Acta Diabetol
DOI 10.1007/s00592-014-0650-7

REVIEW ARTICLE

Updating the natural history of diabetic nephropathy

Giuseppe Pugliese

Received: 9 August 2014 / Accepted: 2 September 2014

Abstract Diabetic nephropathy (DN) is a major cause of morbidity and mortality in patients with both types of diabetes and the leading cause of end-stage renal disease (ESRD) worldwide. The classical, five-stage natural history of DN, after an initial phase of hyperfiltration, is characterized by a progressive increase of albuminuria from normoalbuminuria to proteinuria, followed by a decline of glomerular filtration rate (GFR). Accumulating evidence indicates that clinical course of DN has changed profoundly, likely as a consequence of changes in treatment. In fact, remission/regression of microalbuminuria is a common feature of both type 1 and 2 diabetes which far outweighs progression to proteinuria. Moreover, GFR loss has been shown to occur independently of albuminuria or even in the absence of it. Nonalbuminuric renal impairment probably represents a different pathway to loss of renal function, which might recognize different pathogenic mechanisms, prognostic implications, and possibly therapeutic measures, as compared with the albuminuric pathway. The nonalbuminuric phenotype might be related to macroangiopathy instead of microangiopathy and/or be the consequence of repeated and/or unresolved episodes of acute kidney injury, even of mild degree. Reduced GFR and albuminuria are both powerful risk factor for cardiovascular events, whereas albuminuria appears to predict death and progression to ESRD better than GFR loss. Finally, it is unclear whether reduced GFR and albuminuria warrant different interventions and whether GFR decline may also regress in response to treatment, as proteinuria does. Further epidemiological, pathologic, pathophysiological, and intervention studies are needed to clarify the distinctive features of nonalbuminuric renal impairment.

Keywords Chronic kidney disease · Albuminuria · GFR decline · Cardiovascular disease

Abbreviation

DN	Diabetic nephropathy
ESRD	End-stage renal disease
CVD	Cardiovascular disease
GFR	Glomerular filtration rate
BP	Blood pressure
AER	Albumin excretion rate
RAS	Renin–angiotensin system
eGFR	Estimated GFR
HbA_{1c}	Hemoglobin A_{1c}
TNFR	Tumor necrosis factor receptor
CKD	Chronic kidney disease
NHANES	National Health and Nutrition Examination Survey
DEMAND	Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes
UKPDS	United Kingdom Prospective Diabetes Study
DCCT/EDIC	Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications
NEFRON	National Evaluation of the Frequency of Renal Impairment cO-existing with NIDDM
RIACE	Renal Insufficiency And Cardiovascular Events

Managed by Massimo Porta.

G. Pugliese (✉)
Department of Clinical and Molecular Medicine, "La Sapienza" University of Rome, Via di Grottarossa, 1035-1039, 00189 Rome, Italy
e-mail: giuseppe.pugliese@uniroma1.it

Published online: 09 October 2014

PERCEDIME2	Prevalence of chronic kidney disease in patients with type 2 diabetes in Spain
ADVANCE	Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
MDRD	Modification of Diet in Renal Disease
CKD-EPI	CKD-Epidemiology Collaboration
ARIC	Atherosclerosis Risk in Communities
AKI	Acute kidney injury
KDIGO	Kidney Disease Improving Global Outcomes
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan

Introduction

Diabetic nephropathy (DN) is a major cause of morbidity and mortality in patients with both type 1 and 2 diabetes, with approximately one-third of them suffering from this long-term complication of diabetes [1]. Due to its increasing incidence [2], diabetes mellitus has become the leading cause of end-stage renal disease (ESRD) worldwide [3]. In addition, the marked reduction in the incidence of cardiovascular disease (CVD), but not of ESRD, observed in the last two decades might have favored progression to ESRD by increasing survival of diabetic subjects [4].

A growing body of evidence has indicated that the natural history of DN has changed profoundly during the last decades. This article will review the most relevant literature on this matter, with particular reference to the emergence of the nonalbuminuric phenotype of renal impairment, especially in type 2 diabetes.

Classical view of the natural history of DN

The classical, five-stage natural history of DN (Fig. 1), as depicted by Mogensen [5] mainly, but not exclusively, from studies in patients with type 1 diabetes, starts with hyperfiltration, the independent role of which in the subsequent rise of albuminuria and decline of GFR remains to be elucidated [6]. The second stage, called "silent nephropathy", is characterized by normoalbuminuria or intermittent episodes of microalbuminuria. While the majority of patients with diabetes remain in this phase for their lifetime, approximately one-third of them progress to the third stage, called "incipient nephropathy" and

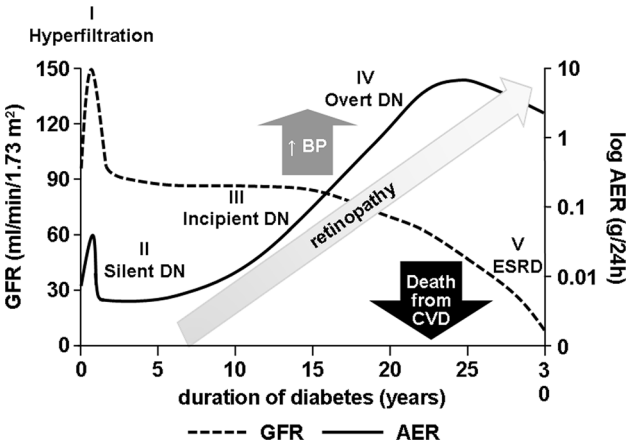

Fig. 1 Classical, five-stage natural history of DN. Stage I (Hyperfiltration): increased GFR associated with nephromegaly and possibly with transient increase of AER; Stage II (Silent DN): GFR and AER return to normal levels, except for transient episodes of microalbuminuria; Stage III (Incipient DN): microalbuminuria becomes persistent; Stage IV (Overt DN): microalbuminuria progresses to macroalbuminuria, BP increases, and GFR starts to decline; Stage V (ESRD): GFR loss progresses at variable rate to ESRD requiring renal replacement therapy, unless death occurs, mainly for CVD. The increase of albuminuria is paralleled by progression of retinopathy. *DN* diabetic nephropathy, *GFR* glomerular filtration rate, *AER* albumin excretion rate, *CVD* = cardiovascular disease, *ESRD* end-stage renal disease

characterized by persistent microalbuminuria. This stage is followed by the fourth one, called "overt nephropathy" and characterized by macroalbuminuria or dip-stick-positive proteinuria, declining glomerular filtration rate (GFR) and elevated blood pressure (BP). Finally, GFR loss progresses at variable rate to ESRD, the fifth and last stage. The increase of albuminuria is usually paralleled by progression of retinopathy, the other main microvascular complication of diabetes.

