

Predictors of Diabetic Nephropathy

Review Article

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Abstract: Diabetic nephropathy (DN) is a leading cause of morbidity and mortality in diabetic patients representing a huge health and economic burden. Alarming recent data described diabetes as an unprecedented worldwide epidemic, with a prevalence of ~6.4% of the world population in 2010, while the prevalence of CKD among diabetics was approximately 40%. With a clinical field hungry for novel markers predicting DN, several clinical and laboratory markers were identified lately with the promise of reliable DN prediction. Among those are age, gender, hypertension, smoking, sex hormones and anemia. In addition, eccentric left ventricular geometric patterns, detected by echocardiography, and renal hypertrophy, revealed by ultrasonography, are promising new markers predicting DN development. Serum and urinary markers are still invaluable elements, including serum uric acid, microalbuminuria, macroalbuminuria, urinary liver-type fatty acid-binding protein (u-LFABP), and urinary nephrin. Moreover, studies have illustrated a tight relationship between obstructive sleep apnea and the development of DN. The purpose of this review is to present the latest advances in identifying promising predictors to DN, which will help guide the future research questions in this field. Aiming at limiting this paramount threat, further efforts are necessary to identify and control independent modifiable risk factors, while developing an integrative algorithm for utilization in DN future screening programs.

Keywords: Diabetes • Chronic kidney disease • Diabetic nephropathy • Risk factors • Predictors • Markers
• Microalbuminuria

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1. Introduction

Diabetes mellitus (DM) is recognized as the single most common cause of chronic kidney disease (CKD) accounting for a huge dialysis cost [1]. DM (type 1 and 2 as well as obesity-dependent diabetes, also known as diabetes [2]) has been described lately as a worldwide epidemic with prevalence reaching ~284 million diabetics, constituting ~6.4% of the world population in 2010 [2,3]. Kidney disease represents an epic complication in diabetics as reflected by CKD prevalence reaching approximately 40% [4] and nephropathy representing one of the most common microvascular complications in type 2 diabetes (Figure 1) [5]. Diabetic nephropathy (DN) occurs in both type 1 and type 2 diabetes mellitus. Progression of DN is often influenced by various factors including age, gender, and hypertension (HTN).

Importantly, smoking is a major preventable yet challenging risk factor leading to DN progression; an oxidative stress often described as “fuel to the fire” [6]. Pathologic abnormalities are noted in patients with long-standing diabetes mellitus before the onset of microalbuminuria. The major glomerular histologic changes found in DN are mesangial expansion, glomerular basement membrane thickening, and glomerular sclerosis [7,8]. In contrast, arteriolar hyalinosis, one of the earliest vascular changes noted in diabetes, was not appreciated in patients with metabolic syndrome [9,10]. Faced with vast inter-individual differences in terms of “glomerular filtration rate (GFR) reduction” along the course of DN progression [11], it is crucial to relentlessly search for markers predicting DN early on, for integration into screening and preventive algorithms. This review will focus on latest known predictors and preventable risk factors of DN in both type 1 and type 2 DM.

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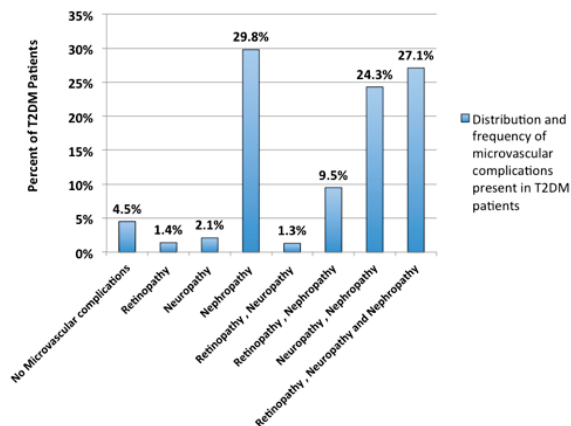


Figure 1. Bar chart demonstrating the prevalence of microvascular complications among type 2 diabetic patients. As illustrated, diabetic nephropathy represents a cornerstone complication in the majority of patients, often in combination with other microvascular complications.

