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Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

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Abstract

Background Kidney dysfunction is a strong predictor of end-stage renal disease and cardiovascular (CV) events. The main goal was to study the clinical correlates of diabetic kidney disease in a large cohort of patients with type 2 diabetes mellitus (T2DM) attending 236 Diabetes Clinics in Italy.

Methods Clinical data of 120 903 patients were extracted from electronic medical records by means of an *ad hoc-developed* software. Estimated glomerular filtration rate (GFR) and increased urinary albumin excretion were considered. Factors associated with the presence of albuminuria only, GFR < 60 mL/min/1.73 m^2 only or both conditions were evaluated through multivariate analysis.

Results Mean age of the patients was 66.6 ± 11.0 years, 58.1% were male and mean duration of diabetes was 11.1 ± 9.4 years. The frequency of albuminuria, low GFR and both albuminuria and low GFR was 36.0, 23.5 and 12.2%, respectively. Glycaemic control was related to albuminuria more than to low GFR, while systolic and pulse pressure showed a trend towards higher values in patients with normal kidney function compared with those with both albuminuria and low GFR. Multivariate logistic analysis showed that age and duration of disease influenced both features of kidney dysfunction. Male gender was associated with an increased risk of albuminuria. Higher systolic blood pressure levels were associated with albuminuria, with a 4% increased risk of simultaneously having albuminuria and low GFR for each 5 mmHg increase.

Conclusions In this large cohort of patients with T2DM, reduced GFR and increased albuminuria showed, at least in part, different clinical correlates. A worse CV risk profile is associated with albuminuria more than with isolated low GFR.

INTRODUCTION

Chronic kidney disease (CKD) is a major cause of morbidity and mortality, and its prevalence is rising worldwide, mostly due to population ageing [1]. Diabetes, a major health problem with global estimates exceeding 382 million people [2], also plays a role in increasing the prevalence of CKD. In fact, ∼40% of patients with diabetes develop diabetic kidney disease (DKD) resulting in albuminuria, reduction of the glomerular filtration rate (GFR), or both [3].

DKD represents a relevant burden on the National Health Services since it is responsible for a large number of all incident cases of end-stage renal disease (ESRD) (nearly half in the USA) [4]. In addition, a growing body of evidence indicates that kidney dysfunction contributes significantly to the increase in cardiovascular (CV) risk observed among diabetics. Several studies have indeed shown that increased urinary albumin excretion (UAE) [5–8] and reduced GFR [9–11] are both associated with CV risk factors and are distinct predictors of cardiovascular events among patients with diabetes. Finally, DKD implies high costs for the health system [4].

A recent cross-sectional analysis attempted to define the temporal trend in DKD among the general population in the USA and showed that its prevalence increased from 2.0% (1988) to 2.8% (2008), which was proportional to the increase observed in diabetes [12]. Prospective data from the UK Prospective Diabetes Study (UKPDS) showed that over a median of 15 years of follow-up, 1544 (38%) of 4031 patients with type 2 diabetes and normoalbuminuria at baseline developed albuminuria and 1449 (29%) of 5032 with normal serum creatinine at baseline developed renal impairment [13]. Recent data from an Italian

study (RIACE) which enrolled 15 773 patients with type 2 diabetes showed that at baseline, 26.9% of patients had albuminuria and 18.7% had low GFR [14]. Data from this [14] and other studies [15–17] support the emerging hypothesis that albuminuria or the isolated reduction of GFR may represent specific phenotypes of kidney dysfunction, with different correlates and, probably, different outcomes in terms of renal and cardiovascular risk. Thus, albuminuria and GFR have been demonstrated to have a different impact on the coronary and peripheral vascular bed, with reduced GFR which was preferentially associated with a high risk of developing coronary events [18].

Given the huge burden of DKD, unravelling its principal epidemiological aspects might help us to better understand the pathophysiological mechanisms and guide the implementation of preventive and therapeutic strategies in order to improve the health outcomes of people with diabetes.

Therefore, the aim of our study is to describe the aggregation of cardiovascular risk factors among patients with various features of kidney dysfunction (i.e. albuminuria, reduction of GFR, or both) in a large cohort of patients with type 2 diabetes attending out-patient diabetes centres.

