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The Burden of Diabetic Kidney Disease in Nigeria-Systematic Review and Meta-Analysis

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Abstract

Background: Diabetic Kidney Disease (DKD) is a microvascular complication of diabetes mellitus. Considering that the burden of diabetes mellitus is rising in Nigeria, there is a need to ascertain the burden of one of its most common complications. The objective of the meta-analysis was to determine the pooled prevalence of DKD in Nigeria and identify its risk factors.

Materials and Methods: The study is a meta-analysis and it followed the PRISMA guidelines. Google scholar, PubMed, AJOL, SCOPUS, medRxiv and the grey literature were systematically searched using appropriate key terms. Statistical analysis was done with Meta XL. The inverse variance heterogeneity model was used for the meta-analysis and heterogeneity was determined using the I^2 statistic and the Cochran's Q test. Publication bias was checked with the Doi plot and LFK index.

Results: Nineteen studies met the eligibility criteria. The total sample size was 56,571. The pooled prevalence of diabetic kidney disease in Nigeria was 28% (95% CI 3-58). The Cochran's Q was 747 ($p<0.001$) while the I^2 statistic was 97.6%. The Doi plot was drawn and the LFK index was 6.22. The most common risk factors for DKD were suboptimal glycemic control, hypertension, and obesity, duration of diabetes, male gender and advancing age.

Conclusion: The prevalence of DKD in Nigeria is high and greater attention should be focused on managing the risk factors so as to alleviate the burden of the disease.

Keywords: Diabetic kidney disease; Diabetic nephropathy; Prevalence; Risk factors; Meta-analysis

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Abbreviations

ACR: Albumin Creatinine Ratio; AJOL: African Journal Online; DCCT: Diabetes Control and Complications Trial; DKD: Diabetic Kidney Disease; eGFR: Estimated Glomerular Filtration Rate; IDF: International Diabetes Federation; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; UKPDS: United Kingdome Diabetes Prevention Study

Introduction

Diabetes mellitus is a chronic metabolic disorder where reduced insulin secretion or action leads to persistent hyperglycaemia with attendant deleterious effects. It is the most common disease encountered in Endocrinology practice in Nigeria [1,2]. In sub-Saharan Africa, Nigeria has the highest number of individuals living with diabetes mellitus [3]. In a meta-analysis, the pooled prevalence of diabetes mellitus among adults in Nigeria was 5.77% [4]. According to the International Diabetes Federation (IDF), the prevalence of diabetes mellitus in Nigeria, as at 2020, was 3% although studies have suggested that the burden of the disease in Nigeria was underestimated by IDF because IDF worked with extrapolated data [4,5]. In terms of hospitalization, about 223 individuals per 100,000 general population get admitted for diabetes and/or its complications yearly in Nigeria, out of which about 22% die [6].

Poorly treated diabetes mellitus is associated with a myriad of microvascular and macrovascular complications. The most commonly documented microvascular complications of diabetes mellitus

are neuropathy, nephropathy and retinopathy [7]. The rising prevalence of diabetes mellitus, especially type 2, in Nigeria would translate to increasing burden of microvascular complications and this is quite worrisome as Nigeria is a low resource setting where most patients pay out of pocket [8]. Interestingly, the presence of microvascular complications independently increases the risk of cardiovascular death in people living with diabetes [9]. This further emphasizes the importance of addressing the microvascular complications of diabetes mellitus.

In Nigeria, the third most common cause of chronic kidney disease is diabetes mellitus, after hypertension and chronic glomerulonephritis although diabetes remains the most common cause of end-stage renal disease globally [10,11]. Diabetic Kidney Disease (DKD), formerly called diabetic nephropathy, is a complication of diabetes mellitus characterized by persistent albuminuria, confirmed on a second occasion at least 3 months apart and/or progressive deterioration of the estimated glomerular filtration rate [12]. It is of remarkable importance to note that individuals diagnosed with DKD tend to die from cardiovascular diseases and infections even before renal replacement therapy is instituted [12]. The natural history of DKD is shown in Figure 1 below [13].