2. Predictors of Diabetic Nephropathy

2.1. Age and Gender

As evident by earlier animal studies, a tight relationship coexists between DN progression and sex hormones. Experiments done in mice were successful in identifying estrogens as an important factor retarding the progression of kidney disease [12,13], in contrast to testosterone that aggravates it [14]. Intrigued with such findings, a recent study by Möllsten et al investigated the elements of gender and age as risk factors of CKD progression in patients with type 1 diabetes [15]. The study was a large, nationwide, population-based cohort study done in Sweden with a median follow-up period of 20 years [15]. It included 11,681 type 1 diabetic patients, with diabetes duration of more than 13 years. It utilized validated research registers (1977-1983) that were connected to the Swedish Renal Registry [15]. During the follow-up period, 127 patients developed ESRD secondary to DN. In both genders, the onset of type 1 DM before 10 years of age was associated with a reduced risk of developing DN [15], going in line with findings of earlier studies [16-22]. The reason explaining this age dependent effect is not clear yet. In type 1 diabetic patients, the overall incidence of end-stage renal disease ESRD was low at 30 years of age, being 4.1% (95% CI, 3.1-5.3) and 2.5% (95% CI, 1.7-3.5) in men and women, respectively. Remarkably, ESRD greatest risk was identified in male patients diagnosed with type 1 DM at 20-34 years of age (hazard ratio (HR) 3.0, 95% CI: 1.5- 5.7) [15]. Surprisingly, in female patients who were diagnosed at the age of 20-34 years, the risk was as low as subjects diagnosed before 10 years of age.

This suggests a higher risk of developing DN for type 1 diabetic male patients of certain age. Although this study does not provide mechanistic evidence on why this happens, future investigations are required to understand the potential role of gender, estrogens and testosterone, and/or pubescence in the development and deterioration of DN [15].

2.2. Smoking

Smoking is known to be a risk factor for several diseases. Several studies suggested a relationship between smoking and development as well as progression of CKD. A recent case-control study of 198 CKD patients, including 56 patients with DN, and 371 matched healthy controls was conducted investigating smoking as a preventable risk factor for CKD development secondary to various causes including DN [23]. Statistical analysis showed that smoking is associated with significantly elevated risk of DN (OR=2.24, CI 95% 1.27-3.96, P= 0.005) [23], with the greatest risk of CKD development among heavy smokers (>30 pack years) as reflected with OR=2.6 (95% CI=1.53-4.41, p < 0.0001) [23]. These results are in line with earlier clinical studies suggesting smoking as a major exacerbating factor for DN progression in both type 1 [24-26] and type 2 diabetics [27,28]. However, this study is suggesting association rather than causation. Larger prospective cohort studies with substantial portion of DN patients would be important to confirm association and reveal whether there is a cause-and-effect relationship between smoking and DN.

On the molecular level, smoking is thought to augment the oxidative process occurring in hyperglycemia. Such mechanism is suggested to be regulated through heightened production of reactive oxygen species (ROS) via NADPH oxidase (NOX), protein kinase C (PKC), and mitogen-activated protein kinase (MAPK) activation [29-32]. Previous animal studies proposed that NOX-4 isoform might have a role in DN pathogenesis based on data showing elevated NOX 4 protein expression in the kidney cortex of diabetic mice [33,34], while NOX 4 blockage leads to diminished glomerular hypertrophy, mesangial expansion, fibronectin production, and proteinuria [34].

In pursuit of understanding such complex molecular pathogenesis linking smoking and DN, a recent study was conducted using type 2 diabetic mice to test the hypothesis that nicotine aggravates renal injury involved in DN in a NOX4-derived ROS dependent manner [35]. Mice were designated to four groups; group 1, 10 healthy control mice; group 2, 10 healthy control mice receiving 100 g/ml nicotine; group 3, 10 diabetic mice; group 4, 10 diabetic mice receiving 100 g/ml nicotine