At least two of these paradigms have been recently challenged, i.e., (1) that microalbuminuria invariably progresses to macroalbuminuria and (2) that GFR loss starts only after macroalbuminuria has developed.

New paradigms in the natural history of DN

Earlier studies in type 1 diabetes showed that the vast majority of patients with microalbuminuria progress to macroalbuminuria over 6–14 years [7–10]. The predictive power of microalbuminuria was lower in subjects with type 2 diabetes, due to the very high death rate from CVD, which censored the natural history of DN in these individuals. In fact, a retrospective analysis reported a 77.6 % 10-year mortality rate, mostly from CVD, and a 22.4 % progression to proteinuria [11], whereas three subsequent prospective studies with much lower mortality rates

showed an average risk of progression of ~40 % [12–14]. In contrast, more recent studies have shown that remission/regression of microalbuminuria is a common feature which far outweighs progression to proteinuria (Table 1).

In type 1 diabetes, the Joslin Study of the Natural History of Microalbuminuria reported a 58 % 6-year cumulative incidence of regression, as defined as a 50 % reduction in urinary albumin excretion rate (AER) from one two-year period to the next; of the 220 subjects followed for 8 years, 99 (45 %) remained microalbuminuric, 88 (40 %) reverted to normoalbuminuria, and 33 (15 %) progressed to proteinuria [15]. Likewise, of 352 microalbuminuric patients from the EURODIAB Prospective Complications Study, 125 (50.6 %) remained microalbuminuric, 178 (35.5 %) reverted to normoalbuminuria, and 49 (13.9 %) progressed to macroalbuminuria [16]. Moreover, of 277 newly diagnosed outpatients consecutively admitted to a tertiary referral center, 79 subjects developed persistent microalbuminuria during a median follow-up of 7.5 years; of them 24 (30.4 %) remained in the microalbuminuric range, 28 (35.4 %) regressed to normoalbuminuria, and 27 (34.2 %) progressed further to persistent macroalbuminuria [17].

In type 2 diabetes, the Steno-2 Study showed that, of 151 microalbuminuric subjects, 58 (38.4 %) remained microalbuminuric, whereas 46 (30.5 %) remitted to normoalbuminuria and 47 (31.1 %) progressed to macroalbuminuria over a 7.8-year follow-up [18]. These results were confirmed in two cohorts of Japanese patients with type 2 diabetes. A cumulative incidence of 51 % for remission and 54 % for regression was observed in 113 patients followed for 8 years, whereas the frequency of progression to overt proteinuria was 28 % [19]. In 94 microalbuminuric patients from the Kashiwa Study, remission to normoalbuminuria and progression to macroalbuminuria occurred in 20 and 16 subjects, respectively, over a 8-year follow-up [20].

Remission/regression of microalbuminuria has been attributed to the increasingly widespread use of blockers of the renin-angiotensin system (RAS), though a relation with these drugs has emerged in some studies [18, 19], but not in others [15, 20, 21]. Independent correlates were also lower levels of CVD risk factors [15, 16, 18–20], i.e., those factors which, if not adequately controlled, predict development of microalbuminuria in patients with normoalbuminuria [12, 16, 17, 20, 21].

Another paradigm that has been recently challenged is that progression microalbuminuria to macroalbuminuria precedes decline of GFR. In fact, a new clinical phenotype has been identified in subjects with type 1 diabetes, the "early renal function decline", which occurs soon after or even before the onset of microalbuminuria, is not conditional on progression to macroalbuminuria, can be diagnosed using serial measurement of cystatin C, and recognizes unique determinants [22].

In fact, of 267 normoalbuminuric and 301 microalbuminuric patients with type 1 diabetes from the Joslin Study of the Natural History of Microalbuminuria, 9 % and 31 %, respectively, showed this phenotype, as defined as an annual decline in estimated GFR (eGFR) >3.3 %. Moreover, the extent of eGFR change was much higher in microalbuminuric versus normoalbuminuric subjects and accelerated loss of eGFR occurred independently of changes in albuminuria, though it was more frequent in patients who progressed to macroalbuminuria and less frequent in those who regressed to normoalbuminuria (68 vs. 16 %) [23]. A more recent analysis of 286 normoalbuminuric and 248 microalbuminuric patients from the Joslin cohort confirmed a 10 and 35 % prevalence of early eGFR decline, respectively, in these individuals [24]. Decliners and nondecliners could be identified also among proteinuric patients. In fact, of 161 patients, 75 showed a eGFR decline below 3.5 ml/min/1.73 m^2 during a 5–18-year follow-up, whereas, in the remaining 86 subjects, loss of renal function was more pronounced. Interestingly, the estimate of early slope predicted the risk of ESRD during subsequent follow-up better than baseline hemoglobin A_{1c} (HbA_{1c}), BP, or albuminuria [25].

Age and baseline HbA_{1c}, but not smoking habits and treatment with RAS blockers, were independent predictors of renal function decline in nonproteinuric patients [23, 24]. An independent association of eGFR loss with inflammatory markers, including tumor necrosis factor receptor (TNFR) 1 and 2, as well as with high-normal levels of uric acid was also observed [24]. Independent correlates of early eGFR loss were similar in proteinuric subjects, with a lower cumulative risk of ESRD in those showing a decrease in HbA_{1c} than in those with stable or increasing values [26] and an association with circulating TNFR-2 [27] and kidney injury molecule 1 [28]. Other reports showed that neutrophil gelatinase-associated lipocalin increases before the onset of microalbuminuria in patients with type 1 diabetes [29] and that high molecular weight adiponectin is an independent predictor of decline of renal function in those with type 2 diabetes [30]. Collectively, these findings prompt the hypothesis that this new phenotype is associated with inflammation and tubular injury rather than with glomerular damage, of which albuminuria is an established marker, thus recognizing different determinants as compared with the classical model of DN [22].

