PATTERNS OF DIABETIC RETINOPATHY PREDICTING DIABETIC KIDNEY DISEASE SEVERITY, AT TIKUR ANBESSA SPECIALIZED HOSPITAL (TASH), COLLEGE OF HEALTH SCIENCES, ADDIS ABABA UNIVERSITY

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A THESIS TO BE SUBMITTED TO THE DEPARTMENT OF INTERNAL MEDICINE, COLLEGE OF HEALTH SCIENCES, ADDIS ABABA UNIVERSITY, IN PARTIAL FULFILMENT OF THE SPECIALITY CERTIFICATE IN INTERNAL MEDICINE

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DECEMBER, 2021
ADDIS ABABA, ETHIOPIA

Declaration

I, the undersigned, declare that this postgraduate thesis is my own work. All sources used for this thesis preparation have been duly acknowledged.
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Abbreviations and Acronyms

ADA – American Diabetes Association
BMI – Body mass index
CKD – Chronic kidney disease
CVD – Cardiovascular disease
DCCT - Diabetes Control and Complications Trial
DKD – Diabetic kidney disease
DME – Diabetic macular edema
DR – Diabetic retinopathy
EDIC – Epidemiology of Diabetes Interventions and Complications
EPHI – Ethiopian Public Health Institute
GCP – Good Clinical Practice
GFR – Glomerular filtration rate
IDF – International Diabetes Federation
IFG – Impaired fating glucose
IRMA – Intraretinal microvascular abnormalities
NPDR – Nonproliferative diabetic retinopathy
NVD – Neovascularization of the disc
NVE – Neovascularization elsewhere
PDR – Proliferative diabetic retinopathy
RAAS - Renin–angiotensin–aldosterone system
TASH – Tikur Anbessa Specialized Hospital
T1DM- Type 1 diabetes mellitus
T2DM – Type 2 diabetes mellitus
UACR – Urine albumin to creatinine ratio
UKPDS – United Kingdom Prospective Diabetes Study
UPCR – Urine protein to creatinine ratio
VEGF – vascular endothelial growth factor

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Abstract

Background: Diabetic retinopathy and diabetic kidney disease are microvascular complications of diabetes mellitus. Patients with diabetic retinopathy are prone to develop diabetic kidney disease. However, there is limited evidence on the relationship between diabetic retinopathy stages and diabetic kidney disease severity.

Objective: To identify the relationship between patterns of diabetic retinopathy and diabetic kidney disease

Methods: A hospital based cross-sectional study was conducted at diabetes clinic of TASH, Ethiopia from June 2021 to July 2021. Structured questionnaire, patients' charts and/or electronic medical records were used to collect data among 101 diabetic patients with diabetic retinopathy aged 18 years and above. Data were cleaned, coded and entered into IBM SPSS version 26 software for analysis. Descriptive and logistic regression analyses were used and P-value < 0.05 was used as statistically significant.

Results: The mean (±SD) age of the participants was 52.9 (±11.8) years. Majority (94.1%) of our diabetic retinopathy patients had nonproliferative retinopathy and 70.3% of diabetic retinopathy patients had concomitant diabetic kidney disease. In multivariable logistic regression analyses, diabetic retinopathy severity (severe nonproliferative diabetic retinopathy to proliferative diabetic retinopathy vs. mild to moderate nonproliferative diabetic retinopathy) [AOR= 3.97; 95% CI: 1.01 - 15.62], T2DM [AOR= 3.74; 95% CI: 1.29 - 10.75], presence of CVD [AOR= 3.18; 95% CI: 1.05- 9.59] were the independent predictors of diabetic kidney disease.

Conclusions: In this study, diabetic retinopathy severity was strongly associated with diabetic kidney disease. Therefore, evaluation of diabetic retinopathy severity at the time of retinal screening is recommended.

Budget grant: Addis Ababa University (AAU), College of Health Sciences, School of Medicine

Key words: Diabetic retinopathy, Diabetic kidney disease, TASH, Ethiopia

1. Introduction

1.1 Background

Diabetes Mellitus is a group of metabolic disorders characterized by persistent hyperglycemia. DM can be classified as type 1, type 2, gestational and other types of diabetes of specific cause.[1] According to the 2019 estimate by IDF, approximately 463 million adults (20-79 years) are living with diabetes globally.

