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Relationship between albuminuric CKD and diabetic retinopathy in a real-world setting of type 2 diabetes: Findings from No blind study

F.C. Sasso [a,*,2], P.C. Pafundi [a,2], A. Gelso [b], V. Bono [c], C. Costagliola [d], R. Marfella [a], C. Sardu [a], L. Rinaldi [a], R. Galiero [a], C. Acierno [a], A. Caturano [a], C. de Sio [a], L. De Nicola [e], T. Salvatore [a], R. Nevola [a], L.E. Adinolfi [a], R. Minutolo [e] on behalf of NO BLIND Study Group[1]

[a] *Unit of Internal Medicine, Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy*
[b] *"Villa dei Fiori" Hospital, Acerra, Naples, Italy*
[c] *IRCCS Fondazione G.B. Bietti, Rome, Italy*
[d] *Department of Medicine & Health Sciences, University of Molise, Campobasso, Italy*
[e] *Unit of Nephrology, Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy*

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Abstract *Background and aims:* Recently, the albuminocentric view of diabetic kidney disease (DKD) in type 2 diabetes (T2DM) has been changing. Therefore, the relationship between diabetic retinopathy (DR) and chronic kidney disease (CKD) has to be addressed according to this new clinical presentation of DKD. The aim of this study was to evaluate, in a real-world setting, the correlation DR–DKD in T2DM.
Methods and results: A total of 2068 type 2 diabetic patients enrolled in a multicenter cross-sectional study were investigated. Albuminuric subjects were largely prevalent among subjects with DR ($p = 0.019$). In the whole study population, no difference in albumin excretion rate (AER) was observed between presence/absence of DR; instead, AER was significantly higher among patients with glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (CKD) ($p = 0.009$), above all in those with CKD and AER $\geq$0.03 g/24 h ($p = 0.005$). Multivariate analysis confirmed that eGFR (O.R. 0.976; 95% C.I.: 0.960–1.028; $p < 0.001$) and AER (O.R. 1.249; 95% C.I. 1.001–1.619; $p = 0.004$) were independently associated with DR and HDL–cholesterol (O.R.: 1.042; 95% C.I.: 1.011–1.120; $p = 0.014$). Additionally, among patients with eGFR <60 mL/min/1.73 m^2 and albuminuria, both eGFR and AER significantly varied between those with/without DR ($p = 0.012$ and $p = 0.005$, respectively), and this finding was observed among only albuminuric patients. Analogous results were obtained considering DR classification. AER was significantly higher among subjects with either proliferative DR (PDR) or severe nonproliferative DR (NPDR), with regard to mild NPDR (0.498 and 0.938 g/die vs. 0.101 g/die; $p < 0.001$, respectively). Similar results were obtained in the specular subgroups.
Conclusion: In T2DM with DKD, the AER seems to be related to the presence of DR. This association is confirmed above all in those with more severe DR.

* Corresponding author. University of Campania "Luigi Vanvitelli", Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, Italy.
E-mail address: ferdinandocarlo.sasso@unicampania.it (F.C. Sasso).
[1] The members of NO BLIND Study Group are listed in Appendix section.
[2] F.C.S. and P.C.P. equally contributed to the study.

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Introduction

Diabetic microangiopathy mainly expresses under diabetic nephropathy (DN) and diabetic retinopathy (DR), which share several risk factors including poor glycemic control and hypertension.

Both DN and DR are largely prevalent among diabetic patients, with a strong negative impact on the outcome of this high-risk population. DN represents the first cause of dialysis in the industrialized countries, especially in Europe and in the US, while DR is the main cause of legal blindness among working age people. In fact, as its symptoms appear late, with lesions already established, the treatment is often ineffective [1–3].

A frequent correlation between DN and DR has been already well known [4]. Moreover, both are associated with a high cardiovascular risk [5,6].