MATERIALS AND METHODS

The Italian health-care system

All Italian citizens, regardless of social class or income, are cared for by a general practitioner as part of the National Health System. It is estimated that over 3 million citizens know they are affected by diabetes in Italy. Care for people with diabetes is mainly provided by a public network of ∼700 diabetes clinics which provide diagnostic confirmation, therapy, prevention and early diagnosis of complications through close patient follow-up by a team of specialists. Most patients are referred to these care units by their general practitioner, and care is free of charge [19, 20].

Patients

In the present report, we describe the results of an analysis that was carried out using the data set of the electronic medical records that were collected between 1 January 2009 and 31 December 2009, on a large sample of patients with a diagnosis of type 2 diabetes [according to American Diabetes Association (ADA) 2003 criteria], who attended 236 Diabetes Clinics in Italy. Approximately, one-third of all the Italian Diabetes Clinics were involved in the present study. They are evenly distributed throughout the country. We identified a population of 415 346 patients of whom 120 903 aged 18 years or older with at least 1 outpatient measurement of serum creatinine and albuminuria in the index year (i.e. 2009) were included in the present analysis. A flow chart of the selection of the patients is provided in Supplementary data, Appendix. Albuminuria was based on one measurement, given findings supporting the good reproducibility of UAE in spite of the intra-individual variability and showing that also a single UAE value represents an accurate predictor of nephropathy stage for clinical and epidemiological purposes [21].

Methods and data collection

The database utilized derives from the Italian Association of Clinical Diabetologists [Associazione Medici Diabetologi (AMD)] initiative which started in 2006 to monitor diabetes care and quality of care [19, 20]. The aim was to identify a set of indicators to be used in the context of continuous quality improvement. All participating clinics used an electronic clinical record system for the everyday management of outpatients, and a software was specifically developed to extract information from all these clinical databases (AMD data). Data from all participating clinics were collected anonymously and were centrally analysed [19, 20].

The core data set included measures and monitoring of glycated haemoglobin (HbA1c), blood pressure, total-cholesterol, low-density lipoprotein (LDL) cholesterol or high-density lipoprotein (HDL) cholesterol and

triglycerides. The use of specific classes of drugs (glucose lowering, lipid lowering and antihypertensive agents), based on ATC codes, was also evaluated. Current smokers were identified in the electronic clinical record based on a specific Yes/No field. In the case of multiple evaluations during the year, the most recent ones were taken into consideration for the analysis. Since normal ranges for glycated haemoglobin, which could not be DCCT aligned in some centres, varied among the clinics, the percentage change with respect to the upper normal values was estimated and multiplied by 6.0 in order to carry out comparison among clinics [22].

Kidney function was assessed by serum creatinine and UAE measurements. GFR was estimated for each patient by using the Chronic Kidney Disease Epidemiology Collaboration formula derived by serum creatinine values [23]. Increased UAE (albuminuria) was diagnosed if the urinary albumin concentration was >30 mg/L, or if the UAE rate was >20 μg/min, or if the urinary albumin-to-creatinine ratio (ACR) was >2.5 mg/mmol in men and 3.5 mg/mmol in women.

DKD was defined as diabetes with albuminuria or low GFR (<60 mL/min/1.73 m^2), or both. Information on the presence of diabetic retinopathy was based on the following ICD-9 CM codes: 95.03, 95.11, 95.12, 362.01, 362.02, 14.24, 362.83, 369.x was also available [19, 20]

Statistical analysis

Clinical characteristics are expressed as mean and standard deviation for continuous variables, and frequencies and percentages for categorical ones. Between-group statistical tests were not applied: in fact, due to the large sample size, even trivial differences would have reached statistical significance.

Multivariate logistic regression analyses, with backward variable selection, were performed to evaluate factors independently associated with an increased likelihood of having isolated low GFR, isolated albuminuria or the simultaneous presence of low GFR and albuminuria. The reference category included patients with absent albuminuria and with GFR≥ 60 mL/min/1.73 m^2. The following covariates were tested because of a proven or suspected relationship with the following outcomes: age, gender, BMI, diabetes duration, HbA1c, systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, retinopathy and glucose-lowering, lipid-lowering and antihypertensive agents. Results are expressed as odds ratio and their 95% confidence interval.