The risk factors for the development of DKD, in addition to sub-optimal glycemic control, include hypertension, obesity, and increasing age, and male gender, duration of diabetes, ethnicity and family history [14]. The earliest structural change in DKD on light microscopy is increased mesangial deposition and cellularity, summarily termed as mesangial expansion [15]. Other morphological changes are glomerular basement membrane thickening, microaneurysms, development of the Kimmelstiel-Wilson nodules and hyaline arteriolosclerosis of the afferent and efferent arterioles [12]. However, recent studies have shown that the progression of DKD may not follow any specific pattern suggesting that DKD is a heterogeneous group of disorders rather than a single entity [16]. A study documented that despite declining eGFR, about 40% of the patients never developed albuminuria [12]. The study concluded that albuminuria is a dynamic and fluctuating phenomenon which does not necessarily follow a clearly defined progressive pattern.

The pathophysiology of DKD involves 4 pathways: metabolic, hemodynamic, inflammatory and fibrotic pathways [12]. The metabolic pathway is mediated by increased oxidative stress, formation of advanced glycation end products and increased flux of glucose through the hexosamine pathway generating a higher level of transforming growth factor-β [15]. The hemodynamic pathway is mediated by the activation of the renin-angiotensin-aldosterone system, elaboration of nitric oxide and the secretion and activation of endothelins. The inflammatory pathway is due to the increased production of transforming growth factor-α and enhanced synthesis of serum amyloid A. The fibrotic pathway is facilitated by transforming growth factor-β, vascular endothelial growth factor and connective tissue growth factor. The various pathways converge and lead to the various functional, biochemical and structural changes seen in DKD.

Microalbuminuria is defined using 24 h urinary protein of 30 mg to 300 mg or albumin creatinine ratio of 30 mg/g to 300 mg/g in at least two out of three samples taken over 3 to 6 months [17]. Values above these ranges are termed 'macroalbuminuria' Screening for microalbuminuria is commenced after the diagnosis of type 2 diabetes mellitus or 5 to 10 years post-diagnosis of type 1 diabetes mellitus and annually thereafter [18]. Diagnosis of diabetic kidney disease is made in the presence of persistent albuminuria (micro- or macro-), presence of diabetic retinopathy and the absence of signs of other forms of renal disease [19]. So, DKD is a diagnosis of exclusion. Management of diabetic kidney disease involves intensive glycemic control, intensive blood pressure control, renin-angiotensin-aldosterone system blockade, and dietary modification, treatment of dyslipidemia and treatment of anemia. Recently, the uses of sodium-glucose transporter 2 inhibitors and glucagon-like peptide 1 agonists have been reported to be beneficial in the management of diabetic kidney disease [20].

Objective

The objective of the systematic review and meta-analysis was to estimate the pooled prevalence of diabetic kidney disease in Nigeria and identify the risk factors so as to intensify the efforts at preventing and managing the disease.

Materials and Methods

Relevant articles and papers were searched on the common medical databases. These databases included Google Scholar, PubMed, African Journal online (AJOL) and SCOPUS. The preprint database, medRxiv was also searched. The grey literature was also searched through the helps of the librarian of a university and experts in the relevant fields in Nigeria. This was done to increase the depth of the retrieved articles and minimize publication bias. The search terms were "diabetes mellitus", "type 2 diabetes", "type 1 diabetes", "complications of diabetes", and "microvascular complications". Other terms used in the search process were "diabetic kidney disease", "diabetic nephropathy", "renal failure", "chronic kidney disease", "end-stage renal disease", "microalbuminuria", "macroalbuminuria" and "Nigeria". The Boolean operators 'AND', 'OR' as well as 'NOT' were used as deemed appropriate to enrich the specificity of the search results.

