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Original Article

ORIGINAL ARTICLE

Evolving kidney disease phenotypes in type 2 diabetes: declining albuminuria and increasing isolated low eGFR

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ABSTRACT

Background. This study investigated the prevalence and clinical correlates of renal phenotypes in two cohorts of type 2 diabetes (T2D) patients, assessed temporal trends, and evaluated associations with treatment regimens. These figures were compared to those previously recorded in a similar, real world cohort 15 years earlier in Italy.
Methods. Clinical data from 378 914 T2D patients attending the AMD network in 2023 in Italy were retrieved and compared to a similar cohort of prevalent patients in 2009. Renal phenotypes were classified as isolated albuminuria, isolated reduced eGFR (<60 ml/min/1.73 m^2), or both. Multivariate logistic regression identified factors associated with these phenotypes.
Results. In the 2023 study cohort, 51.3% of patients showed preserved renal function, 17.9% had isolated low eGFR, 17.4% had isolated albuminuria, and 13.3% exhibited both conditions. Female gender was independently associated with

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isolated low eGFR (OR = 1.28), whereas male gender was linked to albuminuria. Age was significantly related to both renal abnormalities, while longer diabetes duration increased the likelihood of low eGFR.
Conclusions. Compared with the 2009 cohort, the prevalence of CKD in T2D remains stable in 2023, with albuminuric phenotypes decreasing and isolated low eGFR phenotypes increasing. These trends may reflect the aging population and evolving treatment practices, including a growing use of nephroprotective agents such as RAS inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists as well as better control of blood pressure. Longitudinal *ad hoc* studies are needed to address changing clinical scenarios.

Keywords: albuminuria, chronic kidney disease, estimated glomerular filtration rate, type 2 diabetes mellitus (T2D)

KEY LEARNING POINTS

What was known:

- In the last two decades, there has been a significant improvement in the management of type 2 diabetes, thanks also to the introduction in the clinical practice of new classes of drugs.
- More recently, however, there is evidence of a change in the epidemiology of kidney complications.

This study adds:

- This study investigated the prevalence and clinical correlates of renal phenotypes in a cohort of type 2 diabetes (T2D) patients, assessed temporal trends over a 15-year period, and evaluated associations with treatment regimens.

Potential impact:

- The diabetic population is aging, the prevalence of CKD is stable, the albuminuric phenotype is decreasing, and the phenotype associated with low eGFR is increasing.
- These changing renal presentations may be the results of new therapeutic regimens but at the same time could bear influence on treatment choices in clinical practice.

INTRODUCTION

Chronic kidney disease (CKD) is a major public health concern. It already affects ∼1 in 10 individuals worldwide and is estimated to become the fifth leading cause of death by 2040 [1, 2]. CKD is strongly linked to increased mortality and morbidity, primarily due to cardiovascular complications. Diabetes, particularly type 2 diabetes (T2D) that constitutes >90% of all diabetes cases, remains the primary cause of CKD [3]. CKD in patients with diabetes represents a significant burden on national health services, accounting for a large proportion of all cases of end-stage kidney disease: nearly half in the USA and 20% in the EU [4]. Indeed, several studies have shown that both increased urinary albumin excretion (UAE) [5–11] and reduced GFR [5, 6] are independent predictors of CV events.

In the last two decades, there has been a significant improvement in the management of type 2 diabetes, with a trend toward better control of several modifiable risk factors such as arterial hypertension, dyslipidemia, and obesity, thanks also to the introduction of new classes of drugs such as of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1 RA) [12, 13]. As a consequence, we have observed a declining rate of mortality and morbidity for CV disease or amputation while the risk for ESKD remained stable [14, 15].

In 2009, we reported that 36%, 24%, and 12% of patients had albuminuria, low eGFR, and both albuminuria and low eGFR, respectively [16]. Similar data were also reported by another Italian study, although in a smaller population [17].

The present report offers an updated analysis of prevalent renal phenotypes and their clinical and biochemical correlates based on a large cross-sectional survey conducted in 2023 in Italy. These data may be relevant to inform clinical decision-making and improve outcomes in patients with CKD and T2D.