While these studies showed that early loss of eGFR occurred predominantly in albuminuric patients with type 1 diabetes, with low prevalence among normoalbuminuric subjects, other reports have suggested that renal dysfunction often develops in the absence of albuminuria. Two studies published in the 1990s had already reported that reduction of creatinine clearance may occur in patients with both types of diabetes who remain normoalbuminuric [31, 32]. These pioneer observations have been confirmed on a larger scale

Table 1 Studies on the course of microalbuminuria in patients with type 1 and/or 2 diabetes

Study, authors (reference)	Diabetes type	Microalbuminuric patients, *n*	Follow-up, years	Remitted to normo, *n* (%)	Remained micro, *n* (%)	Progressed to macro, *n* (%)	Factors associated with remission to microalbuminuria
Perkins et al. [15]	1	386 (220)*	8	88 (40)	99 (45)	33 (15)	Microalbuminuria of short duration, salutary levels of HbA_{1c} (<8 %), and low levels of systolic BP (<115 mm Hg), total cholesterol (<5.12 mmol/l), and triglycerides (<1.64 mmol/l)
Giorgino et al. [16]	1	352	7	178 (35.5)	125 (50.6)	49 (13.9)	Diabetes duration, baseline AER, and, after adjusting for diabetes duration, HbA_{1c} and AER, waist-to-hip ratio and incidence of peripheral neuropathy
Hovind et al. [17]	1	79	7.5	28 (35.4), 15 transiently, 13 permanently	24 (30.4)	27 (34.2)	ND
Gaede et al. [18]	2	151	7.8	46 (30.5)	58 (38.4)	47 (31.1)	Lower decline of eGFR, initiation of therapy with RAS blockers, and decrease of HbA_{1c}
Araki et al. [19]	2	216 (113)*	8	26 (23.0)	66 (58.4)	21 (18.6)	Use of RAS blockers, microalbuminuria of short duration, and lower tertiles for HbA_{1c} (<6.95 %), and systolic BP (<129 mmHg)
Yamada et al. [20]	2	94	8	20 (21.3)	58 (61.7)	16 (17.0)	Baseline AER, and lower achieved systolic BP
Tabaei et al. [21]	1 + 2	23 (16)*	7	9 (56.3)	6 (37.5)	1 (6.2)	Poor glycemic control and diabetes duration between 10 and 14 years

RAS renin–angiotensin system, *HbA_{1c}* hemoglobin A_{1c}, *BP* blood pressure, *AER* albumin excretion rate, *ND* not determined, *eGFR* estimated glomerular filtration rate

* Number of patients followed for the entire period

in the last decade, in which this nonalbuminuric pathway to chronic kidney disease (CKD) has been shown to occur not only in patients with type 1 diabetes, but also, and to a higher extent, in those with type 2 diabetes (Table 2).

In fact, a cross-sectional analysis of adults with type 2 diabetes from the Third National Health and Nutrition Examination Survey (NHANES III) showed that 36.1 % of subjects with renal impairment were normoalbuminuric and that albuminuria and retinopathy were both absent in 29.8 % of diabetic patients with eGFR below 60 ml/min/1.73 m^2 [33]. Moreover, among 301 patients with type 2 diabetes attending an outpatient clinic in Australia, 39.4 % of those with GFR below 60 ml/min/1.73 m^2, as measured by an isotopic method, were found to be normoalbuminuric [34]. Similar figures were reported in a multicenter, global, cross-sectional study, the Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes (DEMAND); of the 11,573 patients with available data, 22.3 % had an eGFR below 60 ml/min/1.73 m^2 and 40.1 % of them were normoalbuminuric [35].

Longitudinal analysis of patients with type 2 diabetes from the United Kingdom Prospective Diabetes Study (UKPDS) without albuminuria and with normal creatinine at baseline showed that, of the 1,132 individuals who developed renal impairment over a 15-year follow-up, 67.1 % were normoalbuminuric and 50.8 % remained in this category, whereas 16 % became microalbuminuric thereafter [36]. Similar findings, though with lower figures, were observed in the longitudinal analysis of patients with type 1 diabetes from the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC), in which 23.8 % of the 89 subjects developing renal impairment during the 19-year follow-up were normoalbuminuric [37].

Recent large-scale observational studies in subjects with type 2 diabetes reported higher prevalence values of the nonalbuminuric phenotype than those previously observed in the NHANES III cohort, which date back to the period from 1988 to 1994 [33], but similar to those found more recently in the UKPDS [36], thus supporting the concept that the prevalence of the nonalbuminuric phenotype is increasing. In fact, the National Evaluation of the Frequency of Renal Impairment co-existing with NIDDM (NEFRON) study, an incident-driven survey in the primary care setting, showed that 23.1 % had an eGFR < 60 ml/min/1.73 m^2 and 55 % of them had an AER that was persistently in the normal range [38]. The Renal Insufficiency and Cardiovascular Events (RIACE) Italian multicenter study reported that 56.6 % subjects with renal impairment were normoalbuminuric [39]. The prevalence of CKD in patients with type 2 diabetes in Spain (PERCEDIME2) study, another cross-sectional survey in primary care, showed that 18.0 % of patients had renal dysfunction and that 69.4 % of them had normoalbuminuria [40]. Finally, the NHANES 2001–2008, 51.8 % of patients with reduced eGFR were normoalbuminuric [41]. In addition, a high prevalence of the nonalbuminuric phenotype was also detected in diabetic samples from

Table 2 Longitudinal and cross-sectional studies on the prevalence of microalbuminuric renal impairment in patients with type 1 or 2 diabetes

Study, authors (reference)	Diabetes type	Patients with diabetes, *n*	Follow-up, years	Patients with renal impairment*		
				Total, *n* (% of cases)	Nonalbuminuric, *n* (% of total)	With neither albuminuria nor retinopathy, *n* (% of total)
Longitudinal studies						
Molitch et al. [37]	1	1,439	19	89 (6.2)	21 (23.6)	ND
Retnakaran et al. [36]	2	4,006	8	1,132 (28.3)	575 (50.8)	
Cross-sectional studies						
Kramer et al. [33]	2	1,197	NA	171 (14.3)	60 (35.1)	51 (29.8)
MacIsaac et al. [34]	2	301	NA	109 (36.2)	43 (39.4)	32 (29.4)
Dwyer et al. [35]	2	11,573	NA	2,586 (22.3)	1,038 (40.1)	ND
Thomas et al. [38]	2	3,983	NA	920 (23.1)	506 (55.0)	ND
Penno et al. [39]	2	15,773	NA	2,959 (18.8)	1,673 (56.6)	1,280 (43.3)
Rodriguez-Poncelas et al. [40]	2	1,145	NA	206 (18.0)	143 (69.4)	ND
Mottl et al. [41]	2	2,798	NA	575 (20.6)	298 (51.8)	ND
Ninomiya et al. [42]	2	10,640	NA	2,033 (19.1)	1,252 (61.6)	ND
Drury et al. [43]	2	9,795	NA	519 (5.3)	307 (59.2)	ND

ND not determined, *NA* not applicable, *eGFR* estimated glomerular filtration rate

* eGFR < 60 ml/min/1.73 m^2

interventional studies, such as the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. In the ADVANCE study, a factorial, randomized, controlled trial evaluating the effects of BP lowering and intensive blood glucose control on vascular outcomes, 61.6 % of 2,033 subjects with renal impairment had normoalbuminuria [42]. In the FIELD study, a double-blind placebo-controlled trial of fenofibrate, normoalbuminuria was observed in 59.3 % of the individuals with an eGFR < 60 ml/min/1.73 m^2 [43].

