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REVIEW

Risks of rapid decline renal function in patients with type 2 diabetes

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Abstract

Progressive rising population of diabetes and related nephropathy, namely, diabetic kidney disease and associated end stage renal disease has become a major global public health issue. Results of observational studies indicate that most diabetic kidney disease progresses over decades; however, certain diabetes patients display a rapid decline in renal function, which may lead to renal failure within months. Although the definition of rapid renal function decline remained speculative, in general, it is defined by the decrease of estimated glomerular filtration rate (eGFR) in absolute rate of loss or percent change. Based on the Kidney Disease: Improving Global Outcomes 2012 clinical practice guidelines, a rapid decline in renal function is defined as a sustained decline in eGFR of > 5 mL/min per 1.73 m^2 per year. It has been reported that potential factors contributing to a rapid decline in renal function include ethnic/genetic and demographic causes, smoking habits, increased glycated hemoglobin levels, obesity, albuminuria, anemia, low serum magnesium levels, high serum phosphate levels, vitamin D deficiency, elevated systolic blood pressure, pulse pressure, brachial-ankle pulse wave velocity values, retinopathy, and cardiac autonomic neuropathy. This article reviews current literatures in this area and provides insight on the early detection of diabetic subjects who are at risk of a rapid decline in renal function in order to develop a more aggressive approach to renal and cardiovascular protection.

Key words: Type 2 diabetes; Diabetic kidney disease; Rapid decline; Estimated glomerular filtration rate; Albuminuria

Core tip: The progression rate of diabetic kidney disease is highly variable, a rapid decline of renal function can lead to renal failure within months. Risk factors account for rapid decline renal function in patients with type 2 diabetes include ethnic/genetic and demographic factors, lifestyle and health behaviors, advanced albuminuria, poor glycemic control, dyslipidemia and some biochemical abnormalities. Diabetic patients with retinopathy or cardiac autonomic neuropathy are at increased risk of a rapid decline in estimated glomerular filtration rate. Early detection of high-risk groups with a more aggressive multifactorial approach to renal and cardiovascular protection is important.

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INTRODUCTION

Type 2 diabetes is one of the leading causes of chronic kidney disease (CKD) worldwide, and diabetic kidney disease has become a major global public health issue[1]. Early detection and intervention in diabetic kidney disease can help to slow renal function decline, prevent complications, and decrease cardiovascular events, thereby improving survival and quality of life in type 2 diabetics[2]. However, potential causes accounting for variation in diabetic kidney disease and its rate of progression are still largely unexplored. In most cases, disease progresses over decades; however, a rapid decline in renal function can lead to renal failure within months[3]. Thus, in type 2 diabetics, defining high-risk groups and preventing or retarding disease progression is an emerging challenge. This review targets the potential risk factors of a rapid decline in renal function in patients with type 2 diabetes.

