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Review

Prevalence of diabetic kidney disease in prediabetes

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ABSTRACT

Background: Chronic renal failure is a debilitating and expensive complication of diabetes mellitus (DM). It is controversial if kidney disease may occur in prediabetes stages. We systematically reviewed the prevalence of diabetic kidney disease (DKD) as defined by albuminuria or reduced glomerular filtration rate (GFR) in prediabetes.

Methods: We searched for studies reporting the frequency of DKD in prediabetes (impaired plasma glucose, impaired glucose tolerance and glycated hemoglobin). Exclusion criteria were subjects aged < 18 years and type 1 DM. Eleven articles were selected and considered for analysis from a total of 371 abstracts.

Results: DKD prevalence ranged from 4.5% to 26.0% in prediabetics and from 0 to 16.0% in normoglycemics. In two articles, DKD diagnosis was based on eGFR and the prevalence ranged from 4.5 to 21.3%; in six articles, based on albuminuria, between 7.0 and 26.0%; and in three articles, based on combined criteria (eGFR and albuminuria), between 12.3 and 17.7%.

Conclusion: Our findings indicated that DKD occurs in prediabetes stages. Mild glucose metabolism disturbance has a relevant impact on the prevalence of DKD that deserves attention of clinicians and public health authorities. Additional studies with representative samples in different populations are needed to estimate how kidneys are affected by prediabetic states.

1. Introduction

Kidney disease represents a debilitating complication of DM that develops after years of persistent hyperglycemia, and chronic renal failure is a heavy burden for health care systems. In developed countries, DM is the most common cause of renal replacement therapy and end stage kidney disease (American Diabetes Associa, 2018a). The number of diabetic subjects under dialysis has increased in the USA and Europe in parallel to the rates of DM (Collins et al., 2009)' (Van Dijk et al., 2005)' (Bommer, 2002). Some regional studies regarding renal replacement therapy in Brazil has also shown that DM was among the main causes (Pinto et al., 1997; Cherchiglia et al., 2010). According to the Brazilian Chronic Dialysis Survey, DM as a cause of dialysis has increased reaching 28% in 2010 (Sesso et al., 2011) and 41% in 2016 (Sesso et al., 2017). This has mainly been explained by the increase in prevalence of type 2 DM and the survival of diabetic subjects.

The natural history of type 2 DM is characterized by a long period of slightly elevated plasma glucose which already indicates abnormality in glucose metabolism. It is known that such metabolic instability is sufficient to increase cardiovascular risk and macrovascular complications that may even precede the clinical diagnosis of DM (Vistisen et al., 2018). On the other hand, microangiopathy in retina and kidney typically manifests in subjects with overt DM (fasting plasma glucose ≥ 126 mg/dL or 2-h plasma glucose post 75-g glucose load ≥ 200 mg/dL).

According to the American Diabetes Association (ADA), the term prediabetes has been attributed to the conditions of impaired fasting glucose – IFG (between 100 and 125 mg/dL) and impaired glucose tolerance – IGT (2-h post-load between 140 and 199 mg/dL) that are at increased risk for DM (Unwin et al., 2002). Also, glycated hemoglobin (HbA1c) ranging from 5.7 to 6.4% has been used for this purpose (American Diabetes Associa, 2018b). In an American population-based study, approximately 38% of adults were found to be prediabetics (Menke et al., 2015). In the Rotterdam Study, the prevalence of prediabetes was 14%; most importantly, the lifetime risk of subjects aged 45 years for developing prediabetes was 48.7% and the progression rate of prediabetes to DM was 74% (Lithrat et al., 2016). Lower rates reported in Europe may be in part due to prediabetes diagnosed by the

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World Health Organization (WHO) criteria, in which a higher cutoff of fasting plasma glucose (110 mg/dL) is employed (Alberti and Zimmet, 1998).