[35]. The treatment duration lasted for ~10 weeks (such duration is known to be long enough for the development of DN changes [36]). It showed that diabetic mice had increased cortical expression of NOX4 in their kidneys, while diabetic mice treated with nicotine showed heightened proteinuria (1 fold, $P<0.05$), ~20% glomerular hypertrophy ($P<0.05$), mesangial expansion ($P<0.05$), and fibronectin production ($P<0.05$) [35]. Augmented oxidative stress was reflected by ~30% increase in cortical expression of NOX4 ($P<0.05$), increased serine-threonine kinase Akt/protein kinase B (PKB) (Akt/PKB) expressions and phosphorylation [35] (a NOX4-derived ROS dependent kinase known for intensifying renal cell hypertrophy and extracellular matrix accumulation present in DN [34], ($P<0.05$)). Moreover, diabetes was associated with elevated nitrotyrosine expression as a marker of oxidative stress, with nicotine administration leading to even additional elevations in nitrotyrosine ($P<0.05$). These results suggest a role for oxidative stress as a mediator for nicotine-dependent worsening

of DN [35]. Furthermore, nicotine showed a synergistic effect with hyperglycemia on ROS generation and Akt phosphorylation in human mesangial cells [29,35]. These molecular findings, together with the clinical evidence, illustrate that smoking is a cornerstone risk factor with detrimental consequences on DN progression and severity (Figure 2).

2.3. Hypertension

HTN is a major cause of mortality in both type 1 and type 2 diabetics [37,38]. The prevalence of HTN appears to be about 2-folds more in patients with diabetes in contrast to non-diabetic patients, with this relationship being clearer in type 1 DM [39]. Established evidence shows that elevated systolic blood pressure (BP), other coexisting cardiac disease and microvascular complications are all important predictors of mortality in patients with type 1 and type 2 diabetes [40-42].

While earlier studies suggested a tight relationship between HTN and DN, recent reports emphasized an elevated risk of cardiovascular complications in hypertensive non-diabetic patients lacking nocturnal blood pressure fall (BPF) [43-47]. Based on these findings, a prospective study was conducted by Felicio et al exploring the hypothesis that a reduced nocturnal BPF could act as a reliable predictor of DN [48]. The study included 70 patients (32 men and 38 women) with HTN, type 2 DM, and normoalbuminuria. Patients were evaluated using urinary protein excretion (UPE), urinary albumin excretion (UAE), estimated glomerular filtration rate (eGFR), serum creatinine and 24-hours ambulatory BP monitoring (24h ABPM), measured at baseline and by the end of the 2-year follow-up period [48]. All patients were managed with diet modification and oral hypoglycemic medications without resolving to insulin therapy. Patients were classified into 2 groups, the first group represented 20% of patients ($n=14$) who developed either DN ($n=11$) or cardiovascular complications ($n=4$), and the second group represented the remaining 56 patients [48]. Data showed that both groups had similar systolic BP and diastolic BP, however, the first group had a higher nocturnal systolic BP (138 ± 15 versus 129 ± 16 mmHg, $p<0.05$) and nocturnal diastolic BP (83 ± 12 versus 75 ± 11 mmHg, $p<0.05$). No statistically significant difference was found between both groups in terms of the antihypertensive drugs used [48]. Moreover, basal nocturnal systolic BP correlated with the development of DN and cardiovascular complications ($r=0.26$; $P<0.05$) and with the final UAE after 2 years ($r=0.3$; $p<0.05$), while the basal BPF also showed correlation with the final UAE ($r=-0.31$; $p<0.05$) [48]. Remarkably, those who developed DN had a lower nocturnal systolic BPF