EPIDEMIOLOGY OF DIABETIC KIDNEY DISEASE

Diabetic kidney disease is identified clinically through the presence of albuminuria, impaired glomerular filtration rate (GFR), or both[4], and these two biomarkers have been used for the diagnosis, severity classification, and outcome prediction of CKD[5-8]. The categories of albuminuria are defined as microalbuminuria or macroalbuminuria based on a urinary albumin-to-creatinine ratio (UACR) of 30-300 mg/g, or > 300 mg/g, respectively[9,10], and impaired renal function is defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m^2[1,4,10]. International consensus on the incidence of CKD in patients with type 2 diabetes is lacking[11]. Although the prevalence of diabetic CKD is increasing worldwide, there are large differences between regions and ethnicities (Table 1). A report from the UK Prospective Diabetes Study (UKPDS), states that 1544 (38%) of 4031 patients developed albuminuria (microalbuminuria or macroalbuminuria), and 1449 (29%) of 5,032 patients developed renal impairment (based on the Cockroft-Gault formula of eGFR < 60 mL/min per 1.73 m^2) over a 15-year period[12]. Meanwhile, the Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes (DEMAND) study, in which data from 32208 type 2 diabetics from 33 countries were collected, reported that overall global prevalence of microalbuminuria and macroalbuminuria was 39% and 10% respectively, while eGFR below 60 mL/min per 1.73 m^2 occurred in 22% of the 11573 patients with available data[13]. According to the US Renal Data System (USRDS) 2013 report, 3 out of 5 new end stage renal disease (ESRD) patients came from diabetes in Malaysia, Mexico, and Singapore; furthermore in the United States, the odds ratios of diabetes in albuminuria (UACR more than 30 mg/g) and CKD (defined as eGFR below 60 mL/min per 1.73 m^2) were 3.9 and 2.1 respectively[14]. It was recently reported that 30% of CKD in 5584 Chinese patients aged 20-79 years, was associated with dysglycemia (diabetes and prediabetes), independent of age, sex, and hypertension status[15]. It should be noted that some limitations and pitfalls were identified in these epidemiological data, for example, demographic distribution[11], socioeconomic status[16], dynamic changes in the incidence of diabetes, changes in the use of medication (including anti-diabetic drugs and anti-hypertensive drugs), and the improvement of survival rates in diabetic and ESRD patients[11].

DEFINING A RAPID DECLINE IN RENAL FUNCTION

Annual decline in GFR in an individual varies widely depending on race, age, the presence of underlying conditions, the etiology of CKD, and the presence of comorbidities. A previous study reported that age-related eGFR decline is about 0.75-1 mL/min per 1.73 m^2 per year over 40 years of age[17]. Among the healthy population, eGFR decline is approximately 0.36-1.21 mL/min per 1.73 m^2 per year[5,18-21]. A community-based cohort study reported a decline in eGFR of 2.1 and 2.7 mL/min per 1.73 m^2 per year respectively for women and men with diabetes, whereas the rate of decline was 0.8 and 1.4 mL/min per 1.73 m^2 per year respectively for women and men without diabetes[18,22]. In subjects with CKD, a more rapid decline in renal function (ranging 1.03-4.3 mL/min per 1.73 m^2 per year) was noted[10,23-26] (Table 2). Some studies define rapid decline of eGFR in terms of absolute rate of loss, while others define it as percent change (Table 3)[3,27-30]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guidelines for the evaluation and management of CKD, developed by the National Kidney Foundation, a rapid decline in renal function is defined as a sustained decline in eGFR of > 5 mL/min per 1.73 m^2 per year (as estimated using the 2009 CKD-EPI creatinine equation)[31]. It is generally believed that at present, there are a lack of well-controlled studies, which include frequent measurements and a long follow-up period, from which to establish an optimal definition of a rapid decline in renal function[18].

RISK FACTORS OF A RAPID DECLINE IN RENAL FUNCTION

An emerging challenge is the identification of potential factors associated with rapid renal function decline, which would form the basis for the development of strategies to prevent or retard disease progression, and reduce complications, thereby improving disease outcomes and quality of life in type 2 diabetics. Potential risk factors include ethnic/genetic and demographic factors, lifestyle and health behaviors, metabolic and biochemical abnormalities, cardiovascular functional factors, and some clinical symptoms of type 2 diabetes (Figure 1).

Table 1 Prevalence of albuminuria and impaired glomerular filtration rate in diabetic patients