Usually, DR can be more easily diagnosed through *fundus oculi* examination, differently from diabetic renal lesions, as renal biopsy is not systematically performed in patients with diabetes. Furthermore, the finding that nondiabetic renal disease is highly prevalent in patients with diabetes [7] has induced ADA in its "standards of medical care in diabetes" to use the definition "Chronic Kidney Disease (CKD) attributed to diabetes (diabetic kidney disease, DKD)" instead of "diabetic nephropathy" [8].

DN historical classification has put at the core the increase in albuminuria excretion rate (AER) preceding the reduction in eGFR [9,10]. However, the albuminocentric view of DN has been changing in the last years. In fact, recent data from different settings (general population, diabetic clinics, and renal clinics) consistently demonstrated a high prevalence of a nonalbuminuric phenotype of DKD [11–13]. Therefore, the relationship between DR and renal disease has to be addressed according to this new clinical presentation of nephropathy in T2DM.

Consistently, we designed the present study to assess, in a real-life setting, the correlation between DR and DN in type 2 diabetic patients followed by specialists in outpatient clinics by analyzing the data of the **No Blind** study, originally designed for screening of DR [14]. In that database, clinical, laboratory, and pharmacological data necessary for DKD evaluation were collected simultaneously with DR information obtained by using a digital ophthalmoscope [14].

Methods

Design of the study

The data shown in this study are derived from the NO Blind, multicenter, cross-sectional study, which involved nine public Italian outpatient clinics, extended to one year of enrollment.

A total of 2210 patients were assessed for eligibility from November 2016 to November 2017.

As our main focus was on patients with T2DM, the initial inclusion criteria of the No Blind study [14] were modified as follows: women/men aged >14 years, as all diabetes participating centers were specifically for the adults; definite T2DM diagnosis, based on the American Diabetes Association criteria [8], independently of any antihyperglycemic pharmacological therapy, as well as glycemic compensation, expressed as glycated hemoglobin (HbA1c).

We decided to include only patients with T2DM to avoid bias of selection. In fact, the population of patients with T1DM is truly heterogeneous with regard to T2DM for what concerns BMI, rate of hypertension, duration and age of onset, and, above all, therapy, which may impact the onset and the progression of DR.

All patients enrolled in the study underwent both a screening in telemedicine in myosis, with photos taken by a diabetologist through a digital ophthalmoscope and interpreted by an expert ophthalmologist of a reading center, and a standard *fundus oculi* examination in mydriasis by a different ophthalmologist. In this way, the diagnosis of DR was confirmed at least by two independent specialists. The non-diagnostic photos were re-evaluated in mydriasis by a specialist ophthalmologist; hence, the 446 non-diagnostic images excluded from the No Blind Screening study [14] were included here.

As a result of these new criteria, patients considered eligible for the study were 2210, of which 142 (6.4%) were excluded for the following reasons: 69 (3.1%) had T1DM, 24 (1.1%) did not sign the informed consent to the study, and, finally, 49 (2.2%) had cataract or any other ocular pathology. Hence, we obtained a final population of 2068 patients.

The study was approved by the University of Campania Ethics Committee and was conformed to the 1976 Declaration of Helsinki and its later amendments. All patients provided a written informed consent.

Endpoints and data collection

In this paper, the main focus was on the assessment of the relationship between DR and DKD.

The following data were collected in a predefined electronic form: past history, clinical and laboratory parameters, chronic complications of diabetes, and current pharmacological therapy. DR was graded according to the ETDRS classification scale [15].

Statistical analysis

Data are shown as either mean and SD or median and range for continuous variables and as number and percentage for categorical variables. The normal/non-normal distribution was preliminarily assessed through a Kolmogorov–Smirnov Goodness-of-Fit K-S test. Categorical data were compared using either the Pearson chi-square test (with Mantel-Haenszel common odds ratio estimate) or Fisher exact test, when indicated. In the case of normally distributed variables, the t test was instead used. Continuous variables were finally assessed by nonparametric Mann–Whitney U test or Kruskal–Wallis test, when indicated. In addition, we performed a

multivariate logistic regression analysis, adjusted for HbA1c, age, diabetes duration, sex, BMI, waist circumference, smoke, hypertension (defined as either systolic $\geq$130 mmHg or diastolic BP $\geq$ 80 mmHg), heart rate, total/HDL/LDL cholesterol, triglycerides, AER, and eGFR to verify independent predictors of DR.