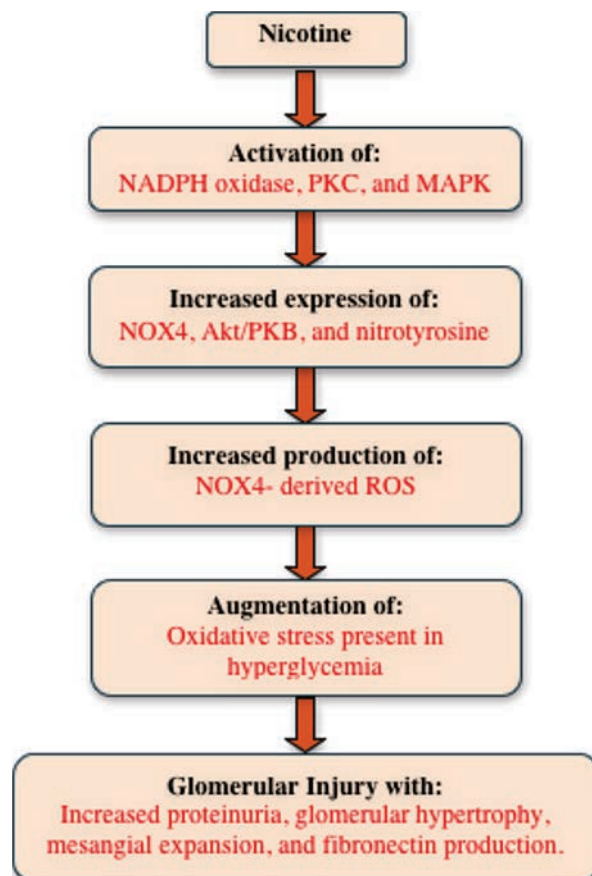


Figure 2. A simplified illustration of the mechanism by which smoking accelerates renal injury. Starting with nicotine dependent activation of NADPH oxidase, PKC, and MAPK, a cascade of pathophysiologic events is initiated ending by augmentation of oxidative stress already present in hyperglycemia with consequent glomerular injury and proteinuria.

(12 ± 5 versus $3 \pm 6\%$, $P < 0.01$) and diastolic BPF (15 ± 8 versus $4 \pm 10\%$, $P < 0.01$) [48]. Notably, patients who had a final UAE below $20 \mu\text{g}/\text{min}$ had a stable nocturnal and diurnal BP. These findings prove that diabetic hypertensive patients with normoalbuminuria develop higher basal levels of both nocturnal systolic and diastolic blood pressure preceding the development of albuminuria[48]. Nonetheless, among the few limitations were; the necessity to validate each of the oscillometric devices in 24h ABPM, identifying the threshold of 24 h ABPM cut-offs for diagnosing HTN in type 2 diabetics and a relatively limited number of patients preventing application of a multivariate analysis [48].

The role of HTN is highlighted even more in a recent study of 196 individuals, including 85 with normoalbuminuria, 66 with microalbuminuria, and 45 with macroalbuminuria [49]. Multivariate analysis revealed that nocturnal diastolic BP, platelet count and eGFR were independent predictors of DN development ($P=0.002$, $P=0.018$ and $P<0.001$, respectively) as well as microalbuminuria ($P=0.029$, $P=0.045$ and $P=0.001$, respectively) [49]. Interestingly, retinopathy progressed in all diabetic patients with enough hyperglycemic exposure, in contrast to DN that developed in only a subgroup of diabetic patients, proving that DN is influenced by other factors in addition to hyperglycemic exposure [49]. In conclusion, growing evidence is suggesting that increased nocturnal diastolic BP, nocturnal systolic BP, and/or lower nocturnal BPF might predict the development of micro or macroalbuminuria.

2.4. Obstructive Sleep Apnea

Based on earlier data identifying obstructive sleep apnea (OSA) and snoring as independent risks for developing insulin resistance [50], a group of investigators studied OSA as an independent risk factor for the development DN and microalbuminuria [51]. It included 237 type 2 diabetic patients, where 60.3% of patients suffered from snoring, while 31.6% complained of excessive daytime sleepiness [51]. Using both the Berlin Questionnaire [52] and past medical records, patients were classified as having either a high or low pre-test risk for OSA [51]. Results showed significantly higher microalbuminuria in patients who snore, reflected by 0.72 ± 0.2 and 0.25 ± 0.04 in snorers and non-snorers, respectively ($P=0.002$)[51], while microalbuminuria was 0.48 ± 0.9 and 0.37 ± 0.1 in patients with high and low pre-test risk for OSA, respectively ($P=0.385$) [51]. However, the study remained limited by utilizing screening methods instead of the gold standard polysomnography

(PSG), a comprehensive recording of the biophysiological changes that occur during sleep.