Despite a clear causal relationship between DM and kidney disease, the presence of DKD in states that precede overt DM is controversial (Echouffo-Tcheugui et al., 2016). This controversy may be at least in part due to underdiagnosis in clinical practice and to heterogeneous criteria for DKD in the early phase of glucose metabolism disturbance. Initial but reversible renal damage in DM has been identified by the presence of glomerular hyperfiltration. Long-term glomerular injury leads to urinary albumin loss that can be assessed by the albumin-creatinine ratio (ACR), commonly used to classify the DKD stages along with reduction in glomerular filtration rate (GFR). Hyperfiltration has been attributed to GFR higher than 125 mL/min/1.73 m^2 while reduced GFR is below 60 mL/min/1.73 m^2.

As far as we know, a compilation of studies investigating the occurrence of DKD in this phase of the natural history of DM is not available in literature. Few publications have reported evidence of DKD in prediabetic categories (De Nicola et al., 2016). Knowledge about renal damage in prediabetic phases is relevant considering the high prevalence rates of prediabetes in populations and potential benefits of interventions in DKD. In PROSPERO databases, no systematic review addressing this issue was found PROSPERO, .

The present study systematically reviewed the reported frequencies of DKD as defined by albuminuria or reduced GFR in subjects with prediabetic conditions (American Diabetes Associa, 2018a; Kidney Disease Improving Global Outcomes - KDIGO, 2012, 2013).

2. Methods

Details of the protocol of this systematic review were registered on PROSPERO and can be assessed on the website (ID Register 103055) PROSPERO, . We followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA 2009) statement which includes a 27-items checklist and a four-phase flow diagram to guide this review. We examined medical literature in English language since 2003 – when the ADA criteria for prediabetes were reported (American Diabetes Associa, 2015) – using the MEDLINE database of the National Library of Medicine, LILACS and SciELO. The reference list of scrutinized reports was also scanned to find more relevant articles.

Studies included in this review should report frequencies of kidney disease in adults with prediabetes, irrespective of the criteria used (fasting plasma glucose, 2-h oral glucose tolerance test or/and HbA1c). Diagnostic values for IFG or IGT were provided in mg/dL or in mmol/L; to unify the units in the text and table all the values and ranges are presented in mg/dL. Although several terms were used to define abnormalities of kidney function in prediabetes, we selected DKD to refer to renal damage reflected by the presence of elevated albuminuria (ACR ≥ 30 mg/g or ACR between 22 and 220 mg/g) and reduced eGFR, calculated by using the Modification of Diet in Renal Disease Study – MDRD or the Chronic Kidney Disease Epidemiology Collaboration – CKD-EPI formula (Kidney Disease Improving Global Outcomes - KDIGO, 2012, 2013). Exclusion criteria were age < 18 years and type 1 DM.

To assess the frequency of DKD in prediabetic categories, the medical subject headings (MeSH) checked were “diabetic kidney disease OR nephropathy prevalence OR frequency AND prediabetes”, “diabetic renal disease prevalence AND prediabetes”, “microalbuminuria OR albuminuria AND prediabetes OR impaired fasting glucose OR impaired glucose tolerance”. A total of 371 articles were identified: 360 articles in MEDLINE, five articles in SciELO and six articles in LILACS databases (Fig. 1). All 371 abstracts were read, 343 were excluded because 308 were not directly related to the purpose, 11 were not in the English language and 24 were duplicate articles. From the remaining 28 reports, 17 were excluded (14 not related to the frequency of prediabetes and three reviews). Thus, eleven articles were selected for a full-text reading and included in the final descriptive analysis.

3. Results

Among eleven selected articles, seven studies were originally mentioned as cohorts (Schöttker et al., 2013; Lin et al., 2017; Tapp et al., 2004; Bahar et al., 2013; Won et al., 2015; Kim et al., 2014; Ali et al., 2018) and four had cross-sectional design (Suzuki et al., 2004; Li et al., 2009; Plantinga et al., 2010; Zhou et al., 2013). Cross-sectional analyses of the cohorts were performed at the baseline (Lin et al., 2017) or at the end (Schöttker et al., 2013; Tapp et al., 2004; Bahar et al., 2013; Won et al., 2015; Kim et al., 2014; Ali et al., 2018) of these studies. Therefore, all the studies allowed estimates of prevalence. There was only one cohort conducted in a German population in which the incidence rate was also provided (Schöttker et al., 2013).