MATERIALS AND METHODS

Data are derived from an initiative of the Italian Association of Clinical Diabetologists [Associazione Medici Diabetologi (AMD)], established in 2004 for continuous monitoring and improvement of diabetes care [18–20]. The initiative involves 296 diabetes clinics, all using an electronic clinical record system for the everyday management of outpatients. *Ad hoc* software was developed to extract information from these clinical databases. Data from all participating centers were collected anonymously and centrally analyzed [18–20]. The database includes information on all patients with T2D who are receiving care during the period between 1 January 2004 and 31 December 2023. In accordance with national guidelines governing retrospective studies utilizing anonymized data, the requirement for obtaining informed consent from patients was not applicable. The core dataset included measurements of HbA1c, blood pressure, serum creatinine, urinary albumin excretion, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and triglycerides. Estimated glomerular filtration rate (eGFR) was estimated for each patient by using the Chronic Kidney Disease Epidemiology Collaboration formula derived from serum creatinine values [21]. Albuminuria was diagnosed if the urinary albumin concentration was >30 mg/l, if the urinary albumin excretion rate was >20 μg/min, or if the urinary albumin-to-creatinine ratio was >2.5 mg/mmol in men

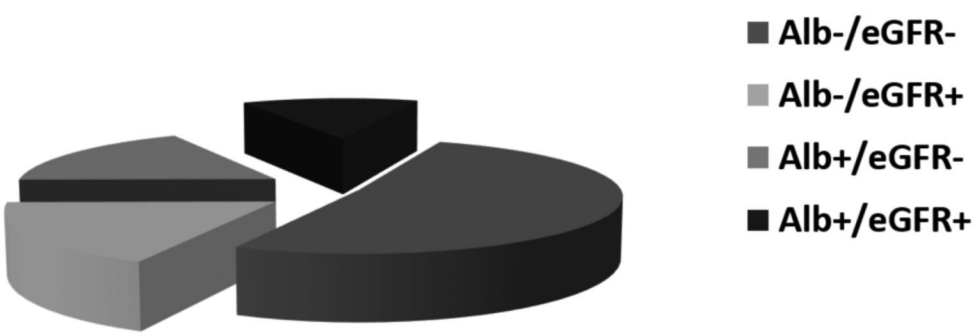

Figure 1: Prevalence of four renal phenotypes among the studied cohort (2023).