RESULTS

The overall frequency of albuminuria, low GFR or both albuminuria and low GFR in our data set was 36.0, 23.5 and 12.2%, respectively. The main clinical characteristics of the study population as a whole and when analysed on the basis of the presence/absence of albuminuria or low GFR are shown in Table 1. Overall, the mean age of patients was 66.6 ± 11.0 years, 58.1% were male, mean duration of diabetes was 11.1 ± 9.4 years, mean HbA1c 7.5 ± 1.5% and 17.6% were smokers.

Table 1. Clinical features of 120 903 patients with type 2 diabetes: whole sample and divided according to the presence/absence of albuminuria or low eGFR

Whole sample	**Alb− and low eGFR−**	**Alb− and low eGFR+**	**Alb+ and low eGFR−**	**Alb+ and low eGFR+**	
n (%)	120 903	63 639 (52.6%)	13 660 (11.3%)	28 806 (23.8%)	14 684 (12.2%)
Male gender n (%)	70 247 (58.1)	35 822 (56.3)	5 776 (42.2)	19 874 (69.0)	8741 (59.5)
Age (years)	66.6 ± 11.0	64.1 ± 10.7	74.0 ± 8.0	65.0 ± 10.8	73.4 ± 8.5
BMI (kg/m^2)	29.7 ± 5.2	29.4 ± 5.2	29.7 ± 5.1	30.2 ± 5.3	30.0 ± 5.2
Serum creatinine (mg/dL)	1.0 ± 0.5	0.8 ± 0.2	1.3 ± 0.5	0.9 ± 0.2	1.6 ± 0.8
eGFR	75.5 ± 1.5	85.1 ± 13.9	48.0 ± 9.8	84.1 ± 14.4	42.8 ± 12.7

Whole sample	Alb− and low eGFR−	Alb− and low eGFR+	Alb+ and low eGFR−	Alb+ and low eGFR+	
Known duration of diabetes (years)	11.1 ± 9.4	9.7 ± 8.6	13.3 ± 10.4	11.0 ± 9.0	15.3 ± 10.5
HbA1c (%)	7.5 ± 1.5	7.4 ± 1.5	7.4 ± 1.4	7.8 ± 1.6	7.7 ± 1.5
Total cholesterol (mg/dL)	186.6 ± 41.0	187.9 ± 40.0	185.7 ± 40.7	185.6 ± 42.3	183.4 ± 42.7
Triglycerides (mg/dL)	148.1 ± 108.2	139.4 ± 99.7	151.1 ± 87.4	157.2 ± 131.0	166.6 ± 108.1
HDL cholesterol (mg/dL)	49.2 ± 13.6	50.4 ± 13.7	49.6 ± 13.8	47.7 ± 13.2	46.5 ± 13.4
LDL cholesterol (mg/dL)	108.2 ± 34.2	110.0 ± 33.8	106.4 ± 34.1	107.1 ± 34.9	103.9 ± 34.4
SBP (mmHg)	139.6 ± 19.1	137.7 ± 18.3	139.5 ± 18.9	141.5 ± 19.5	143. 8 ± 20.5
DBP (mmHg)	79.2 ± 9.8	79.1 ± 9.5	77.3 ± 9.8	80.5 ± 10.0	78.5 ± 10.3
Pulse pressure (mmHg)	60.5 ± 16.5	58.7 ± 15.7	62.3 ± 16.6	61.1 ± 16.6	65.4 ± 18.0
Retinopathy	18.6	14.2	18.5	22.4	30.5
Smokers (%)	17.6	17.5	8.8	23.8	13.4

Alb−, normoalbuminuria; Alb+, albuminuria; eGFR, estimated glomerular filtration rate; BMI, body mass index; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure All the between-group differences are statistically significant with $P < 0.0001$.