Ref.	Population (Nationality)	Albuminuria prevalence	Impaired GFR prevalence
Parving *et al*[13]	International DEMAND study of 33 countries 2006 32208 type 2 diabetic patients	Microalbuminuria: 39% Macroalbuminuria: 10%	22%
Bos *et al*[108] data from: Herman *et al*[109]	Northern Africa Systematic review of PubMed 1990-2012	Egypt 1998: Albuminuria: 21%[109]	Egypt 1998-Outpatient clinics: 6.7%[109]
Hamed *et al*[111]	> 18 years old diabetic patients	Sudan 2008 (insulin treated diabetic patients): Albuminuria: 22%[110]	Egypt 1995-Hospital inpatients: 46.3%[111]
Icks A and Koch M Epidemiology of chronic kidney disease in diseases. In: Wolf G. Diabetes and Kidney Disease[11], data from: Chadban *et al*[112]	Australia AusDiab study: a national population-based cross-sectional survey > 25 years old diabetic patients	8.70% proteinuria-spot urine protein to creatinine ratio (abnormal: > 0.20 mg/mg)	27.60%
Unnikrishnan *et al*[113]	Southern India CURES 45 study 17, 16 type 2 diabetic patients	Microalbuminuria: 36.9% Macroalbuminuria: 2.2%	-
Icks A and Koch M Epidemiology of chronic kidney disease in diseases. In: Wolf G. Diabetes and Kidney Disease[11], data from: Lin *et al*[114]	Taiwan Community-based screening 1999–2001 > 30 years old type 2 diabetic patients	29.40% proteinuria-spot urine protein to creatinine ratio (abnormal: > 0.20 mg/mg)	15.10%
Yang *et al*[115]	China A nationally representative sample from 14 provinces and municipalities > 20 years old diabetic patients	17.30%	19.10%
Lou Arnal *et al*[116]	Spain A survey of 16 Health Centers of the Alcañiz Health Sector 2008 > 18 years old, 3466 type 2 diabetic patients	31.70%	25.20%
Detournay *et al*[117]	France ENTRED data 2007 A survey of the national public prescription claims database Type 2 diabetic patients	-	22%
Collins *et al*[14]	United Status NHANES study 2005-2010 Adult diabetic patients	29.90%	19.30%
Al-Rubeaan *et al*[54]	Saudi Arabia SNDR data > 25 yr, 54670 type 2 diabetic patients	Microalbuminuria: 1.2% Macroalbuminuria: 8.1%	GFR < 30 mL/min per 1.73 m^2: 1.50%

Albuminuria: Albumin-to-creatinine ratio (UACR) > 30 mg/g; Microalbuminuria: UACR 30-300 mg/g; Macroalbuminuria: UACR > 300 mg/g; Impaired glomerular filtration rate (GFR): Estimated GFR < 60 mL/min per 1.73 m^2; DEMAND: Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes study; AusDiab: The Australian Diabetes, Obesity and Lifestyle Study; CURES: Chennai Urban Rural Epidemiology Study; ENTRED: Échantillon national témoin représentatif des personnes diabétiques (National Representative Sample of Diabetic Patients); NHANES: National Health and Nutrition Examination Survey; SNDR: Saudi National Diabetes Registry.

Ethnic, genetic, and demographic factors

Ethnicity is a one of major factors affecting the progression of CKD in diabetic patients. In the United Kingdom, residents of South Asian origin had a higher prevalence of overt proteinuria and a lower prevalence of microalbuminuria compared to those with White European ethnicity[1,32]. In a 5-year retrospective, community-based cohort study of 135 general practices in East London, in which 3855 diabetic patients with an eGFR of < 60 mL/min per 1.73 m^2 were enrolled, renal function decline occurred at a significantly higher rate in South Asians as compared to other ethnicities[33]. According to the USRDS 2012 annual data report[34], ESRD caused by diabetes has increased in African-American, Native American, and Hispanic populations over the past decade[1,2,34]. USRDS 2013 also reported that the contribution of diabetes to ESRD was 59%-61% in Malaysia, Mexico, and Singapore in 2011, and above 40% in Israel, the Republic of Korea, Hong Kong, Taiwan, the Philippines, Japan, the United States, and New Zealand[14]. In summary, diabetic patients of Hispanic, black, Asian, and Maori ethnicity are at a higher risk of a rapid decline in renal function compared to white populations.

