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Proteinuric and Non-proteinuric Diabetic Nephropathy: A Case of Siamese Twins?

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Abstract:

Diabetic nephropathy (DN) is the leading cause of chronic kidney disease (CKD) and its progression to end stage renal disease (ESRD) worldwide, necessitating renal replacement therapy (RRT) in the form of dialysis or transplant. Proteinuria had been the hall mark of diabetic nephropathy until recently, reduced glomerular filtration rate without proteinuria has been frequently observed and labelled as non-proteinuric diabetic nephropathy. The current review discusses the incidence and possible pathophysiology and associated issue with this entity.

Key words: *diabetic nephropathy, nonproteinuric diabetic nephropathy, glomerular filtration rate, microalmuninuria, macroalbuminuria.*

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INTRODUCTION

Diabetic nephropathy (DN) is the leading cause of chronic kidney disease (CKD) and its progression to end stage renal disease (ESRD) worldwide, necessitating renal replacement therapy (RRT) in the form of dialysis or transplant [1, 2]. Historically, diabetic nephropathy has been characterized by glomerular hyperfiltration leading to microalbuminuria as the earliest clinical marker of this disease followed by macroalbuminuria and reduced glomerular filtration rate (GFR), eventually leading to CKD and ESRD [3, 4]. Recent data has challenged our understanding of the natural course of DN, delineating two alternate phenotypes of this disease: proteinuric and non proteinuric DN. The end point of both these phenotypes is ESRD. In this manuscript, we will try to differentiate the clinical presentation, risk/ protective factors, and possible underlying mechanisms of proteinuric DN phenotype from of non proteinuric DN phenotype based on recent discussions and studies in the literature.

HISTORICAL UNDERSTANDING OF DIBETIC NEPHROPATHY:

Proteinuric Subtype

The classical course of DN, as depicted my Mogensen, is a stepwise progression of disease, consisting of glomerular hyperfiltration, microalbuminuria (urinary albumin creatinine ratio, UACR, 30-300 mg/g), macroalbuminuria (UACR>300mg/g), reduced GFR and finally ESRD[5]. This trajectory of disease progression is referred to as classic or proteinuric DN. Microabluminuric stage is referred to as incipient DN, whereas macroalbuminuric stage is labeled overt DN and had been considered as clinical hallmark of diabetic nephropathy. Although microalbuminuria is considered a risk factor for the development of macroalbuminuria, not all patients progress to this stage, and some may regress to normoalbuminuria [6].

Risk Factors

Multiple risk actors have been nominated in the development of this classic form of diabetic kidney disease.

The two main risk factors for DN are hyperglycemia and arterial hypertension [7, 8]. Other risk factors include family history of diabetic kidney disease, genetic predisposition, male gender, smoking history, severe albuminuria; lower baseline estimated GFR (eGFR), older age, diabetes duration, obesity, higher systolic blood pressure and poor glycaemic control [9].

U.K. Prospective Diabetes Study (UKPDS) implicated male sex, increased waist circumference, plasma triglycerides, LDL cholesterol, HbA_{1C}, increased white cell count, smoking history, and antecedent retinopathy. Interestingly, the research team also found reduced eGFR as a culprit in the development of albuminuria and vice versa [10]. In a Swedish study, independent risk factors for albuminuria were high BMI, high HbA_{1C}, smoking history, HDL and male sex[11].

Pathophysiology of Proteinuria

The histopathological manifestation of classic DN is a spectrum of lesions (Class I-IV; table 1) well defined in literature. As detailed in an excellent review by Tervaert et al glomerular basement membrane (GBM) thickening is the earliest structural abnormality in classic DN[12]. Isolated GBM thickening with only mild, nonspecific changes by light microscopy is categorized as Class I. Extracellular matrix (ECM) proteins deposition, such as collagen types IV and VI, laminin, and fibronectin is responsible for GBM width increase. Class II (mild (IIa) or severe (IIb) based on histological parameters), is described as mesangial expansion, also due to increased mesangial ECM components. Mesangial expansion distorts glomerular capillaries reducing the capillary filtration surface[12].

With disease progression, mesangiolysis and further accumulation of mesangial matrix with collagen fibrils, small lipid particles and cellular debris occurs results in round to oval mesangial structure with an acellular, hyaline/matrix core known as Kimmelstiel–Wilson nodules. The presence of at least one Kimmelstiel– Wilson nodule (and less than 50 % glomerulosclerosis) is labeled as class III or Nodular Sclerosis[12].