Despite accumulating evidence on the nonalbuminuric phenotype, one might argue that low GFR associated with normoalbuminuria is an artifact, due to the poor reliability of estimation of GFR and measurement of albuminuria. In fact, though widely used for both epidemiological and clinical purposes, equations for eGFR estimation may not be as precise as the more cumbersome and expensive methods for GFR measurement. However, a high concordance was found between GFR estimated with the Modification of Diet in Renal Disease (MDRD) Study equation and that measured by an isotopic method, and concordance was not lower, if any, among individuals with normoalbuminuria, as compared with those with micro- or macroalbuminuria [44]. Yet, the MDRD Study equation is known to underestimate GFR in subjects with values above 60 ml/min/1.73 m^2. In the RIACE cohort, comparison of estimates obtained with this formula with those calculated using the CKD–Epidemiology Collaboration (EPI) equation showed that prevalence of reduced eGFR was lower with the new method, which also provided a better definition of cardiovascular burden associated with CKD, but reclassification of patients was independent from the level of albuminuria [45]. With regard to albuminuria, measurement is affected by high intra-individual variability. However, when 4,062 RIACE participants who had multiple measurements were analyzed, concordance rate between the first value and the geometric mean was more than 90 % for all classes of albuminuria [46].

Nonalbuminuric renal impairment

Altogether, the above observations indicate that albuminuria and GFR loss may occur separately as complementary, if overlapping, or "twin" manifestations of kidney damage in diabetes [47]. This implies that albuminuria is unable to predict DN and progression to ESRD in all patients [48] and raises important questions on whether these two markers of renal dysfunction differ for pathogenic mechanisms, prognostic implications, and therapeutic measures [47].

Concerning pathogenic mechanisms, the main question is whether or not the albuminuric and nonalbuminuric phenotypes represent two different pathways. The demonstration of remission/regression of microalbuminuria raises the possibility that subjects with nonalbuminuric renal impairment had been microalbuminuric at some point of the natural history of nephropathy and have become normoalbuminuric as a consequence of treatment, particularly with RAS blockers. However, several lines of evidence suggest that the nonalbuminuric form follows a distinct pathway (Fig. 2). Firstly, the longitudinal analyses of the UKPDS and the DCCT/EDIC cohorts confirmed that GFR may decline in patients who had never experienced microalbuminuria [36, 37]. In addition, previous studies in patients with type 2 diabetes have shown that the independent correlates of reduced eGFR and albuminuria differ between each other [36, 49, 50] (Table 3). Finally, nonalbuminuric renal impairment was found to be associated with distinct features, as compared with the albuminuric forms. In the RIACE cohort, nonalbuminuric CKD patients were more frequently female and nonsmoker, but not older,

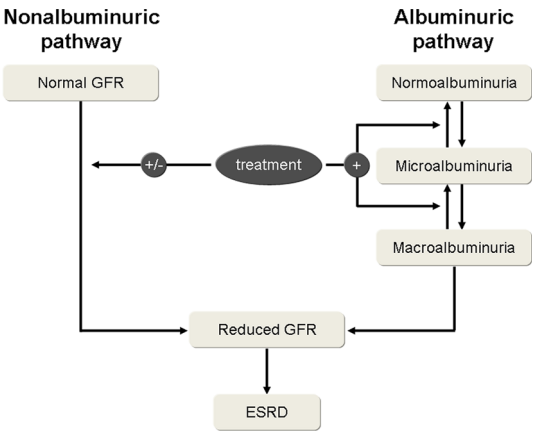

Fig. 2 Nonalbuminuric and albuminuric pathways to loss of renal function. The nonalbuminuric pathway is characterized by loss of GFR independently of albuminuria or even in the absence of it. The albuminuric pathway is characterized by progressive increase of albuminuria from normo- to macroalbuminuria, though this process may be halted or reversed. The nonalbuminuric and albuminuric phenotypes may represent two different pathways to loss of renal function. The nonalbuminuric phenotype might be due to prevailing macrovascular rather than microvascular lesions and/or to repeated or unresolved episodes of acute kidney injury, even of mild degree, whereas the albuminuric phenotype would be a classical manifestation of diabetic microangiopathy. Thus, the two phenotypes would be characterized by atypical vascular and/or tubulo-interstitial lesions versus typical glomerular lesions, respectively. Current treatment, which is more effective on albuminuria than on GFR loss, may favor predominance of the nonalbuminuric phenotype. However, it may also result in continuing GFR decline despite suppressed albuminuria, thus implying that the nonalbuminuric and albuminuric phenotypes are two variants of the same pathway. *GFR* glomerular filtration rate, *ESRD* end-stage renal disease

Table 3 Studies on the independent correlates of reduced eGFR and albuminuria

Study, authors (reference)	Reduced eGFR	Albuminuria
Retnakaran R et al. [36]	Female sex	Male sex
	Lower waist circumference	Higher waist circumference
	Age	Increased triglycerides, LDL cholesterol, HbA_{1c}, and white blood cells
	Increased insulin sensitivity	Former or current smoking status
	Presence of sensory neuropathy	Presence of retinopathy
Yokoyama H et al. [49]	Age	Male sex
	Diabetes duration	Higher BMI and HbA_{1c}
	Lower HbA_{1c}	Presence of retinopathy and neuropathy
	Hyperlipidaemia	
	Nonsmoking status	
Afghahi H et al. [50]	Female sex	Higher BMI and HbA_{1c}
	Lower serum creatinine at baseline	Lower HDL cholesterol
		current smoking

eGFR estimated glomerular filtration rate; *HbA_{1c}* hemoglobin A_{1c}; *BMI* body mass index