The diagnosis of DKD was based on the eGFR (n = 2), on the presence of albuminuria (n = 6; 4 in cohorts and 2 in cross-sectional studies), and three article that used combined criteria (eGFR and albuminuria).

3.1. Studies using eGFR criteria

The German population-based cohort ESTHER included subjects aged between 50 and 74 years without abnormalities of renal function, who were recruited between 2000 and 2002 and followed up for eight years (Schöttker et al., 2013). Prediabetes diagnosis was based on FPG (100–125 mg/dL) or HbA1c (5.7–6.4%); reduced kidney function was defined by eGFR < 60 mL/min/1.73 m^2 according to the CKD-EPI (Kidney Disease Improving Global Outcomes - KDIGO, 2012, 2013). At the end of the follow-up, 18.7% of prediabetic subjects characterized by FPG or HbA1c developed reduced GFR. When both parameters of glucose metabolism (FPG and HbA1c) were altered in prediabetic subjects, their prevalence of 21.3% was significantly higher than in normoglycemic subjects. Descriptive analysis showed that age, smoking, body mass index, systolic blood pressure and also lipids and their medications as well as cardiovascular event were associated with DKD. The difference observed in crude prevalence rates [RR 1.33 (95%CI 1.03–1.73)] did not persist after adjusting for cardiovascular risk factors [RR 1.06 (95%CI 0.71–1.32)].

The REACTION study (Risk Evaluation of cAncers in Chinese diabeTic Individuals) is a nationwide prospective observational study from China that included 250,752 subjects aged ≥ 40 years recruited between 2011 and 2012 (Lin et al., 2017). Prediabetes was defined as FPG (110–125 mg/dL) and/or 2-h plasma glucose (140–199 mg/dL), and DKD as eGFR < 60 mL/min/1.73 m^2 using CKD-EPI criteria (Kidney Disease Improving Global Outcomes - KDIGO, 2012, 2013). Comparing DKD crude prevalence between normoglycemic and prediabetic subjects at the baseline, higher rates were found in prediabetic men (2.6% versus 1.7%) and women (1.9% versus 1.2%) than normoglycemic ones, respectively. Prediabetic subjects were older and had a worse lifestyle and higher mean values of blood pressure and lipids ($p < 0.01$). In univariate regression analysis, prediabetes was associated with a higher risk of DKD in for both sexes but after adjustment for confounders, the association remained only in men [OR 1.15 (95%CI 1.02–1.32)].

3.2. Studies using ACR criteria

In the Australian Diabetes, Obesity and Lifestyle study (AusDiab), 11,247 subjects aged ≥ 25 years were examined in 1999–2000. IFG was defined by FPG (≥110 mg/dL and < 126 mg/dL) and 2-h postload (< 140 mg/dL); IGT by FPG (< 126 mg/dL) and 2-h postload ≥ 140 and < 200 mg/dL (Tapp et al., 2004). Microalbuminuria in men was defined as ACR 22–220 mg/g and in women 31–220 mg/g and macroalbuminuria as ACR > 220 mg/g of creatinine. At the end of the follow-up, a total of 5.1% of subjects with normal glucose tolerance had