Class IV or Advanced Diabetic Glomerulosclerosis consists of more than 50% global glomerulosclerosis and is a result of the same mechanisms of protein deposition and ECM expansion that steered the previous stages from GBM thickening, through mesangial expansion, to nodular sclerosis[12].

Other patterns of injury include tubular interstitial and vascular lesions. For instance, concomitant tubular basement membrane thickening of nonatrophic tubules is apparent from the development of class II glomerular diabetic lesions and becomes more conspicuous in class III and IV. Interstitial fibrosis and tubular atrophy (IFTA) follow glomerular changes in type 1 DN that ultimately lead to ESRD[14]. According to Stout *et al.*, hyalinosis of the efferent arteriole is relatively specific for DN[15].

Class	Description
I	GBM thickening on EM Mild or nonspecific changes on LM
II a	Mild mesangial expansion
IIb	Severe mesangial expansion
III	Nodular sclerosis (at least Kimmelstiel–Wilson lesion)
IV	Advanced diabetic glomerulosclerosis Global glomerular sclerosis in >50% of Glomeruli

Table 1. Classification of Lesions in Diabetic Nephropathy[12]

NEW MODEL OF DIABETIC NEPHROPATHY:

<u>Non-Proteinuric Subtype</u>

Non-proteinuric DN is a new phenotype of non-proteinuric DN. In this model, the predominant clinical feature of both early and late stages of diabetic nephropathy is progressive renal decline, depicted by reduced GFR instead of albuminuria[16]. GFR loss has been shown to occur independently of albuminuria or even in the absence of it[17]. An eGFR of ≤ 60 ml/min/1.73m² is generally considered abnormal[18].

Many clinical longitudinal studies support the notion of non-proteinuric DN. MacIsaac et al surveyed 301 T2DM patients, and found a cohort of 109 patients (36%) with a GFR<60 ml/min/1.73m² out of which 43 (39%) were normoalbuminuric[19]. The NEFRON 11 study collected data of 3,893 individuals with type 2 diabetes presenting consecutively to their general practitioner. It was observed that 23.1% had an eGFR <60 ml/min/1.73 m^2. More than half (55%) of these subjects, were found to have normoalbuminuria on their most recent urinalysis. Most (98%) of these patients were also reported as being persistently normoalbuminuric by their practitioner[20]. Similarly, United Kingdom Prospective Diabetes Study (UKPDS) showed that of 1132 patients who developed diabetic kidney disease, 50.8% remained non-proteinuric over a 15-year follow-up. This evidence that these patients never developed clinically significant albuminuria gives merit to the theory of two distinct phenotypes of diabetic nephropathy[10].

The authors of NHANES 2005-2008 reported the prevalence of nephropathy was 34.5%, the prevalence of impaired GFR (with or without albuminuria) was 17.7% and the prevalence of albuminuria (with or without reduced GFR) was even higher (23.7%)[21]. A noteworthy point here is that in a subset of patients both these

disease processes might be going on collaterally and augmenting each other and albuminuria and GFR loss may represent complementary and/ or overlapping manifestations of kidney damage. In one study, the extent of eGFR change was much higher in microalbuminuric versus normoalbuminuric subjects; it was more frequent in patients who progressed to macroalbuminuria and less frequent in those who regressed to normoalbuminuria[22]. As found in Joslin Clinic study, Krolewski reported prevalence of renal function decline in 10%, 32%, and 50% of patients with normoalbuminuria, microalbuminuria, and proteinuria, respectively[17].

Risk Factors

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]. In a cohort of 660 patients with type 2 diabetes and normoalbuminuria reduced eGFR was found to be associated with higher levels of insulin resistance, total and LDL cholesterol, and triglycerides, and higher prevalence of the metabolic syndrome[25]. UKPDS study also revealed female sex, decreased waist circumference, age, increased insulin sensitivity, and previous sensory neuropathy as independent risk factors for renal impairment[10]. Afghani et al demonstrated that albuminuria or renal impairment was independently associated with high age, high systolic BP and elevated triglycerides whereas risk factors for renal impairment included elevated plasma creatinine at baseline and female sex[11].