Abstracts and texts were critically examined by the authors independently. At least three authors agreed on each article that was selected. This was done to minimize the study selection bias. Studies done from 2000 to 2021 were selected. The outcome variables of interest were the prevalence and risk factors for diabetic kidney disease in Nigeria. The data were initially collected on a spreadsheet before it was transferred to the meta-analysis software. Meta XL version 5.3

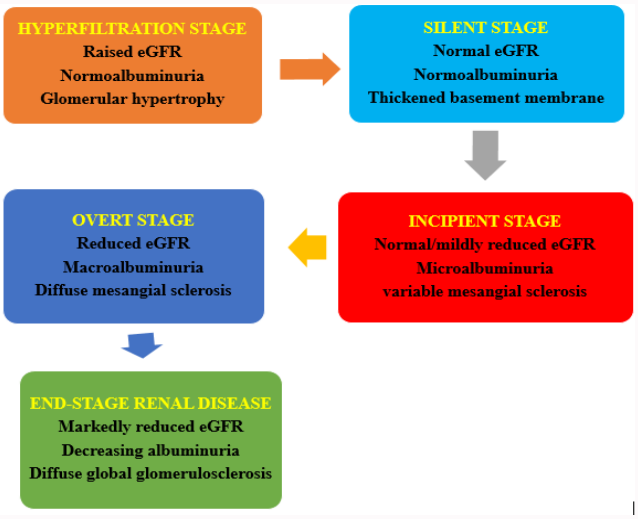

Figure 1: Natural stages of diabetic kidney disease.

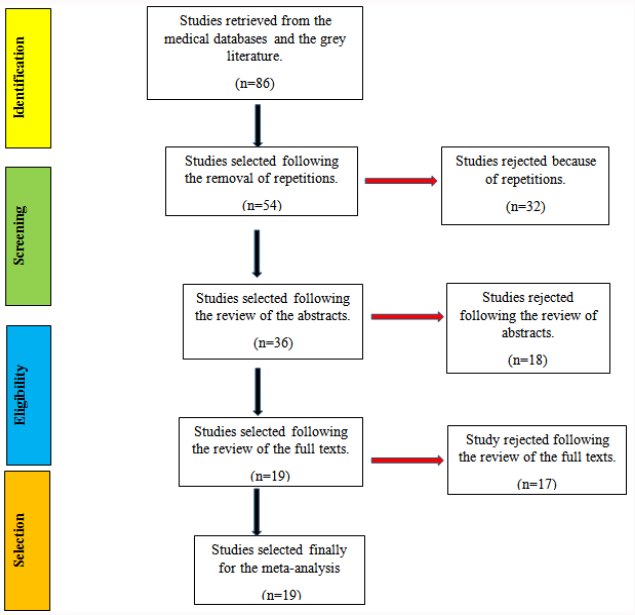

Figure 2: The PRISMA flow diagram of the meta-analysis.

(EpiGear International Ltd.), a meta-analysis add-in software for Microsoft Excel was used for the meta-analysis. The inverse variance heterogeneity model was used for the meta-analysis. Heterogeneity was determined using the I^2 statistic and the Cochran's Q test.

The literature search process and study selection algorithm were done according to the recommended Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA flow diagram is shown in Figure 2.

Results

A total of 19 studies met the eligibility criteria and were selected for the meta-analysis. Table 1 shows the selected studies and the prevalence in each study. The total sample size in this meta-analysis was 56,571 individuals with diabetes mellitus. The prevalence of DKD ranges from 3.2% to 72.6% in the selected studies. Figure 3 shows the regional distribution of the studies on the basis of the 6 geopolitical zones of Nigeria. Figure 4 shows the pattern of diagnostic tool for diabetic kidney disease in the various studies. Slightly more studies (56.3%) of the studies adopted the Albumin Creatinine Ratio (ACR) in diagnosing DKD as compared with estimated Glomerular Filtration Rate (eGFR).

The forest plot is shown in Figure 5 below. The pooled prevalence of diabetic kidney disease in Nigeria is 28% (95% CI 3-58). The Cochran's Q was 747 ($p<0.001$) while the I^2 statistic was 97.6% and these 2 parameters suggest a high level of heterogeneity in the studies. The Doi plot to check publication bias is shown in Figure 6. LFK index is 6.22 which suggest that there might have been some degree of publication bias.