Data reported in Table 1 show some relevant differences among subgroups of patients. In fact, patients with reduced GFR were more likely to be women and, on the average, older when compared with those with albuminuria. The simultaneous presence of albuminuria and low GFR was in general higher in the elderly, but the occurrence of isolated albuminuria and reduction of GFR changed on the basis of age, being 32 and 8.3% in patients <65 years of age and 39 and 33% in those >65, respectively (data not shown). It is noteworthy that 13 660 patients (11%) had an isolated reduction of GFR, i.e. low GFR and normoalbuminuria. This represents about half (48%) of the whole population with low GFR and 18% of those with normoalbuminuria. When compared with patients with both low GFR and albuminuria, diabetic patients with isolated reduction of GFR were more often females, showed similar age, shorter duration of diabetes, higher GFR, lower HbA1c, lower systolic blood pressure (SBP), lower triglycerides and higher HDL cholesterol (Table 1).

While worse glycaemic control shows a stronger association with albuminuria, regardless of the presence of low GFR, both systolic and pulse pressure showed a trend towards higher values in patients with one feature of kidney dysfunction, with the highest values being observed in those with both components of DKD. This occurred despite a parallel trend towards greater prevalence and intensity (i.e. number of drugs, data not shown) of antihypertensive treatment (Table 2). A more atherogenic lipid profile, i.e. higher triglycerides and lower HDL cholesterol, was clearly associated with kidney dysfunction, while total, as well as LDL cholesterol levels were similar in patients with and without DKD, although a greater prevalence of treatment with statins was recorded in the subgroup with either one or both renal abnormalities (Tables 1 and 2).

Table 2. Percentage of patients with T2DM treated with glucose lowering, lipid lowering and antihypertensive agents in the whole sample and in the subgroups of patients divided according to the presence/absence of Albuminuria and low eGFR

Whole sample	Alb− and low eGFR-	Alb− and low eGFR+	Alb+ and low eGFR−	Alb+ and low eGFR+	
Glucose-lowering Rx					
Diet (%)	6.3	7.9	6.3	4.2	3.7
OHA (%)	60.2	66.8	54.0	59.7	38.7
OHA + insulin (%)	17.0	14.4	16.0	22.2	19.2

Whole sample	Alb− and low eGFR-	Alb− and low eGFR+	Alb+ and low eGFR−	Alb+ and low eGFR+	
Insulin (%)	16.5	10.9	23.7	13.9	38.4
Dyslipidaemia					
Lipid-lowering treatment (%)	49.3	46.2	51.0	52.1	55.7
Treatment with statins (%)	45.0	42.5	45.8	47.6	49.8
Treatment with fibrates	2.7	2.4	3.5	2.7	3.2
Arterial hypertension					
Antihypertensive treatment	67.0	58.4	76.9	72.8	84.0
Treatment with ACE-Is/ARBs	61.1	50.9	68.5	70.3	80.3
Antiplatelet Rx					
Aspirin	33.5	30.7	36.0	35.6	39.1

Alb−, normoalbuminuria; Alb+, albuminuria; eGFR, estimated glomerular filtration rate; OHA, oral hypoglycaemic agents; ACE-Is, angiotensina converting enzyme-inhibitors; ARBs, angiotensina II receptor antagonists.

As expected, patients with both albuminuria and low GFR received more intensive glucose-lowering, lipid-lowering and antihypertensive treatment (Table 2); comparing the two groups with one kidney impairment, only small differences were found in terms of lipid-lowering and antihypertensive treatment, while insulin therapy was more frequent in patients with low GFR. As expected, therapy with ACE inhibitors or angiotensin receptor blockers was more frequent in individuals with albuminuria.

The relationship between traits of DKD and traditional diabetes and cardiovascular risk factors was further investigated by multivariate logistic analysis. Age and duration of disease independently affected both features of kidney dysfunction (Table 3). Being female represented a risk factor for isolated low GFR (males versus females: OR = 0.69, 95% CI 0.64–0.73), while male gender was associated with an increased risk of albuminuria (males versus females: OR = 1.89, 95% CI 1.81–1.98). Worse glycaemic control also affected the presence of albuminuria with an increased risk of 7% for every 1% increase in HbA1c (OR = 1.07, 95% CI 1.05–1.09), while it was inversely associated with the risk of low GFR (OR = 0.96, 95% CI 0.93–0.98).

Table 3. Results of multivariate logistic regression analysis (backward models) showing the relationship between traits of DKD and traditional diabetic and cardiovascular risk factors. Reference category for all were patients with normoalbuminuria and eGFR ≥ 60 mL/min/1.73 m^2.