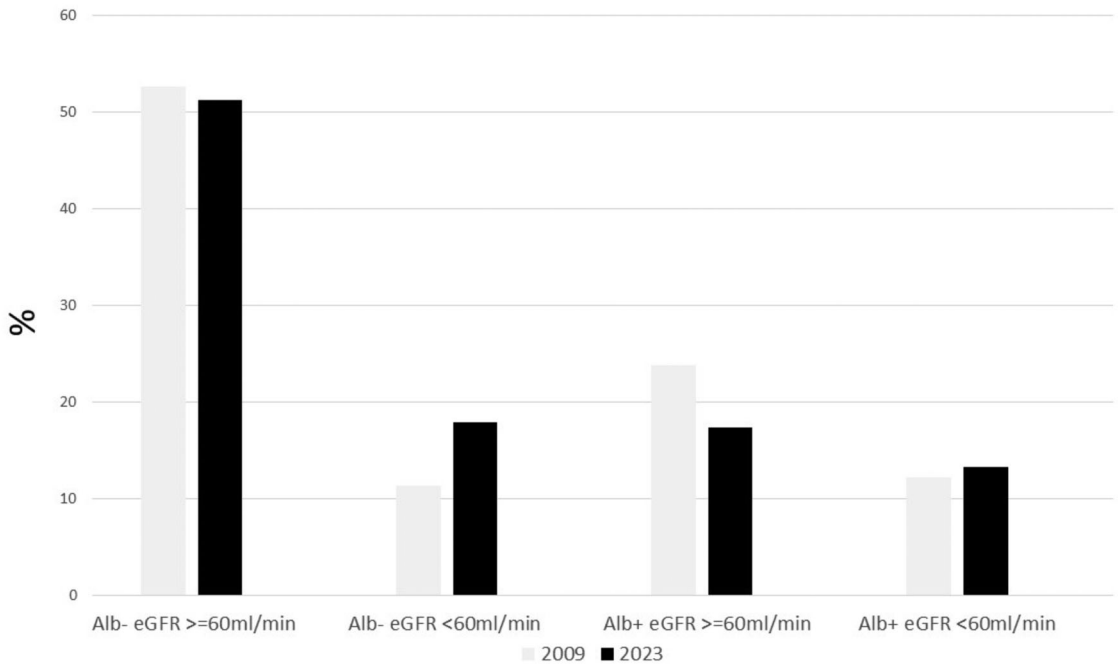

Figure 2: Renal phenotypes: comparison between the 2009 and 2023 cohorts.

or 3.5 mg/mmol in women. Renal risk was assessed using the KDIGO classification [22].

Renal phenotypes were assessed using AMD-Annals data for 2023. A total of 378 914 participants with DM2, for whom albuminuria and eGFR information were available, were evaluated. Patients with missing data on key variables were excluded from the analysis.

Descriptive data are summarized as mean and standard deviation for continuous variables and percentages for categorical variables. Multivariate logistic regression analyses, with backward variable selection, were performed to evaluate factors independently associated with an increased likelihood of having isolated low eGFR, isolated albuminuria, or the simultaneous presence of low GFR and albuminuria. The reference category included patients with absent albuminuria and with eGFR $\geq$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. Multivariable models were used to explore independent associations with renal phenotypes and were not intended for predictive modeling. Results are expressed as odds ratio (OR) and their 95% confidence interval. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc., North Carolina, USA).

RESULTS

A total of 378 914 participants with T2D attending diabetes centers in Italy in the year 2023, for whom information on albuminuria and eGFR was available, were evaluated.

Figure 1 shows the prevalence of the four renal phenotypes in the study population. Half of the patients (51%) had normal renal function (i.e. normoalbuminuria and eGFR $\geq$60 ml/min), 18% had an isolated reduction in eGFR, 17% had isolated albuminuria, and the remaining 13% presented with both albuminuria and a reduction in eGFR.

Table 1: Characteristics of the 2023 study cohort, overall and according to renal phenotype (data are mean ± standard deviation, median, and IQR or percentages).

Characteristics	Overall	Albuminuria, no eGFR ≥60 ml/min	Albuminuria, no eGFR <60 ml/min	Albuminuria, yes eGFR ≥60 ml/min	Albuminuria, yes eGFR <60 ml/min
N (%)	378.914	194.492 (51.3)	67.852 (17.9)	66.076 (17.4)	50.494 (13.3)
Males (%)	59.3	57.8	50.5	68.6	65.1
Age (years)	69.8 ± 10.9	66.9 ± 10.6	75.6 ± 8.9	67.8 ± 10.8	75.9 ± 8.9
BMI (kg/m^2)	28.7 ± 5.4	28.6 ± 5.4	28.7 ± 5.3	28.9 ± 5.6	28.8 ± 5.4
Duration of T2D (years)	13.2 ± 9.8	11.6 ± 9.1	15.5 ± 10.3	12.7 ± 9.4	17.2 ± 10.4
HbA1c (%)	7.1 ± 1.2	7.0 ± 1.1	7.1 ± 1.1	7.2 ± 1.3	7.2 ± 1.2
LDL cholesterol (mg/dl)	81.2 ± 31.9	83.1 ± 32.1	78.3 ± 30.5	81.5 ± 32.9	76.8 ± 31.4
Systolic blood pressure (mmHg)	134.5 ± 18.3	133.7 ± 17.7	132.6 ± 18.2	137.0 ± 18.9	136.7 ± 19.6
Diastolic blood pressure (mmHg)	76.3 ± 10.1	76.9 ± 9.8	74.2 ± 9.9	77.6 ± 10.3	74.9 ± 10.3
eGFR (ml/min/1.73 m^2)	70.4 ± 26.4	85.3 ± 13.6	39.5 ± 18.4	84.1 ± 14.2	36.8 ± 17.0
Smoking (%)	17.6	17.5	11.3	25.3	16.8
Retinopathy (%)	13.2	11.0	13.6	14.9	19.4
Major cardiovascular event (%)[a]	15.6	11.6	19.8	15.7	25.1

[a]Myocardial infarction, stroke, coronary revascularization, coronary by-pass, peripheral revascularization, peripheral by-pass

Table 2: Pharmacological treatments according to renal phenotype in 2023 cohort (data are percentages).