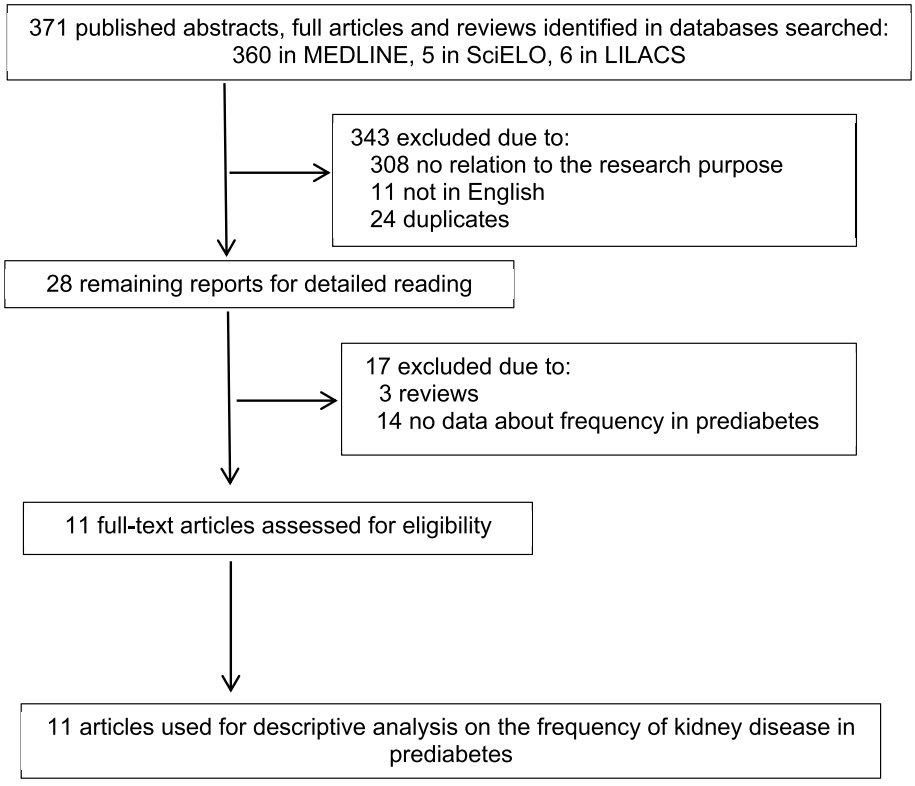

Fig. 1. Summary of articles selection process addressing frequency of kidney disease in prediabetes.

albuminuria (4.3% micro-, 0.8% macroalbuminuria), while the rate in IFG was 9.3% (8.3% micro-, 1.0% macroalbuminuria) and in IGT 11% (9.9% micro-, 1.1% macroalbuminuria). IFG [OR 1.92 (95%CI 1.44–2.56)] and IGT [OR 2.32 (95%CI 1.89–2.83)] were associated with an increased risk of albuminuria, but only IFG remained after adjustments for age, sex, smoking, body mass index, blood pressure and lipids [OR 1.38 (95%CI 1.02–1.87)]. Except for sex, all the covariates were also independently associated with the outcome.

Data of 154 Japanese men aged 20–70 years was collected in Kyoto University Hospital from 1991 to 2001 (Suzuki et al., 2004). The prevalence of microalbuminuria (ACR 30–300 μg/mg of creatinine) was examined in five groups: normal glucose tolerance (NGT), IFG, isolated IGT, combined IGT/IFG and DM. The mean values of ACR were 15.5 ± 2.6 μg/mg in the NGT, 16.2 ± 3.6 μg/mg in the isolated IGT and 42.2 ± 10.7 μg/mg in the IGT/IFG group. Microalbuminuria prevalence was higher in subjects with combined IGT/IFG compared to NGT (26% versus 9%, $p = 0.028$) but not in IGT (14%). Microalbuminuria was associated only with IGT/IFG, this association persisted after adjustment for age and hypertension [OR 4.41 (95%CI 1.17–16.54)], but not when insulin resistance index is added to the model. Partial correlation analysis of ACR with other variables showed that insulin resistance was a strong determinant after adjustment for age.

In a study of 1776 permanent residents aged ≥40 years from a single urban community of Shanghai, China, 754 had normal glucose tolerance, 506 IFG (110–125 mg/dL) and/or IGT (140 and < 200 mg/dL) after a 2-h glucose load and 516 newly diagnosed DM ≥ 200 mg/dL (Li et al., 2009). ACR of 30–300 mg/g was detected in 4.3% normoglycemic and in 6.6% in prediabetic subjects (7.0% for IGT and 8.6% for IFG). IFG and IGT were positively associated with the presence of microalbuminuria after adjustments for sex, age, lifestyle factors, body mass index and blood pressure levels [adjusted OR 1.28 and 1.32, respectively, $p < 0.0001$].