Ethnic differences in the presentation of diabetic kidney disease may reflect either genetic predisposition or differences in public health care policy[1], and thus, genetic studies need to exclude non-genetic confounders. Evidence of genes associated with diabetic nephropathy in type 2 diabetics comes mainly from family-based genome-wide linkage studies[35,36]. Findings from such studies include reports that 7p14.1 [engulfment and cell motility 1 (ELMO1)][37,38], 7q21.1/7q21.3[39] and 18q22.3

Table 2 Decline of estimated glomerular filtration rate in different populations

Population	eGFR decline (mL/min per 1.73 m^2 per year)	Ref.
Healthy		
PREVEND study 6894 subjects	0.55 Estimated using MDRD formula	Halbesma *et al*[5]
Annual health exam, Japan 120727 subjects	0.36 Estimated using MDRD formula modified by a Japanese coefficient	Imai *et al*[19]
ARIC study 13029 subjects	0.47 Estimated using MDRD formula	Matsushita *et al*[20]
Tromso Study, Norway 2249 men and 2192 women	1.21 (men) 1.19 (women) Estimated using MDRD formula	Kronborg *et al*[21]
Aged without diabetes		
2475 men > 65 years old	1.4	Hemmelgarn *et al*[22]
3163 women > 65 years old	0.8	Hemmelgarn *et al*[22]
Aged with diabetes		
490 men > 65 years old	2.7	Hemmelgarn *et al*[22]
445 women > 65 years old	2.1	Hemmelgarn *et al*[22]
CKD		
MDRD study group eGFR 25-80 mL/min per 1.73 m^2, n = 28	3.7	MDRD study group Levey *et al*[23]
eGFR 7.5-24 mL/min per 1.73 m^2, n = 63	4.3	
African Americans with hypertension eGFR 20-65 mL/min per 1.73 m^2 low mean arterial pressure, n = 380 normal mean arterial pressure, n = 374	2.21 1.95	Wright *et al*[24]
Tromso Study, Norway eGFR 30-59 mL/min per 1.73 m^2 3047 subjects	1.03	Eriksen *et al*[25]
eGFR < 60 mL/min per 1.73 m^2 4231 subjects	2.65	Levin *et al*[26]

Data from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group[18]; eGFR: Estimated glomerular filtration rate; CKD: Chronic kidney disease; PREVEND: Prevention of Renal and Vascular End-Stage Disease; ARIC: Atherosclerosis Risk in Communities; MDRD: Modification of Diet in Renal Disease Study.

[carnosine dipeptidase 1 (CNDP1)][40,41] are associated with the development of proteinuria and ESRD in African-Americans; 18q22.3 (CNDP1) is associated with proteinuria and ESRD in American-Indians[4]; and 17p14.1[37], 12q24.11 [acetyl-CoA carboxylase alpha (ACACB)][42], 13q34(rs1411766)[43], and 16q13 [solute-carrier group (SLC12A3)][44] may be associated with proteinuria and ESRD in Japanese[36]. Furthermore, haptoglobin (Hp) is a hemoglobin-binding protein that has a major role in protecting against heme-driven oxidative stress. Previous studies have shown the importance of the Hp genotype in the progression of diabetic nephropathy[45,46]. Moreover, diabetic patients with Hp 2-2 are more likely to develop nephropathy than those with Hp2-1 or Hp1-1[47,48].

Demographic factors may also influence the progression of diabetic kidney disease. Previous studies indicate that age is a significant predictor of progressive albuminuria and renal dysfunction in diabetics[49-54], and most studies reported that male sex is an important independent factor associated with renal function decline in type 2 diabetics[12,50,54,55]; however, some studies have shown an association with female sex[56].

Lifestyle and health behaviors

Smoking is an established factor for increased risk of development and rapid progression of diabetic kidney disease[12,54,57-59]. Also, some studies suggest an association between diet and renal function decline in diabetics, for example in those with high alcohol consumption[58] or a high-protein diet[59]. It has been demonstrated that a high dietary acid load (*e.g.*, in diets high in rice and meat) is associated with rapid progression of diabetic nephropathy to ESRD in Westernized South Asian people[60]. Lack of physical activity is also considered to be a risk factor in diabetic nephropathy[58], with a previous study reporting that high physical activity in women was associated with an improvement in eGFR[21].