Table 2 shows the risk factors for diabetic kidney disease reported from the selected studies. The frequency of the risk factor in the selected studies is depicted in Figure 7.

Discussion

In this meta-analysis, the pooled prevalence of diabetic kidney disease in Nigeria was 28%. Previous studies done in other Sub-

Table 1: Prevalence of diabetic kidney disease in selected studies.

S/No	Study	Year	Sample size	Prevalence
1	Alebiosu [21]	2001	342	28.40%
2	Agaba et al. [22]	2004	65	49.20%
3	Kamen [23]	2007	300	32.70%
4	Chinenye et al. [1]	2008	531	3.20%
5	Onovughakpo-Sakpa et al. [24]	2009	95	72.60%
6	Adejumo et al. [10]	2015	144	30.60%
7	Adewolu & Atoe [25]	2015	46	55.60%
8	Chukwuani et al. [26]	2015	200	58.00%
9	Okafor et al. [27]	2015	203	37.60%
10	Olamoyegun et al. [8]	2015	90	54.50%
11	Halliru et al. [28]	2016	100	34,0%
12	Ufuoma et al. [29]	2016	200	58.00%
13	Adedeji [30]	2017	10	60.00%
14	Bello & Amira [31]	2017	358	53.40%
15	Ekrikpo et al. [32]	2017	102	35.30%
16	Amballi et al. [33]	2018	325	35.10%
17	Agofure et al. [34]	2020	53421	27.90%
18	Chiroma et al. [35]	2020	261	42.90%
19	Orih & Obiorah [36]	2020	120	16.70%

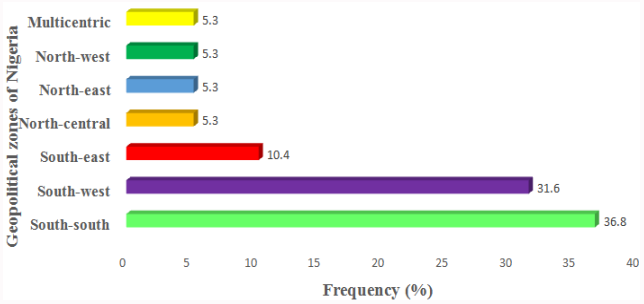

Figure 3: Frequency of studies on DKD done in the various geopolitical zones.

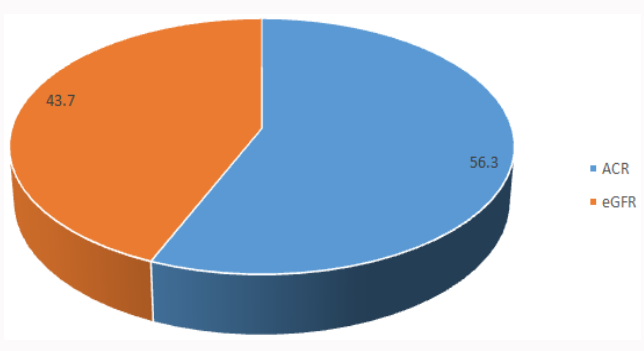

Figure 4: Diagnostic approach to DKD.

Saharan Africa countries have found a prevalence rate of 22% to 36% [37–41]. The wide range in the prevalence rate across the continent was also observed in this meta-analysis. This is probably due to the differences in the socio-demographics of the participants, study designs as well as the diagnostic criteria used in the diagnosis of diabetic kidney disease. The tests of heterogeneity (Cochran's Q

Table 2: Risk factors for diabetic kidney disease in Nigeria.