P values below 0.05 were considered statistically significant. All analyses were performed with SPSS software (IBM, Armonk, New York), version 24, and R software (CRAN® 3.3.4).

Results

General features of the study population

As previously described in the Methods section, we performed all analyses on a final study population of 2068 subjects with T2DM (n = 2068), regularly followed up for one year, from November 2016 to November 2017, in nine outpatient clinics, where all patients underwent *fundus oculi* examination.

The study population was equally distributed for sex: 1051 males (50.2%) and 1017 females (49.8%), with a median age of 66 years [IQR: 57–73 years]. Median duration of diabetes was equal to 8 years [IQR: 4–15 years], with a mean glycated hemoglobin (HbA1c) of 7.3% (56 mmol/mol) [SD: ±1.3%].

Albuminuric subjects were largely prevalent among subjects with DR (p = 0.019). For all patients, we also collected data of the current pharmacological therapy. The enrolled subjects were prevalently under metformin therapy (62.9%). Moreover, more than a half of the study population took statins (54.8%) and an inhibitor of renin-angiotensin system (55.6%). Looking particularly at these data, there was no difference in the prevalence of DR according to the treatment with either an ACEi or an ARB or both, (p = 0.081, p = 0.746, and p = 0.367, respectively).

Subjects with GFR <60 ml/min/1.73 m^2 assumed an ACE I or an ARB more frequently with regard to those with GFR within 90–60 ml/min/1.73 m^2 (respectively, 36.8% vs. 29.3%, p = 0.011, and 43.8% vs. 35.1%, p = 0.005).

Anthropometric, clinical, biochemical, and pharmacological characteristics of the patients are shown in Table 1.

Finally, the *fundus oculi* examination hence allowed for a prevalence of DR in our population equal to 21% (435 of 2068 patients), with a 4.78% (99 cases) of proliferative diabetic retinopathy (PDR), 16.22% (336 cases) of non-proliferative diabetic retinopathy (NPDR) and 5.97% (123 cases) of diabetic macular edema (DME). Among NPDR cases, 49.1% (165 cases) were classified as mild NPDR, 39.65% as moderate (133 cases), and 11.25% as severe (38 cases). All cases of DME were associated with either non-proliferative or proliferative DR.

Analysis according to presence or absence of DR

In comparison with patients without DR, those with DR had lower eGFR and higher AER (Table 1). Accordingly, the prevalence of DR progressively follows a "bell-shaped" ("upside-down-U-shaped") trend across strata of eGFR (eGFR >90 mL/min/1.73 m^2: 30.9%, GFR 60–90 mL/min/1.73 m^2: 47.8%, and eGFR <60 mL/min/1.73 m^2: 21.3%). In particular, DR was significantly prevalent most of all among subjects with eGFR between 60 and 90 mL/min/1.73 m^2 (p = 0.017), while no significant difference was found in terms of DR between subjects with a GFR >90 and those with eGFR <60 mL/min/1.73 m^2 (p = 0.364). Looking at the different distributions according to the type of DR (Fig. 1), severe NPDR and PDR were significantly prevalent in the subgroup with eGFR <60 mL/min/1.73 m^2 (p < 0.001), while no other significant difference was observed in the distribution of the type of DR.

We further analyzed the prevalence of DR according to the stage of CKD, defined according to the most recent KDIGO guidelines [16].

To have the most homogeneous subgroups, we unified CKD stages 3–5. Accordingly, DR was most of all prevalent among subjects with CKD stage 2 (46.5%), with a significant difference with regard to the lower and upper stages (p = 0.006). Looking at the different distributions according to the type of DR, severe NPDR and PDR were significantly prevalent in the subgroup with a severe CKD (stages 3–5) (p < 0.001), while no significant difference was observed in the other stages of CKD with regard to DR classification (p = NS).