The prevalence of DM was 3.2% from a community-based survey conducted in Ethiopia.[75] Prevalence of impaired fasting glucose (IFG) was 9.1% using ADA criteria and metabolic syndrome occurred in 4.8% of study population.[75] Both diabetic retinopathy (DR) and diabetic kidney disease (DKD) are typical microvascular complications of diabetes mellitus. [4, 5]

Diabetic retinopathy is an ocular microangiopathy and is the leading cause of preventable blindness. According to the the International Clinical Diabetic Retinopathy Disease Severity Scale, DR is classified based on Retinopathy Disease Severity Scale.[10] This classification addresses disease stages and provides patients with an opportunity for early interventions to prevent blindness. DR is divided into two major forms as nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). It can also be further classified into mild, moderate and severe NPDR and PDR.

Diabetic kidney disease is clinically defined by persistent albuminuria and/or persistent decreased estimated glomerular filtration rate (eGFR < 60 mL/min/1.73 m2) in the presence of diabetes. The natural history of diabetic kidney disease includes glomerular hyperfiltration, progressive albuminuria, declining GFR, and ultimately, end-stage renal disease (ESRD). Common DKD risk factors include advanced age, family history, hyperglycemia, hypertension, and obesity.

The diagnosis of diabetic kidney disease is often made based on the clinical manifestations, and renal biopsy is only performed in patients with atypical presentations. Although longer diabetes duration, presence of DR, and absence of hematuria are predictors for DKD, clinical differentiation between DKD and non-diabetic kidney disease may sometimes be difficult particularly in type 2 diabetes.[3] Generally, there are two major reasons of performing renal biopsy in DKD patients: for accurate diagnosis and for outcome prediction.[12]

1.2 Statement of the Problem

Globally, the overall prevalence of DR in diabetes patients is 34.6%.[55] Recent meta-analyses done in Ethiopia indicate that the prevalence of DR among diabetic patients is 19%. [27, 30, 33]

Diabetic kidney disease occurs in 30% -40% of diabetic patients and it is the leading cause of CKD worldwide. The prevalence of diabetic kidney disease in Ethiopia ranges from 11.4% to 23.8%.[31, 32, 33, 42, 45] More than 90% of patients with T1DM with diabetic kidney disease have diabetic retinopathy and 60% of patients with T2DM with diabetic kidney disease have diabetic retinopathy.

Studies have shown that the presence of diabetic retinopathy itself may reveal patients at risk for diabetic kidney disease. Diabetic kidney disease can be classified as proteinuric or nonproteinuric DKD (manifests solely as impaired eGFR). The severity of proteinuria is strongly associated with the severity of DKD but the severity of DKD cannot be explained only with the severity of proteinuria.[6]

1.3 Significance of the Study

Diabetic retinopathy is useful for screening diabetic kidney disease. There are few studies that have shown that DR is a risk factor for diabetic kidney disease. However, the association of renal outcome according to DR severity is not well established. There are limited data worldwide and there are no data in Ethiopia on the relationship between patterns of DR and diabetic kidney disease. Therefore, the purpose of this study is to assess the relationship between DR stages and diabetic kidney disease severity. We believe this study will be a baseline study in Ethiopia for further studies.

2. Literature Review

2.1 Epidemiology of DR and DKD

A pooled analysis from 35 population-based studies in the U.S., Australia, Europe and Asia (between 1980 –2008) showed that the overall prevalence of any DR was 34.6%.[55] A meta-analysis which was done in China by Song P et al. indicated that the prevalence of any DR, NPDR, and PDR were 18.45%, 15.06% and 0.99% respectively.[56] Other studies have shown that the prevalence of any DR was 28.5% in the USA and 21.7% in India.[57,58]

A meta-analysis which was done in Ethiopia by Fite et al. showed that the prevalence of DR was 19.48%.[30] This is consistent with another meta-analysis done by Bekele B. (18.57%) and other studies done at TASH (18.57%) and Debre Markos referral hospital (18.9%).[1, 27, 33] It is higher than a study conducted at Arbaminch general hospital (13%), but lower than studies conducted at Menelik II hospital (31.4%) and Jimma university hospital (41.4%).[25, 26, 39] These discrepancies among studies might be due to variations in methodology, setting, comorbidities, diagnostic method, quality of care, and health-seeking behavior among study participants. Three-quarters (75.4%) of DR patients had nonproliferative DR and a quarter (24.6%) proliferative DR.[27]