S/No	Risk factor	Studies
1	Hypertension	Olamoyegun et al. [8], Alebiosu [21], Agaba et al. [22], Kamen [23], Ufuoma et al. [29], Adedeji [30], Bello & Amira [31]
2	Advancing age	Olamoyegun et al. [8], Halliru et al. [28], Ufuoma et al. [29], Chiroma et al. [35]
3	Sub-optimal glycemic control	Olamoyegun et al. [8], Onovughakpo-Sakpa et al. [24], Ufuoma et al. [29], Chiroma et al. [35]
4	Increasing body mass index	Olamoyegun et al. [8], Kamen. [23], Ufuoma et al. [29], Ekrikpo et al. [32]
5	Duration of diabetes	Olamoyegun et al. [8], Onovughakpo-Sakpa et al. [24], Adewolu & Atoe [25]
6	Male gender	Olamoyegun et al. [8], Onovughakpo-Sakpa et al. [24], Chiroma et al. [35]
7	Dyslipidemia	Kamen [23]
8	Diabetic retinopathy	Agaba et al. [22]
9	Hyperuricemia	Chiroma et al. [35]

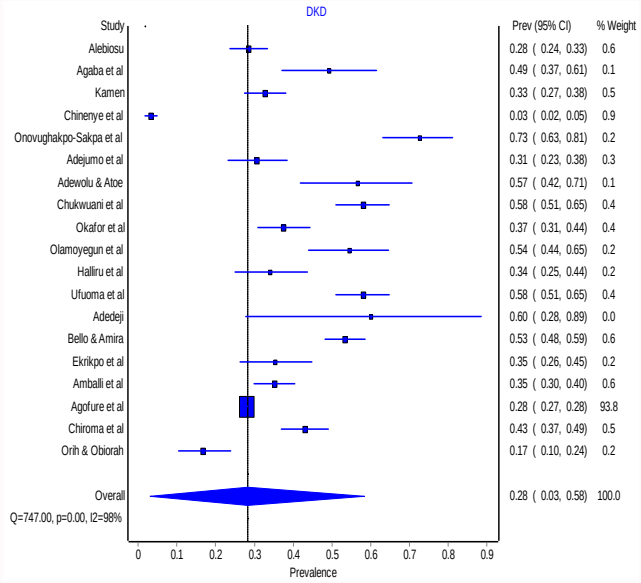

Figure 5: Forest plot of the meta-analysis.

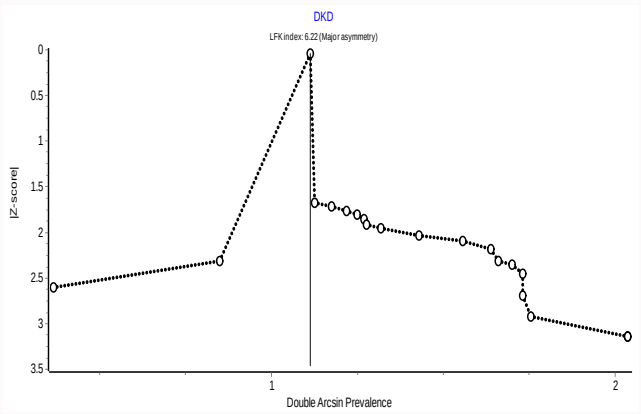

Figure 6: The Doi plot for the meta-analysis.

test and I^2 statistic) earlier mentioned are also in keeping with these observed marked variations in the selected studies. All these are in keeping with the hypothesis that diabetic kidney disease is not a single disease entity but a heterogeneous group of related disorders with a common theme of functional or structural abnormalities of the kidneys in people living with diabetes. This therefore calls for more studies to unravel the various dimensions of the disease.

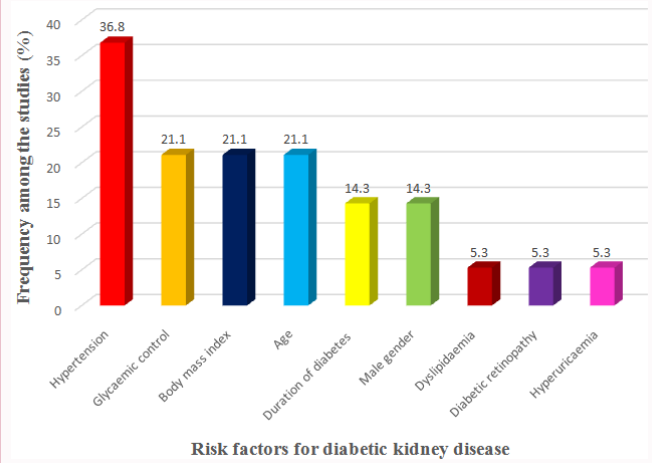

Figure 7: Risk factors of diabetic kidney disease and their frequencies among selected studies.