Moreover, we performed a multivariate logistic regression analysis, adjusted for HbA1c, age, and diabetes duration, inserting the main risk factors for DR (sex, BMI, waist circumference, smoke, hypertension, heart rate, total/HDL/LDL cholesterol, triglycerides, AER, and eGFR) and verified that both eGFR (O.R. 0.976; 95% C.I.: 0.960–1.028; p < 0.001) and AER (O.R. 1.249; 95% C.I. 1.001–1.619; p = 0.004) were independently associated with DR. In addition to these factors, another potential independent predictor for DR was represented by HDL cholesterol (O.R.: 1.042; 95% C.I.: 1.011–1.120; p = 0.014).

In the subgroup with overt CKD (eGFR <60 mL/min/1.73 m^2, n = 329), a strong association between both AER and eGFR with DR persisted (Table 2).

We thus further split this subgroup selecting only patients with eGFR <60 mL/min/1.73 m^2 and AER $\geq$0.030 g/24 h (n = 298). In this case, both eGFR and AER significantly varied between those with or without DR (median 46.9 vs. 50.6 mL/min/1.73 m^2; p = 0.012 and median 0.480 vs. 0.300 g/die; p = 0.005, respectively). This finding was also observed considering the subgroup of patients with only AER $\geq$0.030 g/die. Table 2 shows all data.

Consistent with our findings, the subgroup of retinopathic patients with eGFR >60 mL/min/1.73 m^2, considered both overall and in addition to a normoalbuminuric/albuminuric condition, did not show any statistically significant difference in terms of AER and eGFR with regard to those without DR.

Analysis according to DR classification stages

An analogous result was obtained considering the DR classification.

Table 1 Baseline characteristics of the entire cohort of study (n = 2068).

Parameter	Overall	No DR (n = 1633)	DR (n = 435)	p
Sex, n (%)				
M/F	1051 (50.2)/1017 (49.8)	824 (50.5)/809 (49.5)	227 (52.2)/208 (47.8)	0.523
Age (yrs), median [IQR]	66 [57–73]	65 [56–72]	68 [60–75]	<0.001
Smoke, n (%)	610 (29.6)	490 (30.2)	120 (27.6)	0.291
Waist circumference (cm), mean ± SD				0.652
M	102.9 ± 12.4	102.9 ± 12.4	102.6 ± 12.4	
F	102.2 ± 14.6	102.3 ± 14.8	101.9 ± 13.7	
BMI (kg/m^2), median [IQR]	29 [26–32.5]	29 [26.2–32.5]	29 [26–32.7]	0.563
Duration of diabetes (yrs), median [IQR]	8 [4–15]	8 [3–13]	12 [6–21]	<0.001
HbA1c, % (mmol/mol), mean ± SD	7.3 (56) ± 1.3	7.3 (56) ± 1.3	7.5 (59) ± 1.3	0.004
Hypertension (cutoff ≥ 130/80), n (%)	1185 (58.5)	945 (59)	240 (56.6)	0.368
Hypertension (cutoff ≥ 140/90), n (%)	600 (29.6)	470 (29.4)	130 (30.7)	0.601
Blood pressure (mmHg), mean ± SD				
Diastolic	78.7 ± 7.5	78.9 ± 7.6	77.9 ± 7.3	0.017
Systolic	129.6 ± 13.1	129.6 ± 13.3	130 ± 12.5	0.524
Creatinine (mg/dL), mean ± SD	0.92 ± 0.35	0.91 ± 0.33	0.97 ± 0.41	0.005
eGFR (CKD-EPI), median [IQR]	82.4 [67.1–94.3]	79.5 [62.5–92.4]	83.3 [68.3–94.4]	0.001
eGFR classes, n (%)				0.017
<60 mL/min/1.73 m^2	329 (16.8)	241 (15.6)	88 (21.3)	
60–90 mL/min/1.73 m^2	953 (48.7)	755 (48.9)	198 (47.8)	
>90 mL/min/1.73 m^2	675 (34.5)	547 (35.5)	128 (30.9)	
AER (g/die), median [IQR]	0.270 [0.116–0.420]	0.270 [0.120–0.370]	0.270 [0.098–0.510]	0.099
Cholesterol (mg/dL), mean ± SD				
Total	176.8 ± 37.1	177 ± 36.9	159.6 ± 35	0.592
HDL	46.7 ± 14	46.3 ± 14	45 ± 12.1	0.015
LDL	101.4 ± 33.7	101.9 ± 33.9	85.6 ± 32.2	0.251
Triglycerides (mg/dL), median [IQR]	124 [93–173]	125 [94–173]	122 [87–169.3]	0.170
DR diagnosis, n (%)				
Yes/No	435 (21)/1633 (79)	–	–	n.a.
Diabetes therapies, n (%)				
Insulin	544 (26.4)	359 (22)	185 (42.6)	<0.001
DPP-IV inhibitors	507 (24.6)	391 (24)	116 (26.7)	0.251
GLP-1 agonists	95 (4.6)	74 (4.5)	21 (4.8)	0.801
SGLT2 inhibitors	61 (3)	48 (3)	13 (3)	0.994
Sulfonylureas/Glinides	499 (24.2)	386 (23.7)	113 (26)	0.323
Metformin	1299 (62.9)	1049 (64.4)	250 (57.5)	0.008
Other pharmacological therapies, n (%)				
ACE inhibitors	548 (26.6)	418 (25.7)	130 (29.9)	0.081
Sartanics	643 (31.2)	510 (31.4)	133 (30.6)	0.746
Composite variable (ACEi/ARBs)	1144 (55.6)	894 (55)	250 (57.5)	0.367
Statins	1131 (54.8)	257 (59.2)	874 (53.7)	0.040