Metabolic and biochemical factors

A number of metabolic conditions, such as hyperglycemia[61,62], dyslipidemia[63-65], or being overweight/obese[31,49,66], are widely recognized as being associated with the development of diabetic nephropathy, and are established factors in identifying subjects at a greater risk of disease progression[57]. Previous studies indicate that obesity, hyperglycemia, and dyslipidemia are significant predictors of progressive albuminuria[49-53,67,68]. A recent cross-sectional study reported UACR significantly correlated with metabolic syndrome and its components, including hyperglycemia, central obesity, and high triglyceride lev-

Table 3 Definitions of rapid renal function decline

	Population (Nationality)	Rapid renal function decline	Ref.
Study			
	United States 4380 patients from the community-based CHS ⩾ 65 years old Follow-up: 7 yr 14% with diabetes	> 3 mL/min per 1.73 m^2 per year	Reviewed by KDIGO CKD Work Group[18]: Shlipak *et al*[28] Rifkin *et al*[30]
	Taiwan 577 type 2 diabetes patients from an outpatient department in a hospital-based study 63 years old (mean age) Follow-up: 1 yr	> 3 mL/min per 1.73 m^2 per year	Sheen *et al*[72]
	472 CKD 4-5 patients from an outpatient department in a hospital-based study 65 years old (mean age) 35.4% with diabetes Follow-up: 1.5 yr (17.3 mo)		Tsai *et al*[118]
	Canada 4231 patients with eGFR < 30 mL/min per 1.73 m^2 from a cohort derived from all patients registered in a provincial database Follow-up: 2.5 yr (31 mo)	> 4 mL/min per 1.73 m^2 per year	Levin *et al*[26]
	Italy 1682 type 2 diabetes patients with eGFR ⩾ 60 mL/min per 1.73 m^2 from an outpatient department in a hospital based study Follow-up: 10 yr	> 4% per year	Zoppini *et al*[70]
	Canada 3154 patients with eGFR ⩾ 60 mL/min per 1.73 m^2, from the community based Walkerton Health Study (2002 to 2008) Follow-up: 7 yr	> 5% per year	Clark *et al*[74,119]
	Taiwan 7968 civil servants and teachers ⩾ 50 years old (mean age: 57 years old) Follow-up: 15 yr	> 20% per year	Reviewed by KDIGO CKD Work Group[18]: Cheng *et al*[29]
	Taiwan 167 patients in a hospital based study	> 25% per year	Chen *et al*[85]
Review	Chronic kidney disease Lancet	> 4 mL/min per 1.73 m^2 per year	Levey *et al*[3]
Guideline	KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease KDIGO CKD Work Group	> 5 mL/min per 1.73 m^2 per year	Inker *et al*[10] KDIGO CKD Work Group[18]

CHS: Cardiovascular Health Study; KDIGO: Kidney Disease: Improving Global Outcomes; eGFR: Estimated glomerular filtration rate; CKD: Chronic kidney disease.

els[65,69]. Factors associated with eGFR decline and progressive albuminuria might overlap. During a 10-year follow-up, an observational study of 1682 type 2 diabetics with baseline eGFR ⩾ 60 mL/min per 1.73 m^2 reported that obese patients had a significantly faster age-adjusted annual eGFR decline[70]. A positive association between glycated hemoglobin (HbA1c) and CKD has also been observed in type 2 diabetics, even in the absence of albuminuria and retinopathy[52]. An association between blood glucose, low-density lipoprotein abnormalities, and the progression of renal damage in diabetes has been reported[71]. HbA1c was found to be independently associated with rapid renal function decline in a group of type 2 diabetics without symptomatic cardiovascular disease[72].

