette M, Bezante GP, Deferrari G, Pontremoli R. Mild renal dysfunction and subclinical cardiovascular damage in primary hypertension. Hypertension. 2003;42:14–8.
17. Ninomiya T, Perkovic V, de Galan BE, Zoungas S, Pillai A, Jardine M, Patel A, Cass A, Neal B, Poulter N, Mogensen CE, Cooper M, Marre M, Williams B, Hamet P, Mancia G, Woodward M, Macmahon S, Chalmers J, ADVANCE Collaborative Group. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol. 2009;20:1813–21.
18. Marshall SM. Natural history and clinical characteristics of CKD in type 1 and type 2 diabetes mellitus. Adv Chronic Kidney Dis. 2014;21:267–72.
19. Ruggenenti Piero, Porrini Esteban, Motterlini Nicola, Perna Annalisa, Ilieva Aneliya Parvanova, Iliev Ilian Petrov, Dodesini Alessandro Roberto, Trevisan Roberto, Bossi Antonio, Sampietro Giuseppe, Capitoni Enrica, Gaspari Flavio, Rubis Nadia, Ene-Iordache Bogdan, Remuzzi Giuseppe, BENEDICT Study Investigators. Measurable urinary albumin predicts cardiovascular risk among normoalbuminuric patients with type 2 diabetes. J Am Soc Nephrol. 2012;23:1717–24.
20. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Snapinn SM, Wan Y, Lyle PA. Does albuminuria predict cardiovascular outcomes on treatment with losartan versus atenolol in patients with diabetes, hypertension, and left ventricular hypertrophy? The LIFE study. Diabetes Care. 2006;29:595–600.
21. Schmieder RE, Mann JF, Schumacher H, Gao P, Mancia G, Weber MA, McQueen M, Koon T, Yusuf S, ONTARGET Investigators. Changes in albuminuria predict mortality and morbidity in patients with vascular disease. J Am Soc Nephrol. 2011;22:1353–64.
22. Savarese G, Dei Cas A, Rosano G, D'Amore C, Musella F, Mosca S, Reiner MF, Marchioli R, Trimarco B, Perrone-Filardi P. Reduction of albumin urinary excretion is associated with reduced cardiovascular events in hypertensive and/or diabetic patients. A meta-regression analysis of 32 randomized trials. Int J Cardiol. 2014;172:403–10.
23. Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, Trevisan R, Vedovato M, Gruden G, Cavalot F, Cignarelli M, Laviola L, Morano S, Nicolucci A, Pugliese G, Renal Insufficiency and Cardiovascular Events (RIACE) Study Group. Clinical significance of nonalbuminuric renal impairment in type 2 diabetes. J Hypertens. 2011;29:1802–9.
24. Pugliese G, Solini A, Bonora E, Orsi E, Zerbini G, Fondelli C, Gruden G, Cavalot F, Lamacchia O, Trevisan R, Vedovato M, Penno G, RIACE Study Group. Distribution of cardiovascular disease and retinopathy in patients with type 2 diabetes according to different classification systems for chronic kidney disease: a cross-sectional analysis of the renal insufficiency and cardiovascular events (RIACE) Italian multicenter study. Cardiovasc Diabetol. 2014;13:59. doi:10.1186/1475-2840-13-59.
25. Haller H, Menne J, Mancia G. Awareness and behaviour of European physicians in relation to microalbuminuria and organ damage: an ESH-endorsed survey. J Hypertens. 2010;28:2204–9.
26. Ko SH, Kwon HS, Kim DJ, Kim JH, Kim NH, Kim CS, Song KH, Won JC, Lim S, Choi SH, et al. Higher prevalence and awareness, but lower control rate of hypertension in patients with diabetes than general population: the fifth Korean national health and nutrition examination survey in 2011. Diabetes Metab J. 2014;38:51–7.