Data are expressed as either number and percentage, or median and interquartile range (IQR) or mean ± SD. n.a.: not applicable.
M: Male; F: Female; SD: Standard Deviation; IQR: interquartile range; BMI: Body Mass Index; HbA1c: Glycated hemoglobin; HDL: High-Density Lipoprotein Cholesterol; LDL: Low-Density Lipoprotein Cholesterol; GFR: glomerular filtration rate; AER: Albumin Excretion Rate; DR: Diabetic Retinopathy.

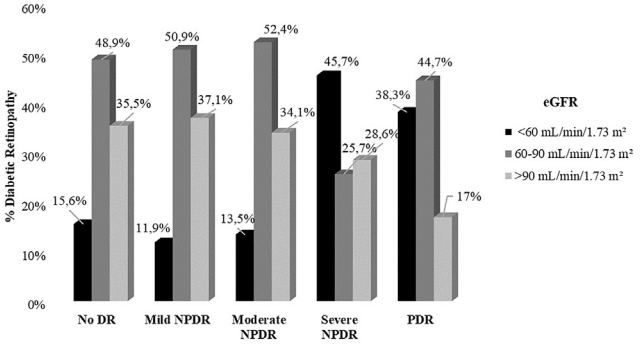

Figure 1 Distribution, according to the type of DR, based on ETDRS grade scale, in the study population according to the three subgroups of glomerular filtrate.

In addition, the comparison between the composite of all NPDR forms and PDR did not show any significant difference with regard to eGFR and AER.

Although the comparison between the composite of NPDR and PDR did not show significant differences in eGFR and AER, we performed a further analysis on the single stages of NPDR, according to the ETDRS classification: mild, moderate, and severe NPDR and proliferative DR (PDR). Our initial findings were confirmed by this sub-analysis.

In particular, AER was significantly higher among subjects with either PDR or severe NPDR with regard to mild NPDR. Additionally, eGFR was significantly lower among subjects with PDR or severe NPDR with regard to mild NPDR.

In addition, the comparison between the moderate and either severe NPDR or PDR showed significant differences both in eGFR and in AER.

Table 2 Association between renal function and diabetic retinopathy according to presence/absence of DR.