Characteristics	Albuminuria, no eGFR ≥60 ml/min	Albuminuria, no eGFR <60 ml/min	Albuminuria, yes eGFR ≥60 ml/min	Albuminuria, yes eGFR <60 ml/min
N (%)	194 492 (51.3)	67 852 (17.9)	66 076 (17.4)	50 494 (13.3)
Metformin (%)	83.5	55.2	83.2	42.2
Sulphonylureas	5.6	6.3	6.2	5.6
Glinides	0.5	1.5	0.5	1.6
Pioglitazone	4.5	3.9	3.9	3.1
Acarbose	0.9	1.8	0.9	1.9
DPP4i	17.8	27.4	16.8	26.8
SGLT2i	36.6	39.1	43.1	40.9
GLP1-RA	35.2	31.8	36.9	31.7
Insulin	26.0	38.9	35.2	52.1
Lipid-lowering agents	70.6	74.5	71.2	74.7
Antihypertensive drugs	63.2	80.9	69.0	82.7
ACEi/ARBs	82.2	77.8	83.7	74.7

Figure 2 compares the current prevalence of the four phenotypes observed in the 2023 cohort with that recorded in 2009. The prevalence of patients with normal renal function has slightly decreased in 2023 from 53% to 51% (relative reduction of 2.5%); people with exclusive reduction of eGFR increased from 11% to 18% (relative increase of 58%), and those with isolated albuminuria decreased from 24% to 17% (relative reduction of 27%). Those presenting with both albuminuria and reduced eGFR slightly increased from 12% to 13% (relative increase of 9.0%).

Table 1 shows the characteristics of the 2023 cohorts based on renal phenotype. The prevalence of male gender was higher in association with albuminuria, while the mean age and mean duration of diabetes were higher in patients with reduced eGFR. HbA1c values are slightly higher in the other groups compared with participants with normal renal function. Participants with both albuminuria and reduced eGFR showed higher triglyceride values, lower HDL cholesterol values, and higher average blood pressure values. They also had a higher prevalence of micro and macrovascular complications.

Table 2 shows current treatments in different renal phenotypes. Metformin use, as expected, was substantially lower in subgroups characterized by reduced glomerular filtration rate, in which the prescription of DPP4i use was conversely higher. The use of SGLT2i and GLP-1 RA was particularly high in participants with albuminuria only (43%). Insulin treatment was more commonly prescribed in patients with albuminuria and reduced eGFR (52%).

Table 3 compares the characteristics of patients in 2009 with those in 2023 within each of the four renal phenotypes. Data show an increase in the prevalence of males in low eGFR groups in the 2023 cohort. In general mean age and duration of diabetes were higher in this more recent cohort. Furthermore, there was a substantial improvement in all groups in metabolic control, lipid profile, and blood pressure values, as well as a reduction in the prevalence of retinopathy. An opposite trend was registered for the prevalence of smokers, which increased in 2023 compared with 2009 in phenotypes characterized by the presence of albuminuria and/or reduced eGFR.

The relationship between traits of CKD and traditional diabetes and cardiovascular risk factors was further investigated by multivariate logistic analysis. Age was independently related to both features of kidney dysfunction (Table 4), while disease duration associated to low eGFR alone or in combination with albuminuria.

Being female was associated with isolated low eGFR (OR = 1.28, 95% CI 1.21–1.36), but less likely with albumin-

Table 3: Patient characteristics according to the renal phenotype: comparison between 2009 and 2023 cohorts (data are mean ± standard deviation or percentages).