Female sex, nonsmoking status, shorter diabetes duration, higher HDL cholesterol and hemoglobin levels were more prevalent in patients of reduced eGFR subtype of DN[26]. Interestingly, they showed decrease prevalence of cardiovascular disease and retinopathy[26].

Pathophysiology of Reduced GFR

The mechanisms of initiation and propagation of this progressively declining GFR phenotype of diabetic kidney disease are not as well understood as that of proteinuric phenotype. Tubular injury and inflammatory damage seems to be the underlying mechanism of this non-proteinuric phenotype.

It has been shown that both urinary and serum neutrophil gelatinase-associated lipocalcin increases before the onset of microalbuminuria in patients with type 1 diabetes[27]. Moreover, other markers of cellular injury including tumor necrosis factor receptor (TNFR) 1 and 2 were found to be independently associated with nonproteinuric DN. Rosolowsky et al found higher serum uric acid and higher urinary albumin excretion rate, older age, and antihypertensive treatment as associated risk factors of reduced GFR[28].Similarly, high molecular weight adiponectin also proved to be an independent predictor of decline of renal function in those with type 2 diabetes as a urinary biomarker [29].

In another study, decreased eGFR (eGFR <60 ml/min/1.73 m^2), was found to be independently associated with an elevated resistive index of the interlobar renal arteries. However, this elevation of resistance index was similar in the three strata of albuminuric status, suggesting that intrarenal vascular disease is less likely pathological mechanisms that determine the relationship between reduced eGFR and albuminuria[30].

Histopathology in Non-Proteinuric Nephropathy

Budhiraja *et al*, analyzed, kidney biopsies of non-proteinuric T2DM patients, with eGFR <60 ml/ min/1.73m^2 and found severe diabetic glomerulosclerosis in the absence of albuminuria. On light

microscopy, all the 10 non-proteinuric diabetic patients had capillary wall thickening; 2 out of 10 patients had severe diffuse mesangial thickening but no nodules, while 8 patients had Kimmelstiel-Wilson nodules on the biopsy. The tubules and tubule interstitium was relatively well preserved and afferent and efferent arteriolar hyalinosis was also observed[31].

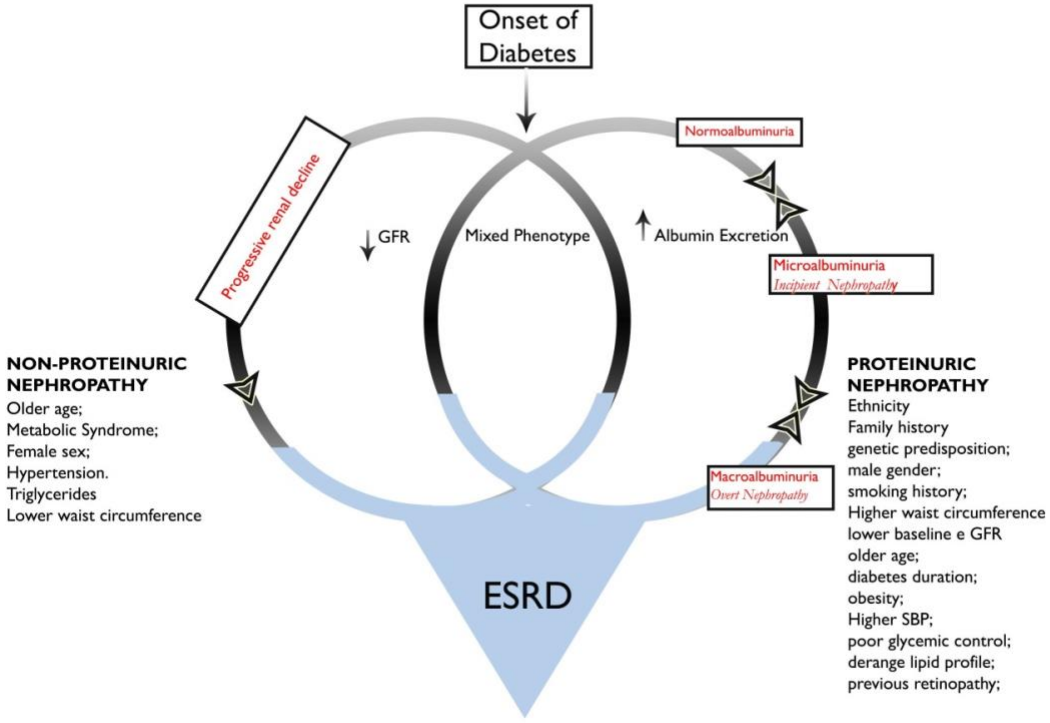

Figure 1: This diagram is a visual representation only to emphasize overlapping relation of proteinuric and non-proteinuric DN. The dimensions do not depict any epidemiological distribution of these phenotypes.