In the subpopulation with eGFR <60 mL/min/1.73 m^2 (n = 329)			
	DR (n = 88)	No DR (n = 241)	
Glomerular filtrate (CKD-EPI), median [IQR]	46.4 [38.6–54.1]	50.6 [42.4–56.5]	0.007
AER, g/die (median [IQR])	0.440 [0.163–0.817]	0.270 [0.111–0.516]	0.009
In the subgroup with eGFR <60 mL/min/1.73 m^2 and AER ≥0.030 g/24 h (n = 298)			
	DR (n = 77)	No DR (n = 221)	
Glomerular filtrate (CKD-EPI), median [IQR]	46.9 [38.8–54.7]	50.6 [43–56.7]	0.012
AER, g/die (median [IQR])	0.480 [0.195–0.885]	0.300 [0.135–0.540]	0.005
In the subgroup with AER ≥0.030 g/24-h (n = 1723)			
	DR (n = 351)	No DR (n = 1372)	
Glomerular filtrate (CKD-EPI), median [IQR]	78.4 [62–97.9]	82.1 [67.7–94]	0.002
AER, g/die (median [IQR])	0.300 [0.150–0.579]	0.270 [0.150–0.418]	0.002

No differences were instead observed between mild and moderate NPDR in terms of eGFR, as well as between severe NPDR and PDR.

These results were further confirmed in the subpopulation with eGFR <60 mL/min/1.73 m^2. Particularly, AER was significantly higher among subjects with either PDR or severe NPDR with regard to mild NPDR. In addition, AER showed significant difference between severe and moderate NPDR, as well as between moderate NPDR and PDR. No differences were instead observed between severe NPDR and PDR.

Finally, in the subpopulation with eGFR <60 mL/min/1.73 m^2 and AER ≥0.030 g/24 h, AER was significantly higher among patients with severe NPDR than among those with either mild or moderate NPDR. No other statistically significant association was found among the other subgroups. All data are shown in Tables 3a and b.

Discussion

The natural history of CKD in diabetes represents a debated issue in the last years. The previous dogma codified in the classification of DN into five grades and put in a mandatory way a pathological AER in a phase that preceded the progressive decline of eGFR until end-stage renal disease [17]. This classification was born from observation in type 1 diabetes, but it was used in T2DM also.

Recently, many observations suggested that a very large proportion of patients with T2DM with eGFR <60 mL/min/1.73 m^2 do not have a micro- or macroalbuminuria [11]. Actually, the reason for this new entity of diabetic CKD is not well known. The exclusion of other diseases that can drive to CKD, such as hypertension or glomerulonephritis, do not justify the apparently recent appearance of this nonalbuminuric nephropathy in T2DM.

It was recently hypothesized that a better glycemic and blood pressure control, in particular by using drugs inhibiting the renin-angiotensin system (RAS), could have modified the natural history of the renal damage in diabetes [12]. Actually, these drugs are very effective in stopping or reducing the renal escape of albumin and allow for a regression of albuminuria [18]. In this way, they strongly act in primary and secondary prevention of albuminuria. Instead, RAS inhibitors are effective in lowering the progression of CKD, but they do not improve eGFR [19].

Table 3a Association between renal function and diabetic retinopathy according to the ETDRS classification of DR.

In the whole study population (n = 2068)				
	NPDR (n = 336)			PDR (n = 99)
	Mild (n = 165)	Moderate (n = 133)	Severe (n = 38)	
eGFR (CKD-EPI), median [IQR]	83.8 [68.3–95.1]	84.9 [68.2–93.2]	64.5 [47.5–95.6]*	65.4 [49.8–82.9]*
AER, g/die (median [IQR])	0.101 [0.039–0.180]	0.360 [0.270–0.559]	0.938 [0.288–1.300]*	0.498 [0.330–1.013]*
In the subpopulation with eGFR <60 mL/min/1.73 m^2 (n = 329)				
	NPDR (n = 52)			PDR (n = 36)
	Mild (n = 19)	Moderate (n = 17)	Severe (n = 16)	
eGFR (CKD-EPI), median [IQR]	48.5 [41.3–53.6]	48.7 [39.7–55.6]	46.9 [35.1–54.8]	42.5 [37–54.9]
AER, g/die (median [IQR])	0.058 [0.028–0.144]	0.345 [0.172–0.559]	0.817 [0.283–1.091]*	0.608 [0.438–1.080]*
In the subgroup with eGFR <60 mL/min/1.73 m^2 and AER ≥0.030 g/24 h (n = 298)				
	NPDR (n = 43)			PDR (n = 34)
	Mild (n = 13)	Moderate (n = 16)	Severe (n = 14)	
eGFR (CKD-EPI), median [IQR]	49.3 [40.9–53.8]	48.8 [42.7–56.4]	46.9 [32.9–53.1]*	42.6 [37.5–55]
AER, g/die (median [IQR])	0.087 [0.044–0.150]	0.345 [0.172–0.559]	0.817 [0.283–1.091]*	0.608 [0.438–1.080]