	Albuminuria, no eGFR ≥60 ml/min		Albuminuria, no eGFR <60 ml/min		Albuminuria, yes eGFR ≥60 ml/min		Albuminuria, yes eGFR <60 ml/min	
Characteristics	2009	2023	2009	2023	2009	2023	2009	2023
N (%)	63 639 (51.6)	194 492 (51.3)	13 660 (11.3)	67 852 (17.9)	28 806 (23.8)	66 076 (17.4)	14 684 (12.2)	50 494 (13.3)
Males	56.3	57.8	42.2	50.5	69.0	68.6	59.5	65.1
Age (years)	64.1 ± 10.7	66.9 ± 10.6	74.0 ± 8.0	75.6 ± 8.9	65.0 ± 10.8	67.8 ± 10.8	73.4 ± 8.5	75.9 ± 8.9
BMI (kg/m^2)	29.4 ± 5.2	28.6 ± 5.4	29.7 ± 5.1	28.7 ± 5.3	30.2 ± 5.3	28.9 ± 5.6	30.0 ± 5.2	28.8 ± 5.4
Duration of DM2 (years)	9.7 ± 8.6	11.6 ± 9.1	13.3 ± 10.4	15.5 ± 10.3	11.0 ± 9.0	12.7 ± 9.4	15.3 ± 10.5	17.2 ± 10.4
HbA1c (%)	7.4 ± 1.5	7.0 ± 1.1	7.4 ± 1.4	7.1 ± 1.1	7.8 ± 1.6	7.2 ± 1.3	7.7 ± 1.5	7.2 ± 1.2
LDL cholesterol (mg/dl)	110.0 ± 33.8	83.1 ± 32.1	106.4 ± 34.1	78.3 ± 30.5	107.1 ± 34.9	81.5 ± 32.9	103.9 ± 34.4	76.8 ± 31.4
Systolic blood pressure (mmHg)	137.7 ± 18.3	133.7 ± 17.7	139.5 ± 18.9	132.6 ± 18.2	141.5 ± 19.5	137.0 ± 18.9	143.8 ± 20.5	136.7 ± 19.6
Diastolic blood pressure (mmHg)	79.1 ± 9.5	76.9 ± 9.8	77.3 ± 9.8	74.2 ± 9.9	80.5 ± 10.0	77.6 ± 10.3	78.5 ± 10.3	74.9 ± 10.3
eGFR (ml/min/1.73 m^2)	85.1 ± 13.9	85.3 ± 13.6	48.0 ± 9.8	39.5 ± 18.4	84.±14.4	84.1 ± 14.2	42.8 ± 12.7	36.8 ± 17.0
Smoking	17.5	17.5	8.8	11.3	23.8	25.3	13.4	16.8
Retinopathy	14.2	11.0	18.5	13.6	22.4	14.9	30.5	19.4
Glucose-lowering treatment								
Diet only	7.9	2.7	6.3	2.2	4.2	1.6	3.7	1.4
OHA*	66.8	71.3	54.0	58.9	59.7	63.2	38.7	46.5
Insulin + OHAI	14.4	21.5	16.0	28.0	22.2	29.5	19.2	34.7
Insulin	10.9	4.5	23.7	10.9	13.9	5.7	38.4	17.4

Table 4: Results of multivariate logistic regression analysis (backward models) showing the relationship between traits of CKD, traditional diabetic and cardiovascular risk factors in the 2023 cohort. Reference category: patients with normoalbuminuria and eGFR ≥60 ml/min/1.73 m^2.