Albuminuria and eGFR are not only biomarkers for the diagnosis and categorization of CKD[4], but are also well-known predictors of renal function decline, ESRD, and death in type 2 diabetics[8,73]. Proteinuria is associated with rapid decline in renal function[49-53], and a previous study suggests that dipstick proteinuria measurement could be used as a screening tool for rapid renal function decline[74].

Abnormalities in cardiovascular function

CKD shares many risk factors with cardiovascular disease[72,75], and dysfunction in one system can often lead to dysfunction in the other[49]. In patients with concomitant hypertension and type 2 diabetes, the risk of progression to ESRD is 7 fold that for age-matched control subjects[49,76]. Hypertension is a significant risk factor for insufficient renal function, cardiovascular events, and death in patients both with and without type 2 diabetes[49,61,77-79]. Previous studies show that systolic blood pressure (SBP) and pulse pressure are stronger predictors than diastolic blood pressure of renal outcomes, and are independent risk factors in the rapid decline of eGFR in type 2 diabet-

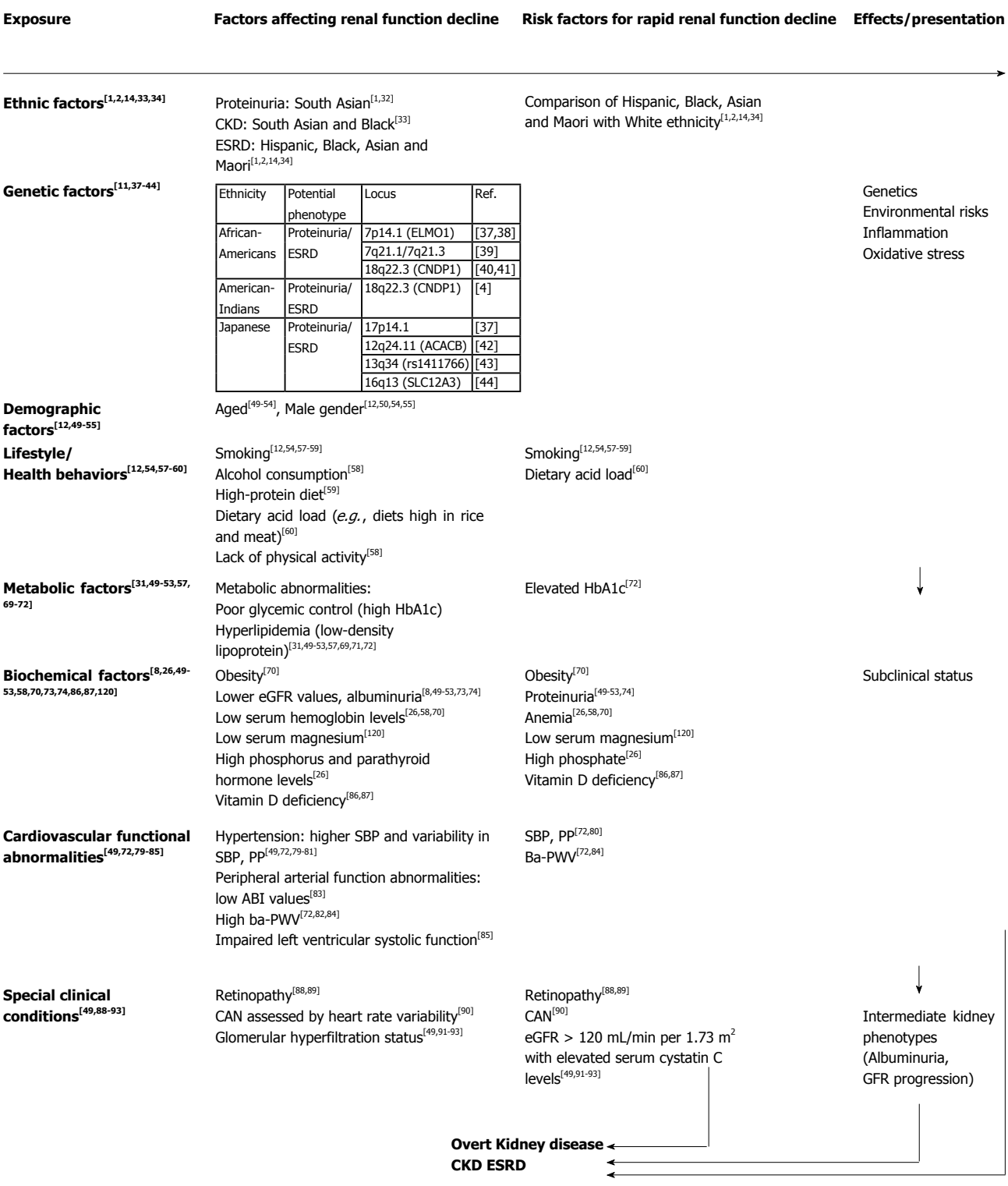

Figure 1 Conceptual model for diabetic kidney disease and potential risk factors of rapid renal function decline. CKD: Chronic kidney disease; HbA1c: Glycated hemoglobin; ESRD: End stage renal disease; eGFR: Estimated glomerular filtration rate; SBP: Systolic blood pressure; ba-PWV: Brachial-ankle pulse-wave velocity; PP: Pulse pressure; CAN: Cardiac autonomic neuropathy; ELMO1: Engulfment and cell motility 1; CNDP1: Carnosine dipeptidase 1; *ACACA*: *Acetyl-CoA carboxylase alpha*; *rs*: *RefSNP (Single Nucleotide Polymorphism) numbers*; SLC: Solute-carrier group.

ics[72,80], while another study suggests that both SBP and variability in SBP are risk factors in the development and progression of diabetic nephropathy[81].