and had lower levels of HbA_{1c}, but not longer diabetes duration, as compared with those with albuminuria, particularly if associated with reduced eGFR. Multiple regression analysis confirmed that the nonalbuminuric phenotype is associated with female gender, but not with HbA_{1c} [39]. In particular, it correlated neither with average HbA_{1c} nor with HbA_{1c}, variability, at variance with albuminuria alone, which correlated with both, and albuminuria plus reduced eGFR, which correlated with HbA_{1c} variability [51]. Moreover, the association of this phenotype with hypertension and retinopathy was weaker than that of the albuminuric forms. As in the NHANES III cohort, the majority of subjects with the nonalbuminuric phenotype did not have retinopathy and the combination of no albuminuria and no retinopathy was detected in 43.3 % of patients with an eGFR below 60 ml/min/1.73 m^2 [39]. As a consequence of the weak association of retinopathy with the predominant nonalbuminuric phenotype, only $\sim$15 % of patients with any CKD had advanced retinopathy, whereas any CKD was found in almost 60 % of subjects with advanced retinopathy [52]. Also in the NEFRON, female gender was associated with the nonalbuminuric phenotype [38], whereas, in the Atherosclerosis Risk in Communities (ARIC) study, the association between HbA_{1c} and incident CKD, though stronger in subjects with albuminuria and retinopathy, was observed even among participants without either abnormality [53]. A previous report in 660 patients with type 2 diabetes and normoalbuminuria showed that subjects with reduced eGFR had higher levels of insulin resistance, total and LDL cholesterol, and triglycerides, and higher prevalence of the metabolic syndrome as compared with those with nonreduced eGFR [54]. Another report in 89 patients with type 1 and type 2 diabetes and eGFR below 60 ml/min/1.73 m^2 showed that subjects with normoalbuminuria were more frequently female and nonsmoker, had shorter diabetes duration, higher HDL cholesterol and hemoglobin levels, and lower prevalence of CVD and retinopathy, as compared with patients with micro- or macroalbuminuria, though for some of these comparisons statistical significance was borderline [44].

The weak association of nonalbuminuric renal impairment with retinopathy and the lack of association with HbA_{1c} of this phenotype have suggested that the prevailing pathology is macroangiopathy instead of microangiopathy [39]. In this view, the increasing prevalence of the nonalbuminuric form might be related to changes in treatment over the last decades, including the tighter control of risk factors and possibly the increasingly widespread use of RAS blockers, which could have been more effective on microvascular than on macrovascular disease. However, this is not the case in type 1 diabetes, as shown by a biopsy study from Caramori et al. [55], in which normoalbuminuric subjects with low GFR had typical (glomerular) microangiopathic lesions that were more pronounced than in those with normal GFR. Conversely, a recent study in patients with type 2 patients, reduced eGFR, and various degree of albuminuria showed that, while typical glomerulopathy was observed in virtually all subjects with micro- or macroalbuminuria, only half of the normoalbuminuric patients had typical lesions and almost all of them had varying degrees of arteriosclerosis [56]. This is consistent with a study showing that patients with reduced eGFR have increased intrarenal resistance index suggestive of small intrarenal artery disease, as compared with subjects with nonreduced eGFR [57]. However, this occurred irrespective of albuminuria [57], and an heterogeneity of renal pathology was previously observed also in microalbuminuric patients with preserved renal function [58], thus suggesting that macrovascular involvement may be a characteristic feature of patients with type 2 diabetes more than of those with the nonalbuminuric phenotype. Further, biopsy studies are required to clarify the pathological correlates of nonalbuminuric renal impairment in subjects with type 2 diabetes.

Another possibility is that this phenotype is produced by unresolved and/or repeated episodes of acute kidney injury

(AKI). Though associated with increased mortality, AKI has traditionally been considered as a benign condition ultimately resulting in full recovery of renal function in patients who survive from an acute episode, due to regeneration of tubular cells lost through apoptosis or necrosis. However, recent evidence has challenged this notion by showing that the regenerative potential of tubular progenitors is limited, with hypertrophy possibly prevailing over proliferation, and might be reduced in renal disorders including DN [59]. Thus, under certain circumstances, complete recovery of renal function might occur despite nephron loss and consequent reduction of renal reserve, due to hyperfiltration of uninjured nephrons, ultimately leading to progressive glomerulosclerosis and tubulointerstitial fibrosis [60]. In fact, several studies have demonstrated that AKI is a risk factor for future development (or progression) of CKD, depending on its severity, duration, and frequency [61] and that the slope of eGFR is not linear in up to one-third of patients [60]. Moreover, even mild, often unrecognized episodes of AKI, such as a 50- or 0.3-mg/dl increase in serum creatinine (i.e., Stage I of the Kidney Disease Improving Global Outcomes–KDIGO—classification), might result in CKD [62], especially in the presence of risk factors, which include advanced age, diabetes mellitus, hypertension, heart failure, pre-existing CKD, and low serum albumin [60, 61]. Indeed, creatinine levels fail to increase in a subset of patients with AKI, as identified by positivity of biomarkers [63]. In diabetic subjects, episodes of AKI might occur frequently, though often in a mild and unrecognized form, due to ischemic, infectious, toxic, or obstructive causes, thus leading to progressive eGFR decline independent of albuminuria. This hypothesis is supported by the observations that, in subjects with type 1 diabetes, early loss of eGFR is associated with markers of inflammations [24, 27] and tubular injury [28] and that circulating TNFR-1 and 2 predict ESRD in individuals with type 2 diabetes [64].

Regarding prognostic implications, the question is how GFR loss and albuminuria each affect prognosis in terms of CVD and renal outcomes. Data from the RIACE cohort [39] showed that the age- and gender-adjusted thresholds at which CVD burden increases in these individuals stand near to or within the normal range for both eGFR (78.2 ml/min/1.73 m^2) and albuminuria (10.5 mg/24 h). Moreover, the prevalence of any CVD was intermediate in the nonalbuminuric phenotype, i.e., higher than that of albuminuria alone and lower than that of albuminuria plus reduced eGFR. This was true especially for coronary events, which correlated more strongly with the nonalbuminuric phenotype than with the albuminuric forms, whereas the opposite was observed for cerebrovascular and peripheral events [65].

The ADVANCE study showed that, over a 4.3-year follow-up, the hazard ratio for CVD events was similar for reduced eGFR and albuminuria, whereas it was markedly higher when both abnormalities were present. Conversely, albuminuria alone appeared to be associated with higher risk for CVD deaths and renal events than reduced eGFR alone [42]. Similar results were previously obtained in a small study showing that, over a 38-month follow-up, no normoalbuminuric patient with reduced eGFR died or developed ESRD, as opposed to five patients with microalbuminuria and 17 with macroalbuminuria [44]. Likewise, the analysis of a population-based district diabetes registry showed that the age-independent annual eGFR decline was 0.3 % in normoalbuminuric, 1.5 % in microalbuminuric, and 5.7 % in macroalbuminuric patients with type 1 and 2 diabetes and mean eGFR above 75 ml/min/1.73 m^2 [66].