	Low eGFR normoalbuminura		Normal eGFR albuminuria		Low eGFR albuminuria	
Independent variables	OR	95%CI	OR	95%CI	OR	95%CI
Age	1.097	1.092–1.101	1.013	1.010–1.016	1.120	1.114–1.126
Female gender	1.280	1.205–1.359	0.604	0.568–0.642	0.615	0.568–0.665
Duration of T2D (years)	1.011	1.008–1.015	—	—	1.012	1.008–1.017
BMI (kg/m^2)	1.017	1.011–1.023	—	—	1.017	1.009–1.025
Smokers (yes vs. no)	—	—	1.725	1.610–1.849	1.552	1.406–1.713
HbA1c (%)	0.935	0.904–0.968	1.056	1.025–1.087	—	—
Systolic blood pressure (mmHg)	0.994	0.092–0.096	1.01	1.008–1.011	1.005	1.003–1.007
Diastolic blood pressure (mmHg)	0.994	0.990–0.997	—	—	—	—
HDL cholesterol (mg/dl)	0.992	0.989–0.994	0.997	0.995–1.000	0.989	0.985–0.992
Triglycerides (mg/dl)	1.004	1.004–1.005	1.001	1.001–1.002	1.006	1.005–1.007
Retinopathy (yes vs. no)	—	—	1.286	1.180–1.401	1.292	1.159–1.441
Treatment with SGLT2i (yes vs. no)	1.341	1.263–1.424	1.309	1.238–1.385	1.581	1.470–1.700
Treatment with GLP1-RA (yes vs. no)	—	—	—	—	0.922	0.852–0.997
Treatment with insulin (yes vs. no)	1.116	1.037–1.200	1.316	1.232–1.405	1.586	1.460–1.722
ACEi-ARB	—	—	1.136	1.052–1.226	0.860	0.785–0.942

uria (OR = 0.60, 95% CI 0.57–0.64) or the simultaneous occurrence of low eGFR and albuminuria (OR = 0.62, 95% CI 0.57–0.67).

Worse glycemic control also affected the presence of albuminuria with an increased risk of 6% for every 1% increase in HbA1c (OR = 1.06, 95% CI 1.03–1.09), while it was inversely associated with the risk of low eGFR (OR = 0.94, 95% CI 0.90–0.97). Higher BMI was associated with a higher likelihood of low eGFR alone or associated with albuminuria. Higher SBP levels were associated with albuminuria alone or associated with low eGFR, while they were inversely associated with low eGFR. CKD was also associated with the typical atherogenic lipid profile. In fact, HDL cholesterol levels were inversely related to the risk of kidney abnormalities.

By contrast, high levels of triglycerides were directly associated with an increased likelihood of having albuminuria and/or low eGFR. Smoking was clearly associated with albuminuria and increased the risk by 73%. By contrast, the use of drugs inhibiting the renin-angiotensin system (i.e. ACE inhibitors or angiotensin receptor blockers) was associated with albuminuria. Retinopathy was associated with a 29% increased risk of albuminuria alone or associated with low eGFR.

Finally, patients with low eGFR and albuminuria, alone or in combination, were more likely to be treated with SGLT2i or insulin.

DISCUSSION

In this report, we present the results of an analysis of an extensive database of patients with T2D, attending the outpatient clinic of the AMD Italian network in 2023. We provide updated information on the prevalence of CKD, its different phenotypes and related CV risk determinants, and prevalent pharmacologic treatment, and compare these data with those of a previous similar cohort attending the same centers in 2009.

The percentage of patients with CKD in 2023 is slightly higher than what we have previously described (i.e. 48.7% vs. 47.4%) [16], indicating a stabilization of the prevalence of CKD, in line with that recently reported by the USRDS [23]. This finding is not unexpected, considering the enhanced management of kidney disease risk factors reported in recent years [24, 25], a trend we also observe in our sample. In addition, the clinical use of medications like RAS inhibitors, as well as the more recent introductions of SGLT2 inhibitors and GLP-1 receptor agonists, has been shown to decrease both the incidence and progression of CKD [26, 27]. On the other hand, the increased survival of patients with T2D and the consequent longer duration of the disease could explain, at least in part, the marginal increase in CKD that we describe.

Overall, as expected, patients with CKD show an unfavorable CV risk profile regarding glycemic control, lipid profile, and blood pressure control compared with patients with preserved kidney function, with some peculiarities. Of patients, 17.9% have low eGFR in the presence of normoalbuminuria (i.e. normoalbuminuric CKD), a percentage higher than that we observed in 2009 (17.9% vs. 11.3%). This is in line with that described by Afkarian *et al.* [28] who showed that among US adults with diabetes from 1988 to 2014, the overall prevalence of diabetic kidney disease did not change significantly. By contrast, the prevalence of albuminuria declined, and the prevalence of reduced eGFR increased. This is an emergent unique CKD phenotype whose clinical outcome is not completely understood. It has, in fact, been associated with a slow kidney disease progression and a high risk for CV events [29–32].