A small cohort study was performed from 2009 to 2011 in an Iranian university hospital, including 45 subjects with IFG, 45 with IGT and 45 with normal glucose tolerance, based on the American Diabetes Association criteria (Bahar et al., 2013). Microalbuminuria (ACR 30–300 mg/g) was detected in 18.0% of IFG, 14.0% in IGT (15.5% overall prevalence rate in prediabetes, $p = 0.005$) and none in the control group. Microalbuminuria rates did not differ between IFG and IGT groups.

Increased albuminuria was investigated in the Korea Health and Nutrition Examination Survey (KNHANES), a national survey conducted at 192 locations since 1998 to 2012 (Won et al., 2015). A total of 5202 subjects were divided into five groups: FPG < 90 mg/dL or normal fasting glucose (NFG1), FPG 90–99 mg/dL or NFG2, FPG 100–109 mg/dL or IFG1, FPG 110–124 mg/dL or IFG2 and FPG ≥ 126 mg/dL as diabetics. Prevalence rates of ACR ≥30 mg/g were gradually higher as FPG increased: 4.1% in the NFG1, 6.0% in the NFG2, 7.6% in the IFG1 and 12.3% in the IFG2 and 23.4% in the diabetes group (P for trend < 0.01). After adjustment for age, sex, hypertension and obesity, the prevalence of albuminuria was significantly higher in the both prediabetic groups compared to NFG1, and also IFG2 had a greater rate than IFG1. Only IFG2 was significantly associated with albuminuria [OR 1.87 (95%CI 1.19–2.94)].

Other results from the Korean population were reported based on the KNHANES 2011–2012 (KNHANES V-2,3)[27]. A total of 8775 subjects were considered prediabetic when FPG was 100–124 mg/dL or HbA1c 5.7–6.4%. Mean values of ACR were higher in the prediabetic group compared to the normoglycemic group, as well as the prevalence of microalbuminuria (6.3% vs. 3.6%). Microalbuminuria in subjects with prediabetes lost significance after adjustment for age, sex and systolic blood pressure [OR 1.14 (95% CI 0.93–1.41)].

3.3. Study using combined criteria

In NHANES, 8188 American subjects aged ≥20 years were examined from 1999 to 2006 (Plantinga et al., 2010). Prediabetes was defined by FPG (100–125 mg/dL) and DKD by ACR (30–300 mg/g) or reduced eGFR (< 60 mL/min/1.73 m^2) according to the MDRD and the

CKD-EPI (Kidney Disease Improving Global Outcomes - KDIGO, 2012, 2013). Reduced eGFR using MDRD equation was observed in 10.6% of normal tolerant subjects and in 17.7% of prediabetic ones ($p < 0.001$); similar prevalence rates were found using CKD-EPI equation (9.2% and 16.6%, respectively, $p < 0.001$), even after adjusted for age, sex and race. Among those with prediabetes and reduced eGFR approximately 20% had micro- or macroalbuminuria.

In a Chinese study including a random sample of 5584 subjects aged 20–79 years from Shanghai, diagnosis of prediabetes was based on FPG 100–125 mg/dL[29]. The prevalence of microalbuminuria (ACR ≥ 30 mg/g) was 12.9% and reduced kidney function by MDRD (GFR < 60 mL/min/1.73 m^2) was 14.1% in prediabetics subjects, while in normoglycemic patients the rates were significantly lower (8.7% and 9.2%, respectively, $p < 0.001$).

The 1988, 2014 NHANES (Ali et al., 2018), having included 27,971 Americans aged 20 years or older, prevalence rates of ACR ≥ 30 mg/g (from 9.3% to 7.7%, $p = 0.118$) and of GFR < 60 mL/min/1.73 m^2 (4.7%–4.6%, $p = 0.769$) showed non-significant decreases. In 2014, overall prevalence rates of DKD were 12.3% in prediabetic subjects and 11.3% in normoglycemic ones.

In summary, in the eleven studies in which DKD prevalence were provided, rates ranged from 4.5% to 26.0% in subjects with prediabetes. Taking into consideration two studies in which diagnosis were based on eGFR exclusively, prevalence varied from 4.5% to 21.3%, while in six in which ACR was used ranged from 6.3% to 26.0%. When both diagnostic criteria were used simultaneously the prevalence ranged from 12.3% to 17.7% (Table 1).