Diabetes is the leading cause of CKD and affects ~40% of type 1 and type 2 diabetic patients.[3] Studies in Ethiopia have shown that diabetic kidney disease was found in 15.7% at Jimma university hospital and in 23% at Menelik II hospital.[32, 39] A recent meta-analysis conducted in Ethiopia shows that the prevalence of diabetic kidney disease is 14.4%. [33] A systematic review done in Ethiopia by Nardos et al. showed that the prevalence of DKD ranges from 1% to 23%.[44]

2.2 DR predicting DKD

DR is the most accurate predictor for diabetic kidney disease. Both proliferative and non-proliferative DR can be associated with diabetic kidney disease. Proliferative DR possibly being the more sensitive of the two.[3] Studies have suggested that DR may prognosticate the renal outcomes in patients with diabetic kidney disease.[2, 3] A study by El-Asrar et al. showed that the prevalence of DKD was found to rise with increasing severity of DR. Retinopathy, especially the presence of PDR, is an independent predictor for DKD and the predictive value of retinopathy for DKD is stronger in patients with T1DM than in those with T2DM.[17] In patients with T1DM, the prevalence of DKD was 17.2%, 23.3%, and 50% in patients with mild to moderate NPDR, severe NPDR, and PDR respectively.[17] In patients with T2DM, the prevalence of DKD was 11.4%, 11.8%, and 45.5% in patients with mild to moderate NPDR, severe NPDR, and PDR respectively.[17] In one study, DR and clinical parameters favoring diabetic kidney disease were found in two thirds of patients with diabetes and CKD stages 1–4.

DR and parameters favoring DKD were associated with a lower eGFR and higher urine protein to creatinine ratio (UPCR).[3] Patients with microalbuminuria and DR showed the fastest GFR decline.[6, 9] A study by Lee WJ et al. showed that the prevalence of any DR, PDR, microalbuminuria, and macroalbuminuria in diabetes patients was 20%, 3.8%, 19.3% and 5.5% respectively.[6] Proteinuria occurs in 15–40% of patients with type 1 diabetes, with a peak incidence around 15–20 years of diabetes and in patients with type 2 diabetes, the prevalence is highly variable, ranging from 5 to 20%.[52]

2.3 Risk factors for DR

Analyses of 35 studies which enrolled a total of 22,896 participants showed that the prevalence of any DR increased with diabetes duration (21.1 vs. 76.3%, comparing <10 with >20 years), HbA1c (18.0 vs. 51.2%, comparing levels <7.0 with >9.0%), and blood pressure (30.8 vs. 39.6%, comparing blood pressure ≤ 140/90 or >140/90), and was higher in people with type 1 than type 2 diabetes (77.3 vs. 25.2%).[59] Other risk factors include increased age, dyslipidemia and obesity.[33, 55]

2.4 Risk factors for DKD

The risk factors for DKD can be modifiable and nonmodifiable. The modifiable risk factors include hyperglycemia, hypertension, dyslipidemia, obesity, and smoking and the nonmodifiable risk factors include older age, male sex, longer duration of diabetes and family history of DKD.[60, 64, 67]

2.5 Pathogenesis

DR and DKD are both microvascular complications of diabetes which lead to inflammation of micro-vessels and endothelial dysfunction.[5] Since DR and DKD share similar pathogenesis and microvascular lesions, it is reasonable to assume that development of DR may predict development and progression of DKD.[4, 5] In addition, glycemic and blood pressure control reduces the incidence and progression of both retinopathy and kidney disease in patients with diabetes, suggesting a common pathogenesis of these two complications.[10]

2.6 Diagnosis of DKD

The diagnosis of DKD is, in most cases, based on the clinical manifestations, and renal biopsy is only performed in patients with atypical presentations.[2] Assessment of proteinuria is helpful in establishing a diagnosis, monitoring the course of the disease and assessing the effectiveness of treatment.[54] Urine albumin to creatinine ratio (ACR) is preferred measure of albuminuria; however, if ACR is not available, protein to creatinine ratio (PCR) can be used in DKD screening, staging, and prognosis.[38] Albuminuria is more sensitive than proteinuria, but measurement of proteinuria is cheaper than that of albuminuria.