Other studies, however (ACCORD), did not confirm these results and reported similar renal and CV risk in patients with low GFR independent of the presence of albuminuria [33].

The results of the multivariate analysis provide several insights into the clinical determinants of CKD in our population. They confirm the strong and independent association between age and both forms of features of kidney dysfunction. At the same time, duration of diabetes is associated with low eGFR in the presence or absence of albuminuria. Female gender is associated with low eGFR, while being male is a risk factor for albuminuria. In addition, our findings also confirm the strong association between glycemic control and albuminuria, according to the results of several observational and interventional studies [34–37] on this topic.

The evidence for obesity as an independent risk factor for CKD has been growing in recent years, and our data fit with those by Zhang *et al.* [38], who recently showed in a large Chinese population with T2D that higher BMI and waist to height ratio were each associated with a greater prevalence of CVD after adjustment for each other.

The association and the potential detrimental effect of arterial hypertension with kidney damage in patients with diabetes has been extensively studied. Our data show a strong and independent association between SBP and albuminuria, confirming several previous studies. Furthermore, we find a direct relationship between SBP and eGFR, supporting the hypothesis that strict BP control could worsen kidney function through renal hypoperfusion. This confirms our previous data [39] and those of other authors [40].

Finally, the strong association between SGLT2i prescription and CKD, mainly with albuminuria, is a clear result of indication bias (Table 4). Notably, the proportion of patients receiving insulin therapy, particularly basal insulin, increases progressively across the three renal disease phenotypes, and is >50% in patients with both albuminuria and a low glomerular filtration rate. It is important to note in this regard that the progressive increase in the use of insulin therapy does not correspond to a reduction in the use of nephroprotective drugs such as SGLT2i and GLP-1RA. This suggests that insulin therapy is generally used alongside these drugs, in accordance with the most current recommendations.

Our study has several limitations but also strengths that deserve to be highlighted and commented on. Among the limitations, laboratory parameters were not centralized, and this can account for some variability. Furthermore, we relied on a single creatinine value to estimate GFR and this could have led to some variability as we could not identify occasional acute changes in serum creatinine in a specific patient. We believe, however, that the large sample size of our study may limit this potential bias. The mean age of the 2023 study cohort was significantly higher than the 2009 one and this may have introduced a selection bias toward the subgroup of patients with greater life expectancy and therefore a better risk profile. On the other hand, the large size of our database, accounting for almost 10% of the T2D population currently living in Italy, represents the major strength of our study. The homogenous geographical distribution of centers participating in the data collection across the country is a further point of strength.

In conclusion, our data clearly show that the diabetic population is aging, the prevalence of CKD is stable, the albuminuric phenotype is decreasing, and the phenotype associated with low eGFR is increasing. These two CKD phenotypes cluster, at least in part, with different risk factors.

We also describe an improved control of traditional cardiovascular risk factors, although optimal control is not yet achieved. The prescription of drugs with beneficial effects on renal progression and cardiovascular mortality is rapidly increasing. Their ability to change hard renal and cardiovascular outcomes will be assessed over the next few years.

AUTHORS' CONTRIBUTIONS

S. De Cosmo, R. Pontremoli, and G. Russo contributed to the study conception, design, data analysis, and drafted the paper, while A. Nicolucci, C. Rossi, and G. Graziano provided statistical analysis. D. Tuccinardi, P. Fioretto, F. Viazzi, G. Sartore, A. Muscarà, P. Piscitelli, R. Candido, and G. Di Cianni critically revised the manuscript for important intellectual content. All authors reviewed and approved the final manuscript. S. De Cosmo is the guarantor of this work, having had full access to all the data and taking responsibility for the integrity of the data and the accuracy of the analysis.

CONFLICT OF INTEREST STATEMENT

None declared.

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DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article.

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