4. Discussion

Our study shows that few articles (Schöttker et al., 2013; Lin et al., 2017; Tapp et al., 2004; Suzuki et al., 2004; Li et al., 2009; Bahar et al., 2013; Won et al., 2015; Kim et al., 2014; Plantinga et al., 2010; Zhou et al., 2013; Ali et al., 2018) assessed DKD prevalence in prediabetic stages and they employed distinct size samples and diagnostic criteria, limiting comparison of rates among the populations investigated. DKD criteria were based on eGFR and/or albuminuria, and prediabetes definition on WHO (Alberti and Zimmet, 1998) or ADA criteria (American Diabetes Associa, 2015). Despite heterogeneity in methodological approaches, relatively high prevalence rates of DKD were reported, reaching up to one quarter of prediabetic subjects. Our review highlighted the important information that kidney damage could occur in a proportion of subjects even before overt type 2 DM, indicating that it may deserve screening and perhaps early intervention.

Some investigators have preferred GFR as the main parameter to detect glomerular injury in disturbances of glucose metabolism, considering that hyperfiltration is a high-risk condition for progressive kidney disease (De Nicola et al., 2016; Melsom et al., 2016). GFR elevation is dependent on increased plasma flow and glomerular pressure, even in the absence of systemic hypertension (Brenner et al., 1996). Hyperglycemia-related hyperfiltration (Ditzel, 1968) is attributed to afferent arteriolar vasodilation that leads to intraglomerular hypertension, increased transcapillary protein loss and tubular sodium reabsorption (Hannedouche et al., 1990). Abnormal GFR can be normalized by plasma glucose control (Jerums et al., 2010), and the microalbuminuria has been considered the hallmark of early diabetic microvascular disease in the kidney. More recently, the International Society of Nephrology has stated that prognosis to chronic kidney disease should be based on both AER and GFR (Kidney Disease Improving Global Outcomes - KDIGO, 2012, 2013). Therefore, for the purpose of the present review, microalbuminuria and reduced GFR were taken as the major search terms for DKD in prediabetes.

Hyperfiltration is hypothesized to be a precursor of intraglomerular hypertension leading to albuminuria and gradual decrease in GFR. How early hyperfiltration occurs duringestablishment of hyperglycemia is unknown. Studies have shown that the frequency of hyperfiltration increases with the glucose levels (Okada et al., 2012; Jones et al., 1991) and that is associated with prediabetes (Magee et al., 2009). Other factors contributetoelevate GFR such as high body index mass, oxidative stress, hyperinsulinemia and inflammatory cytokines (Tomaszewski et al., 2007; Li et al., 2011; Stefanssonet al., 2016).

The deleterious effect of mild elevations in plasma glucose for the microvasculature is corroborated by the identification of retinopathy in 8.1 to 20.9% of prediabetic individuals (Sokolowska-Oracs et al., 2016; Lamparter et al., 2014; Chen et al., 2012). Such findings reinforced our hypothesis that microangiopathy at the renal level should also be present in mild disturbances of glucose metabolism. Other studies verified that individuals in early stages of hyperglycemia as prediabetes had neurodegeneration and/or microvascular alterations (Yazgan et al., 2017; Al Shafaee et al., 2011). As far as pathology is concerned, one study performed renal biopsy in prediabetic condition and found isolated thickening of glomerular capillary basement membrane (Lai et al., 2004). Authors called attention that this abnormality should be differentiated from minimal change nephropathy due to therapeutic implications.