The spot urine PCR is a quick and reliable test that can eliminate the need for a daily 24-h urine collection. A spot urine PCR > 0.2mg/mg is the most commonly reported cutoff value for detecting proteinuria, while a PCR value > 3.5mg/mg confirms nephrotic proteinuria.[54] The severity of urine protein to creatinine ratio (UPCR) can be classified as normal (< 0.05 mg/mg), mildly increased (0.05-0.15 mg/mg), moderately increased (0.15-0.50 mg/mg), and severely increased (> 0.50 mg/mg).[54]

2.7 Treatment of DR and DKD

Current treatment of DR includes blood glucose control, BP control, anti- vascular endothelial growth factor (anti- VEGF), laser photocoagulation or vitrectomy.[11] For type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) showed that HbA1c decrease by 1% reduces the risk of DR by 39%, and in type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) showed that for each 1% decrease in HbA1c level reduces the risk of microvascular events, including DR, by 25%.[63] In the UKPDS, patients having tight BP control had a 34% reduction in DR progression compared with those having conventional control.[62]

DKD is associated with increased cardiovascular morbidity and mortality. So, it is important to identify patients at risk of DKD and initiate protective renal and cardiovascular therapies.[20] Interventions such as glycemic control, BP control and RAAS inhibitors have been shown to slow DKD progression. Hyperglycemia is well known risk factor for DKD and it is recognized that intensive glucose control reduces the risk of DKD.[60]

Beneficial effects of intensive therapy on the worsening of GFR have become evident during long-term combined DCCT/EDIC follow-up, with a risk reduction of 50%. In the DCCT, normalization of blood sugar decreased the risks of microalbuminuria and macroalbuminuria by 39% and 54%, respectively, compared with conventional therapy.[60] Even with long term follow up in observational Epidemiology of Diabetes Interventions and Complications (EDIC) Study, formerly assigned patients to DCCT intensive therapy continued to experience lower rates of microalbuminuria and macroalbuminuria with risk reductions of 45% and 61%, respectively.[61]

In the UKPDS, a reduction in systolic blood pressure by 10 mmHg was associated with a 30% reduction in microalbuminuria.[62] BP lowering and blockade of the RAS are the cornerstones in the treatment and prevention of DKD because large international studies such as Reduction in Endpoints in Noninsulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) Study and Irbesartan Diabetic Nephropathy Trial (IDNT) showed retardation of DKD with effective BP control and RAS blockade.[65, 66]

3. Objectives

3.1 General objective

To identify the relationship between patterns of DR and diabetic kidney disease

3.2 Specific objectives

- To assess DR stages
- To determine DKD severity
- To assess associated risk factors for DKD
- To determine the association of DR severity and DKD severity

4. Methods

4.1 Study design and study setting

A hospital-based cross-sectional prospective study design was conducted at the outpatient diabetes clinic of TASH (a teaching tertiary hospital), college of health sciences, Addis Ababa University, Addis Ababa, Ethiopia from June 2021 to July 2021. The hospital serves approximately 370,000–400,000 patients yearly referred from across the country. The diabetes clinic was established in 1994 and about 12,000 -13,000 diabetic patients visit the clinic yearly.

4.2 Inclusion and Exclusion criteria

4.2.1 Inclusion criteria

Adult patients (≥18 yrs) with diabetic retinopathy who visited diabetes clinic of TASH from June, 2021 to July, 2021

4.2.2 Exclusion criteria

- Female patients who are pregnant
- Patients who are HIV positive
- Patients having established nondiabetic kidney disease
- Patients with kidney transplantation

4.3 Data collection procedures

Data were collected from record review on electronic medical records and/or patient charts and by interviewing the study participants. The questionnaire was prepared in English and was translated to a widely spoken local language. The questionnaire was discussed with data collector nurses prior to data collection.

DR screening was done with slit-lamp biomicroscope by final year ophthalmology residents at the diabetes clinic. A spot urine sample was collected in the clinic and random urine protein-to-creatinine ratio was done at the Ethiopian public health institute laboratory. The serum creatinine was determined at TASH laboratory and the eGFR was calculated by CKD-EPI equation.