2.5. Serum Markers

Extensive efforts have been made to investigate novel serum markers involved in predicting, causing and/or aggravating DN. In particular, serum uric acid (SUA) was investigated by an inception cohort study including 277 patients with newly diagnosed type 1 diabetes with a median follow-up period of 18.1 years, where DN was assessed in terms of micro- and macroalbuminuria [53]. Among those, 263 patients were available for analysis, where SUA was measured at baseline and again after 3 years from the onset of DM, yet before the occurrence of microalbuminuria. During the follow-up period, 23 patients suffered from newly developed macroalbuminuria (urinary albumin excretion rate $>300 \text{ mg}/24\text{h}$), with an incidence of 22.3% (95% CI 10.3–34.3) and 9.5% (3.8–15.2) in patients with SUA levels in the upper 25th percentile ($\text{SUA} >249 \mu\text{mol}/\text{l}$) versus those with SUA in the lower 75th percentile ($P=0.006$), respectively[53]. Although a Cox proportional hazards model (including sex and age as constant covariates) confirmed SUA as independently associated with subsequent development of persistent macroalbuminuria (HR 2.37, 95% CI: 1.04 – 5.37, per 100 $\mu\text{mol}/\text{l}$ elevation in SUA, $P=0.04$), however, this was not the case with microalbuminuria (HR 1.05, 95% CI: 0.66 – 1.69, per 100 $\mu\text{mol}/\text{l}$ elevation in SUA, $P=0.83$). This illustrates that early elevation of SUA in type 1 diabetics is an independent risk factor predicting the development of DN later in life [53].

Intrigued with such relationship, it was crucial to investigate the exact mechanisms underlying SUA and if using xanthine oxidase inhibitors might decrease kidney injury in diabetic mice [54]. For eight weeks, mice were divided into 4 groups with 10 mice per group; group 1: control mice, group 2: control mice receiving allopurinol, group 3: diabetic mice and group 4: diabetic mice receiving allopurinol [54]. Results showed that diabetic mice had higher mean serum uric acid compared to controls ($P < 0.05$) [54]. Diabetic mice receiving allopurinol showed significantly reduced uric acid levels ($P < 0.001$), decreased albuminuria ($P < 0.05$) and attenuated tubulointerstitial damage ($P < 0.01$), though mesangial expansion persisted reflecting glomerular damage [54]. The mechanism of protection of allopurinol was found to be through decreased epithelial cell expression of Inter-Cellular Adhesion Molecule-1 (ICAM-1). In addition, in vitro studies showed that uric acid directly stimulates ICAM-1 expression in renal proximal tubular cells in humans [54]. Notably, allopurinol had no effect on the

oxidative stress in the kidneys [54]. Thus it is quite evident that hyperuricemia potentiates DN development through tubulointerstitial injury, with no effect on glomerular damage. Future clinical trials are necessary to test the benefit of utilizing allopurinol in limiting DN progression.

2.6. Urinary markers

The search for reliable urinary markers predicting DN has been ample as reflected by a recent study by Kanakamani et al, which assessed 670 patients with DM and CKD [55]. It utilized urinalysis to evaluate the predictive role of microalbuminuria in DN patients [55]. It showed no statistically significant correlation between the median diabetic duration and the prevalence of microalbuminuria, as reflected by microalbuminuria prevalence being 25.5% (95% confidence interval (CI), 22.4-29%) and 24.7% in those with median diabetic duration of 5 years and DM of < 1 year, respectively [55]. Moreover, the duration of DM, duration of hypertension, smoking, body mass index (BMI), waist circumference, and insulin therapy were not significantly correlated with microalbuminuria in a multivariate analysis [55]. On the other hand, macroproteinemia was prevalent in 16.2% (95% CI, 13.5-19.1%) in those with median duration of DM of 5 years in contrast to 6.2% in those with <1 year of DM. In addition, multiple regression analysis identified glycated hemoglobin (>8.0%), retinopathy, and calcium channel blockers intake as risk factors predicting both microalbuminuria and macroproteinuria [55]. Waist circumference was associated with macroproteinuria but not with microalbuminuria [55]. Accordingly, these data support the rising understanding that microalbuminuria is pathophysiologically distinct from DN.