*$p < 0.05$ for what concerns differences between mild/moderate NPDR and severe NPDR/PDR, respectively.

Table 3b Association between renal function and diabetic retinopathy according to the ETDRS classification of DR.

	eGFR, p-value	AER, p-value
In the whole study population (n = 2068) [mild NPDR − n = 165, moderate NPDR − n = 133, severe NPDR − n = 38, PDR − n = 99]		
Mild NPDR vs. severe NPDR	<0.001	<0.001
Mild NPDR vs. PDR	0.005	<0.001
Moderate NPDR vs. severe NPDR	0.010	<0.001
Moderate NPDR vs. PDR	<0.001	p < 0.001
In the subpopulation with eGFR <60 mL/min/1.73 m^2 (n = 329) [mild NPDR − n = 35, moderate NPDR − n = 22, severe NPDR − n = 8, PDR − n = 27]		
Mild NPDR vs. severe NPDR	0.256	0.001
Mild NPDR vs. PDR	0.179	0.015
Moderate NPDR vs. severe NPDR	0.768	0.006
Moderate NPDR vs. PDR	0.476	0.025
In the subgroup with eGFR <60 mL/min/1.73 m^2 and AER ≥0.030 g/24 h (n = 164) [mild NPDR − n = 27, moderate NPDR − n = 12, severe NPDR − n = 5, PDR − n = 14]		
Mild NPDR vs. severe NPDR	0.109	<0.001
Mild NPDR vs. PDR	0.351	0.201
Moderate NPDR vs. severe NPDR	0.874	0.041
Moderate NPDR vs. PDR	0.179	0.366

NPDR: nonproliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; AER: albumin excretion rate.

Our findings highlighted that both eGFR and AER were independently associated with DR.

In particular, eGFR was significantly lower in subjects with DR with regard to those without retinopathy. Moreover, in retinopathic subjects with renal failure (eGFR <60 mL/min/1.73 m^2), AER was significantly higher than in those without DR. This association was confirmed in the subpopulation with CKD and albuminuria.

Interestingly, in patients with severe NPDR and PDR and an eGFR <60 mL/min/1.73 m^2, AER was higher and eGFR was lower than those in patients with either mild or moderate NPDR. Conversely, in the presence of CKD and albuminuria, only AER was higher in the subgroup with severe DR.

Altogether, these data indicate that in patients with T2DM with a moderate or severe CKD, the AER is related to the risk of DR. This association is confirmed particularly in albuminuric nephropathic subjects and, above all, in those with more severe DR.

Unexpectedly, the highest prevalence of DN appears in the group of subjects with GFR within 60–90 ml/min/1.73 m^2. Thus, the prevalence of DR in the studied population is not distributed according to a linear model in relation to GFR. Notably, subjects with GFR<60 ml/min/1.73 m^2 assumed more frequently ACEi or ARBs than subjects with GFR within 90–60 ml/min/1.73 m^2. Therefore, it is suggestive to hypothesize a protective action of these drugs on DR [20]. However, our findings confirm the previous observation that GFR values < 99 ml/min/1.73 m^2 correlate with an increased risk of DR [21].

Actually, our study confirms the previous data reported by Fioretto et al. on patients with T2DM about the correlation between severe DR and albuminuria [22].