In contrast, in another study typical glomerular changes were less commonly seen in normoalbuminuric patients than albuminuric, indicating a diverse array of pathological changes involved in non-proteinuric DN as compared to those in proteinuric DN. Ekinci et al compared renal biopsy findings in patients with type 2 diabetes and eGFR <60 ml/min/1.73 m^2, associated with either normoalbuminuria (n = 8), microalbuminuria (n = 6) or macroalbuminuria (n = 17). They utilized Fioretto classification, categorized as category 1 (C1), defined by normal or near normal renal structure, category 2 (C2), typical DN with predominantly glomerular changes, and category 3 (C3), defined by disproportionately severe interstitial, tubular, or vascular damage and few or no glomerular changes. Typical glomerular changes (C2) of DN were observed in 22 of 23 subjects with micro- or macroalbuminuria compared with 3 of 8 subjects with normoalbuminuria (P = 0.002). By contrast, predominantly interstitial or vascular changes (C3) were seen in only 1 of 23 subjects with micro- or macroalbuminuria compared with 3 of 8 normoalbuminuric subjects (P = 0.08)[32]. Similarly, Caramori and associates compared normoalbuminuric T1D patients with low and

normal eGFR and confirmed that reduced GFR is associated with more advanced diabetic glomerular lesions[33].

Chronic kidney disease can also develop as a result of acute kidney injury[34, 35]; multiple subclinical episodes of AKI might also be responsible in the development of non-proteinuric DN, possibly due to hypovolemia.

It is also observed that retinopathy is less frequent in non-proteinuric phenotype as compared with proteinuric phenotype, supporting the view that proteinuric and non-proteinuric DN are two different phenotypes rather than two variants of a same disease[36, 37].

Because any phenotype is a product of genetic and environmental factors, it can be assumed that both proteinuric and non-proteinuric types of DN have different genetic factors at play. Therefore, ethnic and/or genetic association studies may also help us better understand the candidate genes of these phenotypes. Bhalla et al analyzed differences in the prevalence of proteinuric and non proteinuric diabetic nephropathy between various ethnicities and discovered that Chinese, Filipinos, Hispanics and Non-Hispanic Blacks (NHBs) exhibited significantly higher odds of proteinuric DKD than Non Hispanic Whites (NHWs). Conversely, Chinese, Hispanic, and NHB women and Hispanic men had significantly lower odds of nonproteinuric DKD than NHWs[38].

CONCLUSION

It is likely that a proportion of non-proteinuric DN group might be 'converts' from proteinuric DN, likely due to increased rate of treatment with RAAS blocking agents. It is also possible that due to increasing awareness for screening DKD by calculating eGFR and measuring albuminuria we are able to identify more proteinuric DN patients. Therefore, the two different clinical presentations of diabetic kidney disease warrant holistic evaluation of patients with diabetes for both albuminuria and reduced GFR as both of these are important independent predictors of cardiovascular disease and deteriorating renal function and any one of these processes cannot solely predict the development of the other[39, 40]. Current Standards of Care in Diabetes guidelines by American Diabetic Association also recommend the same[41].

As different methods of GFR estimation may under- or over-predict, development of novel clinical markers is the need of day. A great body of work is being carried out on elucidation of such markers including Neutrophil gelatinase-associated lipocalcin (NGAL) Kidney injury molecule-1 (KIM-1) and Fibroblast growth factor (FGF) among many others. However, the development of these phenotypes is at the nascent stage and they are only rarely used in clinical decision making[42].

Figure depicts the overlapping and to and fro movement of both phenotypes, like a case of conjoined Siamese twins. Further research is needed not only for employment of better predictive biomarkers but also to clarify the non proteinuric phenotype's epidemiology, pathogenesis, risk factors, prognosis, and best treatment strategy.

Conflict of Interest: None declared

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