In keeping with these findings, the new KDIGO CKD classification, which is based on both eGFR and albuminuria instead of eGFR alone, reflects the fact that reduced eGFR may not be accompanied with albuminuria, that, if present, predicts worse renal and CVD outcomes [67].

Finally, concerning therapeutic measures, the main questions are whether albuminuria and GFR loss warrant targeted therapeutic interventions and whether treatment may halt or slow down eGFR decline as it does successfully with proteinuria. We do not have answers to these questions yet, due to the lack of intervention trials specifically targeting subjects with the nonalbuminuric phenotype.

On the one side, RAS blockade is more effective on proteinuria than on GFR loss, though rate of eGFR decline in proteinuric patients was lower with irbesartan than with amlodipine, even if it became evident only after 18 months of treatment [68]. Therefore, this intervention might not be successful in patients with nonalbuminuric renal impairment [47]. Moreover, treatment with RAS blockers increases susceptibility to renal ischemia induced by several causes (atherosclerosis, nonsteroidal anti-inflammatory drugs, sepsis, hypercalcemia, hepatorenal syndrome, immunosuppressants, radiocontrast agents, etc.) by preventing the rise of efferent arteriolar resistance [69].

On the other side and perhaps paradoxically, subjects with nonalbuminuric renal impairment might be the ones who are benefitting the most from RAS inhibition, because their proteinuria might have remitted. Interestingly, a relationship between a decrease in albuminuria and a decrease in eGFR has been demonstrated in some studies [15, 18] and a pooled analysis of interventional studies has shown that, in both types of diabetes, the initial decrease in albuminuria with treatment does not predict the subsequent decline in eGFR in early nephropathy, but it does in advanced disease [70]. Moreover, a post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study clearly showed that both baseline albuminuria and changes in albuminuria in the first 6 months of therapy were related to the degree of

long-term renal protection in proteinuric subjects with type 2 diabetes [71]. These observations support the use of albuminuria as surrogate endpoint of cardiorenal outcomes in intervention trials, as recently recommended by a Scientific Workshop, though only in selected circumstances in which proteinuria occurs [72] that is not the rule in DN.

Conclusions

Accumulating evidence indicates that the natural history of DN has changed profoundly, likely as a consequence of changes in treatment. In fact, remission/regression of microalbuminuria is a common feature of both types of diabetes which far outweighs progression to proteinuria. Moreover, a new clinical phenotype has emerged, in which eGFR loss occurs independently of albuminuria or even in the absence of it.

Nonalbuminuric renal impairment probably represents a different pathway to loss of renal function, which might underlie macroangiopathy instead of microangiopathy as prevailing pathology. In addition, it may be the consequence of repeated and/or unresolved episodes of AKI, even of mild degree. Moreover, reduced eGFR and albuminuria are both powerful risk factors for CVD events, whereas albuminuria appears to predict death and progression to ESRD better than eGFR loss. Finally, it is unclear whether reduced eGFR and albuminuria require different interventions and whether eGFR decline may also halt or regress in response to treatment, as proteinuria does.

Further, epidemiological, pathologic, pathophysiological, and intervention studies are needed to better characterize the distinctive features of the nonalbuminuric phenotype, thus improving management of CKD in diabetic individuals.

Acknowledgments The content of this article was the subject of the 12th Ruth Osterby Lecture, given by Professor Pugliese at the 27th Annual General Meeting of the European Diabetic Nephropathy Study Group (EDNSG), which was held in London, UK, on May 16–17, 2014. The Author thanks the RIACE Investigators for participating in the studies cited in this article. The RIACE study cited in this article was supported by the Research Foundation of the Italian Society of Diabetology (Fo.Ri.SID) and the Diabetes, Endocrinology and Metabolism (DEM) Foundation, and by unconditional grants from Eli-Lilly, Takeda, Chiesi Farmaceutici and Boehringer-Ingelheim.

Conflict of interest None.

Human and animal rights This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Reutens AT, Atkins RC (2011) Epidemiology of diabetic nephropathy. Contrib Nephrol 170:1–7
2. Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27:1047–1053
3. Ritz E, Rychlík I, Locatelli F, Halimi S (1999) End-stage renal failure in type 2 diabetes: a medical catastrophe of worldwide dimensions. Am J Kidney Dis 34:795–808
4. Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D, Williams DE, Geiss L (2014) Changes in diabetes-related complications in the United States, 1990–2010. N Engl J Med 370:1514–1523
5. Mogensen CE (1999) Microalbuminuria, blood pressure and diabetic renal disease: origin and development of ideas. Diabetologia 42:263–285
6. Jerums G, Premaratne E, Panagiotopoulos S, MacIsaac RJ (2010) The clinical significance of hyperfiltration in diabetes. Diabetologia 53:2093–2104
7. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H (1982) Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet 1:1430–1432
8. Parving HH, Oxenbøll B, Svendsen PA, Christiansen JS, Andersen AR (1982) Early detection of patients at risk of developing diabetic nephropathy: a longitudinal study of urinary albumin excretion. Acta Endocrinol (Copenh) 100:550–555
9. Mogensen CE, Christensen CK (1984) Predicting diabetic nephropathy in insulin-dependent patients. N Engl J Med 311:89–93
10. Mathiesen ER, Oxenbøll B, Johansen K, Svendsen PA, Deckert T (1984) Incipient nephropathy in type 1 (insulin-dependent) diabetes. Diabetologia 26:406–410
11. Mogensen CE (1984) Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 310:356–360
12. Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, Tohjima T, Kawamori R (1998) Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. Diabetes Care 21:116–120
13. Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M (1993) Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. Ann Intern Med 118:577–581
14. Ahmad J, Siddiqui MA, Ahmad H (1997) Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. Diabetes Care 20:1576–1581
15. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS (2003) Regression of microalbuminuria in type 1 diabetes. N Engl J Med 348:2285–2293
16. Giorgino F, Laviola L, Cavallo Perin P, Solnica B, Fuller J, Chaturvedi N (2004) Factors associated with progression to macroalbuminuria in microalbuminuric type 1 diabetic patients: the EURODIAB Prospective Complications Study. Diabetologia 47:1020–1028
17. Hovind P, Tarnow L, Rossing P, Jensen BR, Graae M, Torp I, Binder C, Parving HH (2004) Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: inception cohort study. BMJ 328:1105
18. Gaede P, Tarnow L, Vedel P, Parving HH, Pedersen O (2004) Remission to normoalbuminuria during multifactorial treatment preserves kidney function in patients with type 2 diabetes and microalbuminuria. Nephrol Dial Transplant 19:2784–2788
19. Araki S, Haneda M, Sugimoto T, Isono M, Isshiki K, Kashiwagi A, Koya D (2005) Factors associated with frequent remission of microalbuminuria in patients with type 2 diabetes mellitus. Diabetes 54:2983–2987
20. Yamada T, Komatsu M, Komiya I, Miyahara Y, Shima Y, Matsuzaki M, Ishikawa Y, Mita R, Fujiwara M, Furusato N, Nishi