In addition to blood pressure, peripheral arterial functional markers are also associated with renal function in type 2 diabetics[82]. A low ankle-brachial index was found to be significantly associated with a low eGFR[83]. Also, arterial stiffness is associated with incident albuminuria and decreased eGFR[72,84], and brachial-ankle pulse-wave velocity (ba-PWV) values are independently associated with rapid renal function decline in type 2 diabetics without symptomatic cardiovascular disease[72]. One study

reports that impaired left ventricular systolic function and increased ba-PWV are independently associated with a rapid decline in renal function[85].

Miscellaneous

Some other factors, such as low hemoglobin levels and electrolyte imbalance, may cause a rapid progression in diabetic kidney disease. Conditions including anemia, low serum magnesium levels, and high phosphorous and parathyroid hormone levels, are associated with rapid renal function decline in type 2 diabetics[26,58,70]. Furthermore, vitamin D deficiency associated with albuminuria was an independent risk factor in diabetic nephropathy after adjusting for demographic factors, hypertension, dyslipidemia, smoking status, and medication use[86,87].

Type 2 diabetic patients with additional microvascular complications, such as retinopathy or neuropathy, may also experience a rapid decline in renal function. Several studies have demonstrated that the rate of renal disease progression in type 2 diabetics with retinopathy is faster than that observed in those without retinopathy[88,89]; thus, screening for retinopathy may be helpful in identifying high-risk patients. Another study on cardiac autonomic neuropathy that assessed heart rate variability suggests that this is also an independent predictor of eGFR decline and could also be used as an identifying factor[90].