4.4 Sample size and sampling procedure

All consecutive diabetic patients who were screened and had DR at diabetes clinic of TASH in the specified study period and who fulfilled the inclusion criteria were enrolled in the study

4.5 Data analysis

Collected data were verified, cleaned and checked for quality before analysis. Data were entered into the IBM SPSS statistic software version 26 manually. Descriptive statistics such as frequency, percentage, mean and standard deviation (SD) were used to describe and summarize data. Continuous variables were presented as mean ± standard deviation and were compared by

t-test. Categorical variables were expressed as frequency and percentage. Bivariable and multivariable logistic regression analyses were used to assess association between independent and dependent variables. Odds ratio (OR) with 95% confidence level was used and P-value of < 0.05 was considered as statistically significant.

4.6 Operational definitions

Based on International Clinical DR Disease Severity score, four stages of DR are operationally defined as follows:

Mild NPDR – micro-aneurysms only

Moderate NPDR – mild NPDR plus small bleeds (dot and blot hemorrhages), leaks (hard exudates) or cotton wool spots

Severe NPDR/ pre-proliferative DR – defined by any of the following: hemorrhage/ microaneurysm in all 4 quadrants, venous beading in 2 or more quadrants, Intraretinal microvascular abnormalities (IRMA) in at least 1 quadrant

PDR – defined by the presence of new vessels on the disc and elsewhere (NVD, NVE) or vitreous/pre-retinal hemorrhages

Diabetic macular edema – retinal thickening and edema involving the macula

Diabetic kidney disease - refers to spot UPCR ≥ 0.15 mg/mg and/or reduced eGFR (< 60 mL/min/1.73 m^2) in the setting of diabetes. DKD is classified into 5 stages based on eGFR:

Stage 1 DKD: eGFR ≥ 90 mL/min/1.73 m^2

Stage 2 DKD: eGFR between 60 – 89 mL/min/1.73 m^2

Stage 3A DKD: eGFR between 45 – 59 mL/min/1.73 m^2

Stage 3B DKD: eGFR between 30 – 44 mL/min/1.73m^2

Stage 4 DKD: eGFR between 15 – 29 mL/min/1.73 m^2

Stage 5 DKD: eGFR < 15 mL/min/1.73 m^2

Classifications of body mass index (BMI):

Underweight - < 18.5 kg/m^2

Normal – 18.5 to 24.9 kg/m^2

Overweight – 25 to 29.9 kg/m^2

Obesity – BMI of 30 kg/m^2 and above

Uncontrolled lipid profile - is defined as total cholesterol ≥ 200 mg/dl, triglycerides ≥ 150 mg/dl, LDL cholesterol ≥ 100mg/dl and/or HDL cholesterol (< 40 mg/dl in male, < 50 mg/dl in female) regardless of statin therapy.

4.7 Ethical considerations

Ethical approval obtained from the research ethical review committees of department of Internal Medicine and Addis Ababa University, College of Health sciences. The aim of the study was explained and informed written consent was obtained from the study participants.

4.8 Dissemination of results

The results of the study will be presented to Addis Ababa University, College of Health sciences, department of Internal Medicine. The manuscript will also be sent for reputable journal publication.

5. Results

5.1 Socio-demographic characteristics of the study participants

Of the total of 110 sample size, 101 patients were analyzed. 9 patients were excluded from analysis due to incomplete documents. Of these, 55 (54.5%) participants were females and 46 (45.5%) were males. The mean (±SD) age of the participants was 52.9 (±11.8) years. Most participants were married 71 (70.3%). In this study, majority of the participants 74 (73.3%) attended at least secondary level of education. Most participants were Orthodox Christians 76 (75.2 %) and majority participants 95 (94.1%) came from urban area. (Table 1)

Table 1. Socio-demographic characteristics of the study participants (N= 101)

Variables	**Number (N)**	**Percent**
Sex		
Male	46	45.5
Female	55	54.5
Age in years		
20-40	17	16.8
41-60	55	54.5
> 60	29	28.7
Marital status		
Single	16	15.8
Married	71	70.3
Divorced	6	5.9
Widowed	8	7.9

Religion		
Orthodox	76	75.2
Muslim	15	14.9
Protestant	8	7.9
Others	2	2.0
Residence		
Urban	95	94.1
Rural	6	5.9
Educational status		
No formal education	4	4.0
Primary (Grade 1-8)	23	22.8
Secondary (Grade 9-12)	39	38.6
College/University	35	34.7
Job status		
Having job	40	39.6
Not having job	61	60.4
Smoking status		
Never	91	90.1
Ex-smoker	8	7.9
Current smoker	2	2.0
BMI		
Underweight	3	3.0
Normal	37	36.6
Overweight	36	35.6
Obese	25	24.8