K, Aizawa T (2005) Development, progression, and regression of microalbuminuria in Japanese patients with type 2 diabetes under tight glycemic and blood pressure control: the Kashiwa study. Diabetes Care 28:2733–2738
21. Tabaei BP, Al-Kassab AS, Ilag LL, Zawacki CM, Herman WH (2001) Does microalbuminuria predict diabetic nephropathy? Diabetes Care 24:1560–1566
22. Perkins BA, Krolewski AS (2009) Early nephropathy in type 1 diabetes: the importance of early renal function decline. Curr Opin Nephrol Hypertens 18:233–240
23. Perkins BA, Ficociello LH, Ostrander BE, Silva KH, Weinberg J, Warram JH, Krolewski AS (2007) Microalbuminuria and the risk for early progressive renal function decline in type 1 diabetes. J Am Soc Nephrol 18:1353–1361
24. Krolewski AS, Niewczas MA, Skupien J, Gohda T, Smiles A, Eckfeldt JH, Doria A, Warram JH (2014) Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria. Diabetes Care 37:226–234
25. Skupien J, Warram JH, Smiles AM, Niewczas MA, Gohda T, Pezzolesi MG, Cantarovich D, Stanton R, Krolewski AS (2012) The early decline in renal function in patients with type 1 diabetes and proteinuria predicts the risk of end-stage renal disease. Kidney Int 82:589–597
26. Skupien J, Warram JH, Smiles A, Galecki A, Stanton RC, Krolewski AS (2014) Improved glycemic control and risk of ESRD in patients with type 1 diabetes and proteinuria. J Am Soc Nephrol. doi:10.1681/ASN.2013091002
27. Skupien J, Warram JH, Niewczas MA, Gohda T, Malecki M, Mychaleckyj JC, Galecki AT, Krolewski AS (2014) Synergism between circulating tumor necrosis factor receptor 2 and HbA_{1c} in determining renal decline during 5-18 years of follow-up in patients with type 1 diabetes and proteinuria. Diabetes Care 37:2601–2608
28. Sabbisetti VS, Waikar SS, Antoine DJ, Smiles A, Wang C, Ravisankar A, Ito K, Sharma S, Ramadesikan S, Lee M, Briskin R, De Jager PL, Ngo TT, Radlinski M, Dear JW, Park KB, Betensky R, Krolewski AS, Bonventre JV (2014) Blood kidney injury molecule-1 is a biomarker of acute and chronic kidney injury and predicts progression to ESRD in type I diabetes. J Am Soc Nephrol. doi:10.1681/ASN.2013070758
29. Lacquaniti A, Donato V, Pintaudi B, Di Vieste G, Chirico V, Buemi A, Di Benedetto A, Arena A, Buemi M (2013) "Normoalbuminuric" diabetic nephropathy: tubular damage and NGAL. Acta Diabetol 50:935–942
30. Kopf S, Oikonomou D, von Eynatten M, Kieser M, Zdunek D, Hess G, Morcos M, Forsblom C, Bierhaus A, Groop PH, Nawroth PP, Humpert PM (2014) Urinary excretion of high molecular weight adiponectin is an independent predictor of decline of renal function in type 2 diabetes. Acta Diabetol 51:479–489
31. Lane PH, Steffes MW, Mauer SM (1992) Glomerular structure in IDDM women with low glomerular filtration rate and normal urinary albumin excretion. Diabetes 41:581–586
32. Tsalamandris C, Allen TJ, Gilbert RE, Sinha A, Panagiotopoulos S, Cooper ME, Jerums G (1994) Progressive decline in renal function in diabetic patients with and without albuminuria. Diabetes 43:649–655
33. Kramer HJ, Nguyen QD, Curhan G, Hsu CY (2003) Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 289:3273–3277
34. MacIsaac RJ, Tsalamandris C, Panagiotopoulos S, Smith TJ, McNeil KJ, Jerums G (2004) Nonalbuminuric renal insufficiency in type 2 diabetes. Diabetes Care 27:195–200
35. Dwyer JP, Parving HH, Hunsicker LG, Ravid M, Remuzzi G, Lewis JB, DEMAND Investigators (2012) Renal dysfunction in the presence of normoalbuminuria in type 2 diabetes: results from the DEMAND study. Cardiorenal Med 2:1–10
36. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR; UKPDS Study Group (2006) Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes 55:1832–1839
37. Molitch ME, Steffes M, Sun W, Rutledge B, Cleary P, de Boer IH, Zinman B, Lachin J, Epidemiology of Diabetes Interventions and Complications Study Group (2010) Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. Diabetes Care 33:1536–1543
38. Thomas MC, Macisaac RJ, Jerums G, Weekes A, Moran J, Shaw JE, Atkins RC (2009) Nonalbuminuric renal impairment in type 2 diabetic patients and in the general population (national evaluation of the frequency of renal impairment cO-existing with NIDDM [NEFRON] 11). Diabetes Care 32:1497–1502
39. 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 (2011) Clinical significance of nonalbuminuric renal impairment in type 2 diabetes. J Hypertens 29:1802–1809
40. Rodriguez-Poncelas A, Garre-Olmo J, Franch-Nadal J, Diez-Espino J, Mundet-Tuduri X, Barrot-De la Puente J, Coll-de Tuero G (2013) RedGDPS Study Group Prevalence of chronic kidney disease in patients with type 2 diabetes in Spain: PERCEDIME2 study. BMC Nephrol 14:46
41. Mottl AK, Kwon KS, Mauer M, Mayer-Davis EJ, Hogan SL, Kshirsagar AV (2013) Normoalbuminuric diabetic kidney disease in the U.S. population. J Diabetes Complications 27:123–127
42. 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 (2009) Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol 20:1813–1821
43. Drury PL, Ting R, Zannino D, Ehnholm C, Flack J, Whiting M, Fassett R, Ansquer JC, Dixon P, Davis TM, Pardy C, Colman P, Keech A (2011) Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetologia 54:32–43
44. Rigalleau V, Lasseur C, Raffaitin C, Beauvieux MC, Barthe N, Chauveau P, Combe C, Gin H (2007) Normoalbuminuric renal-insufficient diabetic patients: a lower-risk group. Diabetes Care 30:2034–2039
45. Pugliese G, Solini A, Bonora E, Orsi E, Zerbini G, Giorgino F, Cavalot F, Pontiroli AE, Baroni MG, Morano S, Nicolucci A, Penno G (2011) The Chronic Kidney Disease Epidemiology Collaboration (CKD–EPI) equation provides a better definition of cardiovascular burden associated with CKD than the Modification of Diet in Renal Disease (MDRD) Study formula in subjects with type 2 diabetes. Atherosclerosis 218:194–199
46. Pugliese G, Solini A, Fondelli C, Trevisan R, Vedovato M, Nicolucci A, Penno G, Renal Insufficiency And Cardiovascular Events (RIACE) Study Group (2011) Reproducibility of albuminuria in type 2 diabetic subjects. Findings from the Renal Insufficiency And Cardiovascular Events (RIACE) study. Nephrol Dial Transplant 26:3950–3954
47. de Boer IH, Steffes MW (2007) Glomerular filtration rate and albuminuria: twin manifestations of nephropathy in diabetes. J Am Soc Nephrol 18:1036–1037