Special issues

Glomerular hyperfiltration and rapid renal function decline in type 2 diabetes: A longitudinal study of 600 type 2 diabetics with albuminuria < 200 μg/min, found that those with an eGFR > 120 mL/min per 1.73 m^2 had a higher risk of albuminuria progression (hazard ratio: 2.16) compared with those without baseline hyperfiltration; over a 4-year follow-up, renal function decline was relatively rapid, at an annual rate of up to 3.37 mL/min per 1.73 m^2[91]. Another study evaluated type 2 diabetic Pima Indians selected from participants in the Diabetic Renal Disease Study, with a baseline iothalamate clearance above the median for the entire study cohort (120 mL/min per 1.73 m^2) to give a study group with a normal or elevated GFR[92]. After a mean follow-up of 3.8 years, it was shown that directly measured GFR declined at 4.4% per year, and supposed that an increase in serum cystatin C provide means for detecting early renal function decline in diabetes[92]. Measurement of serum cystatin C may help to identify groups at high risk of renal function decline based on hyperfiltration status[49,93].

Non-albuminuric diabetic kidney disease: Renal insufficiency in the absence of albuminuria in patients with type 2 diabetes is another issue that should be noted. In a 1977 study of type 2 diabetic adults, 13% had an eGFR < 60 mL/min per 1.73 m^2, and 30% had neither albuminuria nor retinopathy[94]. Furthermore, data from UKPDS[12], DEMAND[13], and Atherosclerosis risk in Communities (ARIC)[52] studies suggests that the occurrence of renal impairment in type 2 diabetics without albuminuria is not unusual[49]. Microalbuminuria and reduced eGFR have been suggested as markers of different pathologic processes, with microalbuminuria associated with endothelial dysfunction and reduced eGFR being a renal manifestation of systemic atherosclerosis[49,95]. These patients are at higher risk of CKD progression, as the absence of proteinuria may lead to delays in the diagnosis and treatment of diabetic nephropathy[1,49].

POSSIBLE MANAGEMENT STRATEGIES

A number of therapeutic interventions for diabetic kidney disease have been developed over the past few decades[96]. Several studies have demonstrated increased activity in the renin-angiotensin-aldosterone system in diabetic patients with nephropathy[97,98]. Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) treatment for diabetics with hypertension can reduce renal damage and may reduce cardiovascular complications[97-99]; thus, ACEI or ARB are recommended as a first-line treatment for diabetics with hypertension[2,10,98,100,101]. However, based on the ONTARGET trial, acute dialysis, hyperkalemia, and hypotension tended to be more frequent with the use of both ACEI and ARB; thus, dual inhibition of the renin-angiotensin system is not recommended[102]. Primary multifactorial interventions aimed at slowing progression of diabetic nephropathy include combination therapy targeting hyperglycemia, hypertension, microalbuminuria, and dyslipidemia[59]. The Steno-2 study, of 151 type 2 diabetics with baseline microalbuminuria who underwent multifactorial treatment, reported that at a 7.8-year follow-up 46 patients showed remission to normoalbuminuria, improved hypertensive and glycaemic control were independent predictors for remission, and that kidney function may have been preserved through a slower rate of eGFR decline[103]. Other studies provide evidence that intensive multifactorial management is more effective than conventional treatment[104-107]. In addition to blood pressure, glycemic and lipid control, lifestyle modifications such as cessation of smoking, protein restriction in diets, weight reduction[2,59], light to moderate exercise[4], and vitamin C[104,105] and vitamin D supplementation[26], may be helpful in preventing or slowing the progression of diabetic kidney disease[2,26,59].

CONCLUSION

The progression of diabetic kidney disease is highly variable. According to the KDIGO 2012 clinical practice guidelines for the evaluation and management of CKD, a rapid decline in renal function was defined as a sustained decline in eGFR of > 5 mL/min per 1.73 m^2 per year. Associated risk factors in patients with type 2 diabetes include ethnic/genetic and demographic factors, lifestyle and health behaviors, advanced albuminuria, poor glycemic control, dyslipidemia, and some biochemical abnormalities. Diabetic patients with retinopathy or cardiac

autonomic neuropathy are at increased risk of a rapid decline in eGFR. Furthermore, those with glomerular hyperfiltration and elevated serum cystatin C may also be at increased risk of a rapid decline in renal function. Early detection of high-risk groups with a more aggressive multifactorial approach to renal and cardiovascular protection is important.

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