Furthermore, a population-based cohort study analyzed data collected on 3431 individuals with DM in Salford, UK with the aim of identifying the rate of progression of CKD in DM patients in relation to their eGFR (calculated utilizing four-variable modified diet in renal disease (MDRD) formula) and existence of albuminuria (using urinary albumin-creatinine ratio (UACR) data) [56]. Data were analyzed using longitudinal mixed effect dynamic regression models and variables were set according to the maximum likelihood. Results showed that in diabetic patients, eGFR declined at a rate of 5.7%, 1.5% and 0.3% per year in those with macroalbuminuria, microalbuminuria and without albuminuria, respectively, regardless of age ($P < 0.0001$) [56]. Thus, this adds further evidence that there is a pivotal prognostic value of albuminuria in DN progression. However, the study was limited by using creatinine-based estimation (MDRD)

formula that is known to underestimate GFR decline in DM [56,57].

With sufficient evidence proving tubulointerstitial injury as a major contributor to the pathophysiology underlying DN [58,59], it was suggested that a more precise prediction of DN could be achieved by supplementing micro and macroalbuminuria (as markers of glomerular injury) with a marker of tubular damage such as urinary liver-type fatty acid-binding protein (u-LFABP) (Figure 3) [60]. Accordingly, u-LFABP was evaluated by an inception cohort of 165 patients with type 1 DM and persistent normoalbuminuria at baseline [60]. Baseline log u-LFABP predicted the development of microalbuminuria (adjusted hazard ratio (HR) 2.3 (95% CI 1.1-4.6)), macroalbuminuria (HR 2.6 (1.2-5.4)), and mortality (HR 3.0 (1.3-7.0)) [60]. Notably, systolic BP, diastolic BP and HbA1c were all higher in patients who progressed to develop micro- and macro-albuminuria in contrast to those classified as having persistent normoalbuminuria ($P < 0.05$ and $P = 0.02$, respectively) [60]. These results illustrate that heightened u-LFABP occurs in diabetics earlier, before glomerular damage is identifiable (normal levels of urinary albumin excretion rate (UAER)), reflecting early tubular injury [60]. These results should be intercepted with caution since u-LFABP was analyzed in a single 24h urine sample, urine samples were

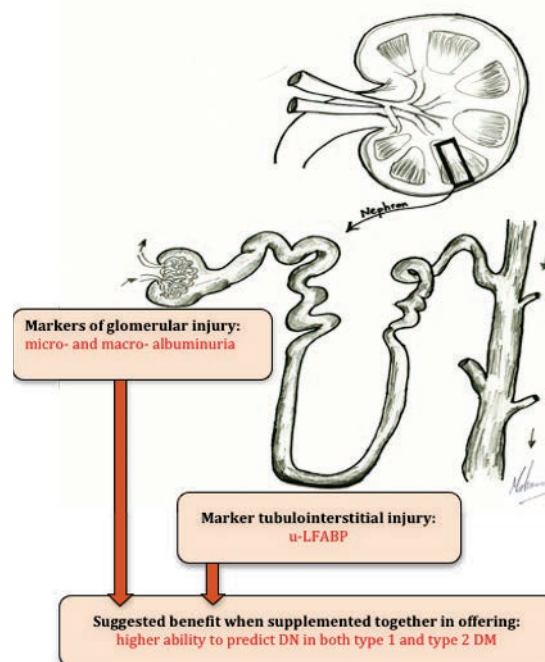


Figure 3. A simplified diagram illustrating urinary markers of DN development and progression, including markers of glomerular injury and tubulointerstitial injury. Recent evidence suggest a higher predictor ability when markers of glomerular injury are supplemented by u-LFABP, a marker of tubulointerstitial injury. Artwork provided as a courtesy of Mahmoud R Gaballa, MD

frozen at -20°C for ~ 18 years before analysis and urine samples before 1990 were lost so the analyzed urine samples were from 1990–2008 (although this is thought to only underrate the predictive power of u-LFABP) [60]. Moreover, another group of investigators assessed u-LFABP in predicting DN development in type 2 diabetic patients [61]. It included both a cross-sectional analysis, including 140 type 2 diabetic patients and 412 healthy individuals, and a longitudinal analysis, where 104 patients were followed for 4 years. Results demonstrated that the level of u-LFABP reflects the severity of DN ($P < 0.05$). High u-LFABP level was considered a risk factor for the progression of DN (adjusted HR 7.285, 95% CI 2.425 – 21.883, $P < 0.0001$), suggesting its ability as an early screening tool as well as predictor of DN [61]. Although these findings introduce u-LFABP, a urinary marker of tubular inflammation, as a supplement to albuminuria in predicting DN development in both type 1 and type 2 diabetic patients, other studies produced contradicting results [62]. Additional studies are needed to clarify the overall predictive role of combining both tubular and glomerular markers.