Most of the selected studies were done in Southern Nigeria. This might raise some questions about the generalizability of the findings of the meta-analysis to the whole nation because regional differences in the prevalence of hypertension, diabetes, obesity and other risk factors for diabetic kidney disease had been earlier documented by various authors [4,42,43]. There is a need to conduct appropriately designed studies on the prevalence and risk factors of DKD in the Northern geo-political zones of Nigeria so as to be able to ascertain the burden of the disease in such areas.

This meta-analysis shows that there is lack of consensus in the definition of DKD across the various studies. This may be due to lack of Nigerian guidelines on the diagnosis of diabetic kidney disease and the various authors had to adapt the foreign guidelines. While some studies (43.7%) defined diabetic kidney disease using eGFR, others (56.3%) defined it with albuminuria. There have been controversies on the merits and demerits of each diagnostic criterion and this call for a national consensus on how to define diabetic kidney disease because the drawbacks of missing patients in the early stage of the disease are quite enormous [44]. A systematic review on diabetic nephropathy in Africa has also identified the same challenge of adopting different criteria in diagnosing DKD [45]. Interestingly, most of the newer guidelines are beginning to incorporate both manifestations (albuminuria and declining eGFR) in the diagnosis and prognosis of DKD [46].

The most commonly reported modifiable risk factors for DKD, in this systematic review, were hypertension, poor glycemic control

and obesity. Various landmark trials such as the United Kingdome Diabetes Prevention Study (UKPDS) and Diabetes Control and Complications Trial (DCCT) have clearly demonstrated an incontrovertible association between poor glycemic control and the development of DKD [47]. Additionally, other clinical trials have demonstrated a delay or outright prevention of diabetic kidney disease by ensuring tight glycemic control. Previous studies done in other continents have also alluded to the relationship between poor glycemic control and the onset of DKD [48-50].

This review also found out that hypertension was quoted as a major risk factor by various studies on DKD in Nigeria. Previous studies had also reported a similar finding [51,52]. Concerning the association between obesity and the development of DKD, a study in China documented a significant association between body mass index and proteinuria, just as was found in the present meta-analysis [53]. The mechanisms by which obesity exacerbates DKD include insulin resistance, dyslipidemia, activation of the renin-angiotensin-aldosterone system and the activation of the sympathetic nervous system [54].

Other risk factors for diabetic kidney disease identified in this meta-analysis were the male gender, age of the patient, duration of diabetes, dyslipidemia and diabetic neuropathy. These risk factors have also been reported by various authors in their studies [51,55]. This meta-analysis has highlighted the enormous burden of DKD in Nigeria and it is high time intense efforts were put in place to address these risk factors so as to alleviate the burden of the disease.

Limitations

The studies selected did not cut across all the regions equally due to the dearth of such studies in Northern Nigeria. Similarly, the lack of consensus in the diagnostic criteria limits the generalizability of the findings.

Strengths

The numbers of studies selected were fairly large and the total sample size was also large enough. The meta-analysis spanned about two decades which suggests a wide coverage. This meta-analysis did not only establish the pooled prevalence of DKD in Nigeria but also highlighted the risk factors that need to be focused on so as to mitigate the burden of the disease.

Conclusion

The prevalence of diabetic kidney disease in Nigeria is high. Efforts should be intensified to achieve a tight glycemic control, optimal blood pressure control, healthy weight as these can go a long way in alleviating the burden of DKD in Nigeria.

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