48. Caramori ML, Fioretto P, Mauer M (2000) The need for early predictors of diabetic nephropathy risk: is albumin excretion rate sufficient? Diabetes 49:1399–1408
49. Yokoyama H, Sone H, Oishi M, Kawai K, Fukumoto Y, Kobayashi M, Japan Diabetes Clinical Data Management Study Group (2009) Prevalence of albuminuria and renal insufficiency and associated clinical factors in type 2 diabetes: the Japan Diabetes Clinical Data Management study (JDDM15). Nephrol Dial Transplant 24:1212–1219
50. Afghahi H, Cederholm J, Eliasson B, Zethelius B, Gudbjörnsdottir S, Hadimeri H, Svensson MK (2011) Risk factors for the development of albuminuria and renal impairment in type 2 diabetes–the Swedish National Diabetes Register (NDR). Nephrol Dial Transplant 26:1236–1243
51. Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, Morano S, Cavalot F, Lamacchia O, Laviola L, Nicolucci A, Pugliese G, Renal Insufficiency And Cardiovascular Events Study Group (2013) HbA1c variability as an independent correlate of nephropathy, but not retinopathy, in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicenter study. Diabetes Care 36:2301–2310
52. Penno G, Solini A, Zoppini G, Orsi E, Zerbini G, Trevisan R, Gruden G, Cavalot F, Laviola L, Morano S, Nicolucci A, Pugliese G, Renal Insufficiency And Cardiovascular Events (RIACE) Study Group (2012) Rate and determinants of association between advanced retinopathy and chronic kidney disease in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicenter study. Diabetes Care 35:2317–2323
53. Bash LD, Selvin E, Steffes M, Coresh J, Astor BC (2008) Poor glycemic control in diabetes and the risk of incident chronic kidney disease even in the absence of albuminuria and retinopathy: atherosclerosis Risk in Communities (ARIC) Study. Arch Intern Med 168:2440–2447
54. Kramer CK, Leitão CB, Pinto LC, Silveiro SP, Gross JL, Canani LH (2007) Clinical and laboratory profile of patients with type 2 diabetes with low glomerular filtration rate and normoalbuminuria. Diabetes Care 30:1998–2000
55. Caramori ML, Fioretto P, Mauer M (2003) Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients: an indicator of more advanced glomerular lesions. Diabetes 52:1036–1040
56. Ekinci EI, Jerums G, Skene A, Crammer P, Power D, Cheong KY, Panagiotopoulos S, McNeil K, Baker ST, Fioretto P, Macisaac RJ (2013) Renal structure in normoalbuminuric and albuminuric patients with type 2 diabetes and impaired renal function. Diabetes Care 36:3620–3626
57. MacIsaac RJ, Panagiotopoulos S, McNeil KJ, Smith TJ, Tsalamandris C, Hao H, Matthews PG, Thomas MC, Power DA, Jerums G (2006) Is nonalbuminuric renal insufficiency in type 2 diabetes related to an increase in intrarenal vascular disease? Diabetes Care 29:1560–1566
58. Fioretto P, Mauer M, Brocco E, Velussi M, Frigato F, Muollo B, Sambataro M, Abaterusso C, Baggio B, Crepaldi G, Nosadini R (1996) Patterns of renal injury in NIDDM patients with microalbuminuria. Diabetologia 39:1569–1576
59. Romagnani P, Remuzzi G (2013) Renal progenitors in non-diabetic and diabetic nephropathies. Trends Endocrinol Metab 24:13–20
60. Chawla LS, Kimmel PL (2012) Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. Kidney Int 82:516–524
61. Coca SG, Singanamala S, Parikh CR (2012) Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 81:442–448
62. Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE 2nd, Perkins RM (2012) Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. Kidney Int 81:477–485
63. Kline J, Rachoin JS (2013) Acute kidney injury and chronic kidney disease: it's a two-way street. Ren Fail 35:452–455
64. Niewczas MA, Gohda T, Skupien J, Smiles AM, Walker WH, Rosetti F, Cullere X, Eckfeldt JH, Doria A, Mayadas TN, Warram JH, Krolewski AS (2012) Circulating TNF receptors 1 and 2 predict ESRD in type 2 diabetes. J Am Soc Nephrol 23:507–515
65. 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 (2012) 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 35:143–149
66. Hoefield RA, Kalra PA, Baker PG, Sousa I, Diggle PJ, Gibson MJ, O'Donoghue DJ, Middleton RJ, New JP (2011) The use of eGFR and ACR to predict decline in renal function in people with diabetes. Nephrol Dial Transplant 26:887–892
67. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3:1–150
68. Evans M, Bain SC, Hogan S, Bilous RW, Collaborative Study Group participants (2012) Irbesartan delays progression of nephropathy as measured by estimated glomerular filtration rate: post hoc analysis of the Irbesartan Diabetic Nephropathy Trial. Nephrol Dial Transplant 27:2255–2263
69. Abuelo JG (2007) Normotensive ischemic acute renal failure. N Engl J Med 357:797–805
70. Jerums G, Panagiotopoulos S, Premaratne E, Power DA, MacIsaac RJ (2008) Lowering of proteinuria in response to antihypertensive therapy predicts improved renal function in late but not in early diabetic nephropathy: a pooled analysis. Am J Nephrol 28:614–627
71. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM (2004) Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int 65:2309–2320
72. Levey AS, Cattran D, Friedman A, Miller WG, Sedor J, Tuttle K, Kasiske B, Hostetter T (2009) Proteinuria as a surrogate outcome in CKD: report of a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J Kidney Dis 54:205–226