Nephrin is a podocyte protein crucial for the inter-podocyte slit membrane structure and maintenance of an intact filtration barrier [63]. Experimental renal diseases are associated with the loss of nephrin protein into urine [64]. Qibo et al measured urinary nephrin in 66 patients with Type II diabetes and in 11 healthy controls [65]. A urine nephrin-to-creatinine ratio (UNCR) was calculated and nephrinuria was defined as UNCR > 0.1 mg/g. Remarkably, UNCR correlated positively with urine albumin-to-creatinine ratio (UACR) ($p < 0.0001$), and negatively with serum albumin ($p = 0.001$) and eGFR ($p = 0.005$). They found 54% with nephrinuria among diabetic patients with normoalbuminuria suggesting that elevated UNCR (nephrinuria) might precede the detection of microalbuminuria and in turn be an earlier biomarker of DN [65]. Analysis of UNCR in large cohort studies might support or refute the use of UNCR as an early biomarker for DN. This might identify potential candidates for earlier treatment for renal protection among diabetic patients.

2.7. Eccentric Ventricular Hypertrophy and Anemia

Earlier studies proved left ventricular hypertrophy (LVH) to be more prevalent and pronounced in patients with DN [66], while left ventricular (LV) mass index was elevated parallel to progressive urinary albumin excretion elevations [67]. These findings triggered exploring left ventricular geometric patterns (LVGP) (identified utilizing echocardiography) as a novel independent risk factor

for the progression of DN [68]. Through a retrospective cohort analysis of 150 diabetic patients (90 males and 60 females) and study duration of 30.1 ± 19.4 months, progressive DN developed in 53 patients (35.3%) [68]. LVGPs were defined based on patients' cardiac relative wall thickness (RWT) on echocardiography, while LVH was identified utilizing calculated LV mass indexed to body surface area [68]. Patients were categorized according to the RWT and the presence of LVH into 4 groups; normal ventricle group (normal LV mass, $\text{RWT} \leq 0.42$), concentric remodeling group (normal LV mass, $\text{RWT} > 0.42$), concentric hypertrophy group (LVH, $\text{RWT} > 0.42$), and eccentric hypertrophy group (LVH, $\text{RWT} \leq 0.42$). Each group represented 14.0%, 12.0%, 46.7%, and 27.3% of the total study cohort, respectively [68]. The prevalence of eccentric LVH heightened as the stage of CKD progressed, being 8.3%, 23.7%, 23.9%, and 46.9% in patients with CKD stages 1, 2, 3, and 4, respectively [68]. Furthermore, multivariate Cox regression analysis confirmed eGFR (relative risk (RR)=0.979, 95% CI: 0.963–0.996, $P=0.014$), eccentric hypertrophy ($\text{RR}=2.839$, 95% CI: 1.167–6.906, $P=0.021$), and hemoglobin levels ($\text{RR}=1.781$, 95% CI: 1.035–4.027, $P=0.040$) as significant predictors of the outcome of DN [68]. However, the study was limited by the retrospective design with a modest sample size, while other important risk factors such as tobacco smoking and retinopathy were not accounted for [68]. These results suggest anemia and eccentric hypertrophy as promising independent predictors of DN. In the meantime, although most anemic patients are treated with erythropoietin, there is a substantial portion of them whose anemia are not fully corrected. There are studies that looked at the "erythropoietin-resistant anemia" with more details and attributed this to hyporesponsiveness to erythropoietin [72]. Some patients with overt resistance to erythropoietin stimulating agents (ESAs) are found to have marked elevation of inflammatory cytokines [73]. A recent research article suggested a dose-response relationship [74]. Inrig et al found a direct relationship between ESA dose and soluble Epo receptor in CKD patients as a potential modulator of erythropoietic response to ESA therapy, which could explain the erythropoietin resistance in anemia.