Dependent variables						
	Low eGFR normal albuminuria		**Albuminuria normal eGFR**		**Low eGFR and albuminuria**	
Independent variables	**OR**	**95%CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age (by 1 year)	1.12	1.11–1.12	1.01	1.01–1.01	1.12	1.12–1.13
DBP (by 5 mmHg)	0.97	0.95–0.99	1.04	1.03–1.05	NS	NS
SBP (by 5 mmHg)	0.98	0.97–0.99	1.03	1.02–1.03	1.04	1.04–1.05
Total cholesterol (by 10 mg/dL)	1.04	1.02–1.07	1.05	1.04–1.06	1.07	1.04–1.10
HDL-C (by 5 mg/dL)	0.93	0.92–0.95	0.95	0.94–0.96	0.88	0.86–0.89
LDL-C (by 10 mg/dL)	0.96	0.93–0.98	0.95	0.94–0.96	0.94	0.91–0.96
Triglycerides (by 10 mg/dL)	1.02	1.02–1.03	NS	NS	1.03	1.02–1.03

Dependent variables

	Low eGFR normal albuminuria		Albuminuria normal eGFR		Low eGFR and albuminuria	
Independent variables	**OR**	**95%CI**	**OR**	**95% CI**	**OR**	**95% CI**
BMI (by 1 kg/m^2)	1.03	1.02–1.03	1.03	1.02–1.03	1.05	1.04–1.05
Duration of diabetes (by 1 year)	1.01	1.00–1.01	1.01	1.01–1.01	1.02	1.01–1.02
HbA1c (by 1%)	0.96	0.93–0.98	1.07	1.05–1.09	0.97	0.95–1.00
Males versus females	0.69	0.64–0.73	1.89	1.81–1.98	1.52	1.42–1.63
Smokers (yes versus no)	0.84	0.76–0.93	1.55	1.47–1.64	1.22	1.11–1.34
Oral agents versus diet	0.88	0.78–0.99	1.47	1.34–1.62	1.14	0.98–1.32
Oral agents + insulin versus diet	1.09	0.93–1.26	2.12	1.90–2.37	2.01	1.70–2.39
Insulin versus diet	2.06	1.78–2.38	1.96	1.75–2.20	5.59	4.74–6.59
Use of antihypertensive drugs	1.60	1.42–1.80	1.36	1.26–1.48	2.67	2.34–3.05
Use of ACE inhibitors and/or ARBs	1.24	1.13–1.37	1.33	1.23–1.42	1.24	1.12–1.36
Use of statins	1.10	1.03–1.17	NS	NS	1.17	1.09–1.25
Retinopathy	NS	NS	1.41	1.33–1.49	1.64	1.52–1.77

OR, odds ratio; 95% CI, 95% confidence of intervals; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; BMI, body mass index; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers.

Higher SBP levels were associated with albuminuria, with a 4% greater risk of simultaneously having albuminuria and low GFR for each increase of 5 mmHg. It is noteworthy that the use of antihypertensive drugs was related to both features of kidney dysfunction.

Renal dysfunction was also associated with the typical atherogenic lipid profile. In fact, HDL-cholesterol levels were inversely related to the risk of kidney abnormalities, while high levels of triglycerides were directly associated with an increased probability of having albuminuria. The risk of albuminuria and low GFR increased by 3% for every 10 mg/dL increase in triglycerides. Smoking was clearly associated with albuminuria and increased the risk by 55%, while the use of drugs inhibiting the renin–angiotensin system (i.e. ACE inhibitors or angiotensin receptor blockers) was associated with both low GFR and albuminuria.

Finally, as expected, the use of insulin was strongly associated with more advanced renal dysfunction.

CONCLUSIONS

We analysed data derived from a large database providing important hints regarding factors associated with different types of DKD.

Overall, patients with DKD showed an unfavourable CV risk profile with regard to glucose control, lipid profile and blood pressure despite similar treatment when compared with those without renal involvement, although with some peculiarities. Interestingly, the occurrence of isolated albuminuria seems to be associated with a much worse risk profile (i.e. higher values of HbA1c, worse triglycerides and HDL cholesterol and blood pressure levels) when compared with the presence of isolated GFR reduction. While the cross-sectional design of the study does not allow to draw any pathogenetic conclusions, our findings are in agreement with the unfavourable prognostic power of macroalbuminuria that was observed in recent meta-analyses [24].