5.2 Clinical characteristics of the participants

Among the patients, only 1% developed macular edema. Regarding therapies, 8.9% had history of laser therapy, 1% had history of intravitreal injection treatment and 7.9% of the patients had history of diabetic retinopathy related surgical treatment. Over two third of the patients had history of hypertension and 54.5% were on anti-hypertensive drugs. Majority of participants (80.2%) had type 2 diabetes. More than half of our patients (60.4%) had mild NPDR. (Table 2)

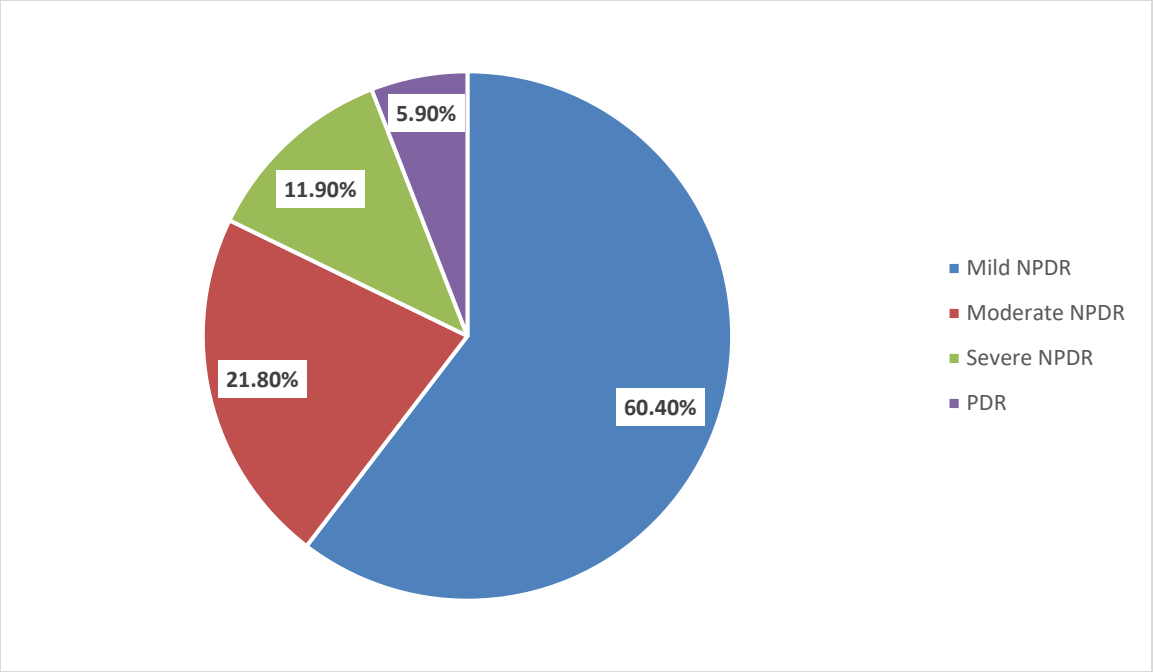

Figure 1 Types of diabetic retinopathy

Table 2. Clinical Characteristics of the participants (N = 101)

Variable	**Frequency**	**Percent**
Type of DM		
T1DM	20	19.8
T2DM	81	80.2
Duration of DM		
0 to 10 yrs	29	28.7
>10 yrs	72	71.3
Types of retinopathy		
Mild NPDR	61	60.4
Moderate NPDR	22	21.8
Severe NPDR	12	11.9

Proliferative DR	6	5.9
Duration of retinopathy (yrs)		
New (diagnosed on the day of enrolment)	52	51.5
< 5	39	38.6
5-10	9	8.9
>10	1	1
Family history of DKD		
No	93	92.1
Yes	8	7.9
Current SBP in mmHg		
<140mmHg	55	54.5
≥140 mmHg	46	45.5
Current DBP in mmHg		
<90 mmHg	74	73.3
≥90mmHg	27	26.7
Presence of CVD		
Yes	29	28.7
No	72	71.3
Types of CVD		
IHD only	10	34.5
HF only	1	3.4

HHD only	7	24.1
PAD only	1	3.4
Stroke only	4	13.8
Others	6	20.6
Number of CVD	N = 29	
1	26	89.7
≥ 2	3	10.3
DKD		
Yes	71	70.3
No	30	29.7