Recently, Man et al. affirmed that the association between glomerular filtrate and DR remained unclear, although suggesting that lower levels of eGFR were associated with both the presence and severity of DR [23]. Our results corroborate this hypothesis, also in accordance with recent studies [24].

Instead, Zhang et al. proved a better association between DR and AER rather than with eGFR, although both represent important DR risk factors [25], data also confirmed by our findings. Nevertheless, the association between AER and DR in clinical studies should be studied more in depth, as it is still controversial [26].

A recent interesting population-based, cross-sectional study showed that high urine albumin-tocreatinine ratio (UACR) and/or low eGFR appeared to be associated with DR in patients with T2DM [27]. Unfortunately, these data were obtained from a primary healthcare electronic database of medical records, therefore not directly from centers of secondary care, in the context of a study designed with this aim. Moreover, no data were available about the relationship between DN and DR, according to ETDRS classification of DR.

Therefore, it is intriguing to hypothesize that proteinuria might represent a link between DR and DN, similarly between DN and CVD [28,29]. Interestingly, a cluster of micro/macrovascular risk seems to be the main target for primary and secondary prevention in patients with T2DM.

However, this study presents some limitations. First, the cross-sectional nature of this investigation precludes any cause–effect relationship. In addition, the cohort is not extremely large. Nevertheless, this is a multicentric study and the RD and CKD prevalence were observed to be very similar to the National and Western Countries rates, making the cohort representative to be studied.

In conclusion, DR was independently associated with the classic cluster of renal damage in diabetes (GFR <60 mL/min/1.73 m^2 and AER >0.030 g/24 h) despite the high prevalence of the new nonalbuminuric phenotype of DKD. In particular, patients with both albuminuria and CKD had AER and GFR strongly associated with DR. Patients with severe NPDR showed an AER that is

significantly higher than that in those with mild/moderate NPDR.

These findings, which report data from secondary care centers, seem to suggest a strict relationship between DR and albuminuria in T2DM with CKD.

However, further longitudinal observations are needed for a more in-depth analysis of the role of albuminuria in both the development and the progression of DR.

Authors' contributions

Conception and design: FC Sasso and A Gelso.

Development of methodology: FC Sasso, A Gelso, C Costagliola, and V Bono.

Acquisition of data: V Bono, R Galiero, C Acierno, A Caturano, C de Sio, and NO BLIND Study Group.

Analysis and interpretation of data: PC Pafundi, FC Sasso, and R Minutolo.

Writing, review, and/or revision of the manuscript: PC Pafundi, FC Sasso, A Gelso, C Costagliola, L Rinaldi, R Marfella, C Sardu, R Galiero, C Acierno, A Caturano, C de Sio, T Salvatore, L De Nicola, R Minutolo, R. Nevola, and LE Adinolfi.

Study supervision: FC Sasso, PC Pafundi, and R Minutolo.

All authors read and approved the final draft of the manuscript.

Conflicts of interest

None of the authors have any financial/conflicting interests to disclose.

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Statement of informed consent

Written informed consent was obtained before the examination from each patient, as well as the approval from our institutional ethics committee.

Appendix

No-Blind Involved centers.

(1) Diabetology Complex Operative Unit (C.O.U.) of the A.O.U. of University of Campania (Prof. Dario Giugliano - Dr. Maria Ida Maiorino);

(2) Diabetology Complex Operative Unit (C.O.U.) of University of Naples Federico II (Prof. Gabriele Riccardi – Dr. Lutgarda Bozzetto);

(3) Internal Medicine Complex Operative Unit (C.O.U.) of University of Naples Federico II (Dr. Vincenzo Guardasole);

(4) ASL Napoli 1 (Dr. Rosaria Di Palo);

(5) ASL Napoli 2 (Dr. Ornella Carbonara);

(6) ASL Napoli 2 (Dr. Michele Riccio);

(7) ASL Napoli 3 (Dr. Giosetta De Simone);

(8) ASL Napoli 3 (Dr. Luigi Lucibelli);

(9) ASL Salerno (Dr. Stefano Masi).

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