Furthermore, although albuminuria and reduced GFR are independently related to an increased cardiovascular risk profile, they also show different clinical correlates, suggesting that these two well-known prognostic markers may—at least in part—recognize different pathogenetic mechanisms. Again, this

is in keeping with the results of the CKD Consortium meta-analysis [24] indicating that these two markers of renal damage actually do carry independent prognostic information.

The presence of DKD entails a significantly worse outcome in patients with diabetes, and although microalbuminuria has been shown to progress to overt proteinuria and progressive renal failure only in a limited number of patients, it is widely known to be the harbinger of greater CV morbidity and mortality. Thus, our data showing a relatively high prevalence of renal abnormalities in diabetic patients attending out-patient clinics in Italy support the need to implement more effective, large-scale, preventive and therapeutic strategies. Greater emphasis should especially be placed on preventing the onset of increased urine albumin excretion since this condition seems to be a feature of a more unfavourable CV risk phenotype, and is associated with worse metabolic control and higher BP values despite more vigorous treatment.

Recent studies have highlighted the large number of diabetic individuals with low GFR in the absence of elevated UAE (the so-called non-albuminuric renal impairment) [14–17]. Again, our findings are in agreement with those reported by the UKPDS which showed that half of the patients with low GFR are normoalbuminuric [13]. The role of this renal condition in terms of clinical outcome is still not completely clear. However, our results which show better glycaemic and blood pressure control as well as better lipid profile among patients with non-albuminuric renal impairment suggest a minor CV risk in the absence of albuminuria, in agreement with Rigalleau *et al.* [16], who showed, in a relatively small cohort of patients, that the risk of DKD progression or death is lower in patients with normoalbuminuria when compared with those with both low GFR and albuminuria.

Our finding of relatively lower blood pressure levels in the subset of patients with isolated GFR abnormalities might also suggest different pathogenetic mechanisms and features at the renal level, possibly characterized by haemodynamic changes (hypoperfusion) rather than atherosclerotic ones in the absence of albuminuria.

As expected, smoking is associated with albuminuria alone or in combination with low GFR while, not surprisingly, we found a lower prevalence of patients with isolated low GFR among smokers. This finding supports the hypothesis of Chuahirun *et al.* [25] who found in patients with type 2 diabetes that the effect of smoking was mediated by albuminuria. Using drugs inhibiting the renin–angiotensin system was associated with an excess risk of having impaired renal function; this is likely due to indication bias.

It is worth to note that the overall percentage of patients under lipid lowering or ACE/ARB anti-hypertensive medications was relatively low in our cohort, despite the recommendations of guidelines, specifically in the presence of diabetes and microalbuminuria. As a matter of fact, a number of studies have identified gaps in prescribers' adherence to clinical guideline recommendations, also among patients with diabetic nephropathy [26–32].

Our study has several limitations as well as strengths that deserve to be acknowledged and commented upon. First of all, laboratory parameters were not measured in a single centralized laboratory and this may have led to considerable variability, especially in the evaluation of serum creatinine (and therefore GFR estimation). Although creatinine determination cannot always be referred to IDMS procedures, most laboratories around the country currently use the Jaffè method which has been shown to have good reproducibility. In addition, we have information on albuminuria only as a categorical trait. One more limitation is the missing data on previous CVH/IHD event.

On the other hand, the large size of the database and the homogeneous geographical distribution of the recruiting centres are clearly major strengths of the study.

In conclusion, in this large cohort of patients with T2DM, reduced GFR and increased albuminuria show, at least in part, different clinical correlates. In fact, while systolic and diastolic blood pressure, glucose control and lipids (i.e. total and HDL cholesterol) are associated with isolated albuminuria, only lipids (i.e. total and HDL-cholesterol and triglycerides) appear to affect isolated low GFR. This result underlines the relevant role of albuminuria whose association with an unfavourable burden of CV risk factors seems to be even stronger than that of a reduction in GFR.

Greater therapeutic emphasis should be placed on the implementation of therapeutic strategies to correct modifiable risk factors and prevent CV diseases in the presence of DKD, especially in those with albuminuria.

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