Among the studies reviewed, the range of DKD prevalence rates in prediabetes were wide, varying from a minimum of 4.5% to a maximum of 26.0%. Taking into consideration two studies in which diagnosis was based on eGFR or six studies that used ACR, rate variation was similar. Presuming that microalbuminuria should precede the reduction of GFR in the natural history of DKD, higher prevalence rates could be expected using AER rather than GFR. However, wide ranges were observed independent of the parameter used, and, when both were simultaneously considered, the rate found was in the mid-range. Several factors could be contributing to these findings. It is known that renal function is dependent on age, ethnicity, genetic susceptibility, degree and duration of the hyperglycemic excursions, presence of comorbidities such as obesity, hypertension, smoking and others (Levey et al., 2003). We point as main reasons for such variability differences in age range, sample size and genetic predisposition to renal diseases. It is known that the CKD prevalence is higher in Japanese population than in other Asian countries and the United States; according to the Japanese Society for Dialysis Therapy, the prevalence of subjects under dialysis reach more than 2000 per million inhabitants (Iseki, 2008). Contrastingly, low prevalence was reported in China although rates have increased over the years (Zhang et al., 2012). The finding of our review regarding the frequencies of DKD markers in prediabetes is in agreement with a meta-analysis performed with nine cohort studies indicating that this condition is associated with an increased risk of progressing to clinical nephropathy (Echouffo-Tcheugui et al., 2016).

In ten out of eleven articles, IFG, IGT or increased HbA1c was associated with DKD even after adjusting for cardiovascular risk factors (Lin et al., 2017; Tapp et al., 2004; Suzuki et al., 2004; Li et al., 2009; Bahar et al., 2013; Won et al., 2015; Kim et al., 2014; Plantinga et al., 2010; Zhou et al., 2013; Ali et al., 2018). Only one article reported no significant association after adjustments, suggesting that prediabetes *per se* would not deteriorate renal function independent of other renal factors (Schöttker et al., 2013). Despite not providing DKD prevalence data in the subset with prediabetes, the Framingham Heart Study showed that associated cardiovascular risk factors, but not isolated prediabetes, explained the relationship with chronic kidney disease (Fox et al., 2005). Therefore, lack of association in some studies may suggest that glycemic levels could affect population differently depending for instance on its genetic susceptibility.

This review has limitations. Our search included articles from 2003, but it is possible that studies could have been published before this date. Since only eight studies were eligible, an ideal representative sample of world populations was not available. Different population characteristics (age, ethnicity, sex distribution, prevalence of obesity and comorbidities) were included because of the paucity of studies in literature. For the same reason, different diagnostic criteria of DKD and prediabetes were used. Since some studies included older participants,

Table 1
Studies regarding frequency of diabetic kidney disease in prediabetes compared to normoglycemic subjects.