2.8. Renal Hypertrophy

Based on the hypothesis that renal hypertrophy precedes glomerular hyperfiltration occurring as DN unfolds, a study was conducted confirming that large kidneys in diabetics predict DN progression [69]. In this study, the investigators assessed 75 patients with DM and CKD, including 55 type 2 diabetics and 20 type 1

diabetics, where their kidney length was measured utilizing ultrasound imaging (U/S) [69]. The inclusion criteria included CKD defined by a GFR < 60 mL/min/1.73m² or an Albumin Excretion Rate (AER) >30 mg/24H, for patients not requiring dialysis at the time of inclusion. The mean diabetes duration was 17±9 years and the median duration of the follow-up period was 61±19 months [69]. Patients were categorized according to U/S into either having “large” kidneys (median kidney length=118±10 mm) or “small” kidneys (median kidney length=98±8 mm), with the kidneys leaning to be smaller in patients with advanced renal disease (p=0.08). Through the follow-up period, 9/11 patients who had to start dialysis belonged to the group with large kidneys, in spite of a 40% higher initial GFR[69]. The initial attributes were similar between both groups, although those with large kidneys had lower serum creatinine and higher GFR (p < 0.05). Remarkably, the serum creatinine increased over time in those with large kidneys (140 (50-952) versus 103 (50-371) micromol/L, P=0.002), whereas it stayed constant in those with small kidneys (129 (69-283) versus 125 (79-320) micromol/L, P< 0.05) [69]. This difference persisted in those with severe degrees of renal failure. The study was limited by using eGFR based on the Mayo Clinic Quadratic equation [69], rather than measuring GFR via Cr-EDTA clearance, which might reveal more significant differences in patients with mild and moderate CKD [69,70]. Moreover, kidney length was determined by several operators, however, the degree of variation is thought to be acceptable [71]. Thus, renal size by U/S could potentially be a vital predictor of DN progression that needs to be reproducible.

3. Conclusion

CKD is a dreadful complication with high prevalence among diabetic patients being responsible for elevated morbidity, mortality and a huge dialysis cost. Several studies have been conducted with the aim of

evaluating conventional and novel markers in predicting the development and progression of DN. Recent studies have identified age, gender, sex hormones, smoking, hypertension, obstructive sleep apnea, eccentric ventricular hypertrophy, anemia, renal hypertrophy, serum markers, and urinary markers as promising predictors of DN development. While there is a substantial danger from the increasing prevalence of DN, we suggest a potential algorithm for DN prediction and early detection (Figure 4). Although it is not inclusive, but will encourage further proving the currently suggested predictors as well as exploring new potential ones. Further efforts are necessary to identify definite strategies for practical implementation in future screening programs. Prevention is better than cure!

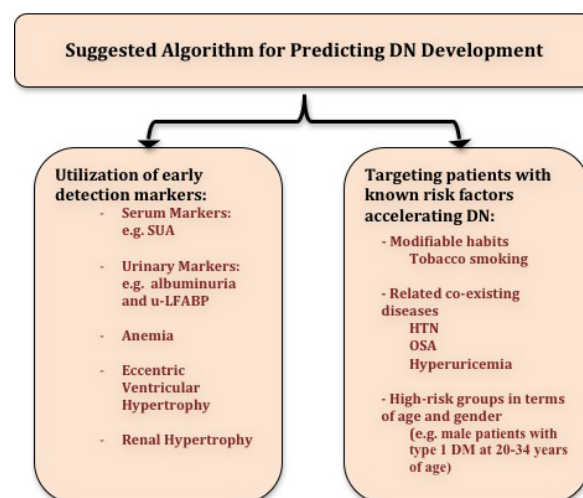


Figure 4. A suggested simplified algorithm utilizing various tools with the attempt of early predicting of DN. Utilizing two parallel approaches, early detection markers and screening high-risk individuals might constitute a promising methodology in prediction and prevention of DN development.

Conflict of Interest

Non declared.

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