Reference	Study Design	Population/Sample	DKD Criteria	Prediabetes Criteria	DKD Prevalence Prediabetes *vs* Normal
Schöttker B et al., 2013 (Schöttker et al., 2013)	Cohort[#] with cross-sectional analysis	3538 subjects aged 50–74 years	eGFR < 60 mL/min/1.73 m^2	Fasting plasma glucose and HbA1c	Reduced eGFR: 18.7%[a] and 21.3%[b] *vs* 16.0% RR 1.06 (95%CI 0.71–1.32)[k]
Lin L et al., 2016 (Lin et al., 2017)	Cohort with cross-sectional analysis	250,752 subjects ≥40 years	eGFR < 60 mL/min/1.73m^2	Fasting plasma glucose and/or oral glucose tolerance test	Reduced eGFR: 4.5% *vs* 1.7% OR for men 1.15 (95%CI 1.02–1.32)[m]
Tapp RJ et al., 2004 (Tapp et al., 2004)	Cohort with cross-sectional analysis	11,247 adults ≥25 years	ACR 22–220 mg/g for men; 31–220 mg/g for women	Fasting plasma glucose and oral glucose tolerance test	Elevated ACR: 9.3%[e] and 11.0%[f] *vs* 5.1% OR for IFG 1.38 (95%CI 1.02–1.87)[l]
Suzuki H et al., 2004 (Suzuki et al., 2004)	Cross-sectional	154 Japanese men aged 20–70 years	ACR 30–300 mg/mg	Oral glucose tolerance test	Elevated ACR: 14%[f] and 26%[g] *vs* 9.0% (p = 0.028)
Li XY et al., 2008 (Li et al., 2009)	Cross-sectional	1776 Chinese subjects > 40 years: 506 IGT, 516 newly diagnosed DM, 754 normoglycemic	ACR 30–300 mg/g	Fasting plasma and oral glucose tolerance test	Elevated ACR: 7.0%[f] and 8.6%[e] *vs* 4.5% (p < 0.0001) OR 1.28[e] and 1.32[f]
Bahar A et al., 2013 (Bahar et al., 2013)	Cohort with cross-sectional analysis	135 subjects: 90 with prediabetes and 45 normoglycemic	ACR 30–300 mg/g	Fasting plasma glucose and oral glucose tolerance test	Elevated ACR: 15.5% *vs* 0%
Won JC et al., 2014 (Won et al., 2015)	Cohort with cross-sectional analysis	5202 subjects > 19 years	ACR ≥30 mg/g	Fasting plasma glucose	Elevated ACR: 7.6%[c] and 12.3%[d] *vs* 4.1% and 6.0% OR 1,87 (95% CI 1.19–2.94)[l]
Kim CH et al., 2014 (Kim et al., 2014)	Cohort with cross-sectional analysis	8775 subjects aged ≥ 19 years	ACR 30–300 mg/g	Fasting plasma glucose or HbA1c	Elevated ACR: 6.3% *vs* 3.6% OR 1,14 (95% CI 0.93–1.41)[l]
Platinga LC et al., 2010 (Plantinga et al., 2010)	Cross-sectional	8188 subjects ≥20 years: 2272 prediabetics, 1125 DM, 4791 normoglycemic	ACR ≥30 mg/g and eGFR 15–59 mL/min/1.73m^2	Fasting plasma glucose (≥100–125 mg/dL)	Combined criteria: 17.7% *vs* 10.6% (p < 0.001)
Zhou Y et al., 2013 (Zhou et al., 2013)	Cross-sectional	5584 subjects aged 20–79 years	ACR ≥30 mg/g and eGFR < 60 mL/min/1.73m^2	Fasting plasma glucose (≥100–125 mg/dL)	Combined criteria: 12.9%[h] and 14.1%[i] *vs* 8.7% and 9.2% (p < 0.001)
Ali MK et al., 2018 (Ali et al., 2018)	Cohort with cross-sectional analysis	27,971 subjects ≥20 years	ACR ≥30 mg/g and eGFR < 60 mL/min/1.73m^2	Fasting plasma glucose or HbA1c	Combined criteria: 12.3% *vs* 11.3%

ACR, albumin-creatinine ratio eGFR, estimated glomerular filtration rate DM, diabetes mellitus.
[#] 8-year incidence was calculated.
[a] Prediabetes defined by fasting plasma glucose or HbA1c.
[b] Prediabetes defined by both fasting plasma glucose and HbA1c.
[c] Fasting plasma glucose 100–109 mg/dL.
[d] Fasting plasma glucose 110–124 mg/dL.
[e] Subjects with IFG.
[f] Subjects with IGT.
[g] Combined IGT/IFG.
[h] Prevalence of microalbuminuria.
[i] Prevalence of reduced GFR by MDRD.
[k] Adjusted for age and body mass index.
[l] Plus lifestyle and blood pressure.
[m] Plus medications and lipids.

other kidney disease risk factors were present; however, the majority has made adjustments for cardiovascular risk factors. Comparisons of DKD prevalence between prediabetic and normoglycemic subjects were available for all the studies. None performed kidney biopsy to assure that abnormal exams were really attributed to diabetic nephropathy. Marked reduction of kidney function in prediabetic phases deserves thorough investigation regarding the etiology of nephropathy and rule out other causes of renal involvement.

5. Conclusion

In conclusion, using eGFR and/or ACR as proxies of DKD, our findings indicate that this diabetic microvascular complication affects subsets of prediabetic populations at variable frequencies, varying from 4.5 to 26.0%. We suggest that this should be considered a public health concern until more data is available in literature. Mild glucose metabolism disturbance seems to have a relevant impact on the incidence and prevalence of kidney disease that deserves attention from clinicians and health authorities. Since the initial stage of DKD is reversible, it is of great interest to make an early identification of prediabetic subjects with incipient renal dysfunction in order to avoid the debilitating and costly stage of renal failure. Further studies to be conducted in representative samples in different populations are needed to estimate how kidneys are affected under prediabetic states.

Conflicts of interest

No conflicts of interest are declared.

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