5.3 Laboratory profiles of the study participants

Of the study participants, a single urine dipstick was done for 73 patients and majority (46.6%) of them had a proteinuria of +1 and above. The lipid profile status of 86 (85%) patients was known. Among these, 62.8% of participants had uncontrolled lipid profile status, and more than three-fourths of the participants had FBS level of > 130 mg/dl on the day of study enrolment. Majority of participants (63.4%) had UPCR of ≥ 0.15 mg/mg but only 11 (10.9%) participants had eGFR < 60 mL/min/1.73 m^2. (Table 3)

Table 3. Laboratory profiles of the study participants

Variable	**Number**	**Percent**
Urine dipstick	N = 73	
Negative	32	43.8
Trace	7	9.6
+1	11	15.1
+2	12	16.4
≥ +3	11	15.1
Lipid profile	N = 86	

Controlled	32	37.2
Uncontrolled	54	62.8
GFR (mL/min/1.73 m^2)	N = 101	
Stage 1	66	65.3
Stage 2	24	23.8
Stage 3A	6	5.9
Stage 3B	1	1
Stage 4	3	3
Stage 5	1	1
UPCR (mg/mg)	N = 101	
< 0.15	37	36.6
0.15- 0.50	45	44.6
>0.50	19	18.8
Average FBS (mg/dl)	N = 99	
70 -130	24	24.2
>130	75	75.8
HbA1C (%)	N = 80	
≤ 7	11	13.8
>7	69	86.3

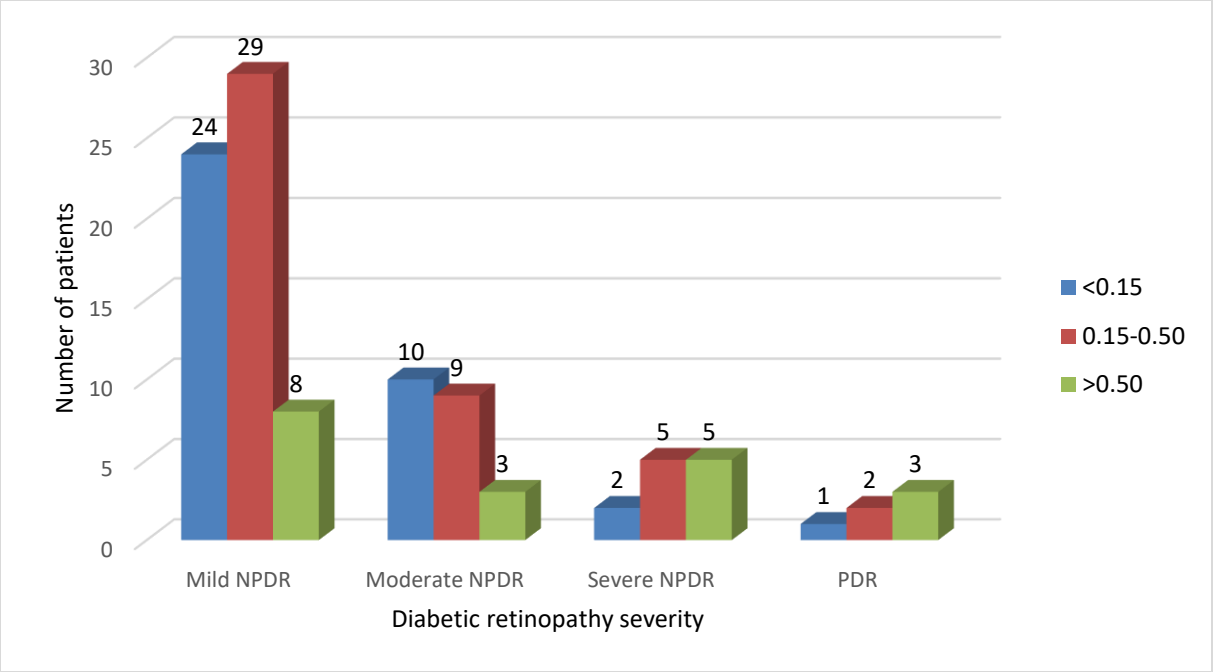

Figure 2: The relationship between DR severity and UPCR (mg/mg)

5.4 Medication pattern of the study participants

With regard to medications, 78% of the patients were on insulin therapy of whom the majority of patients (56.4%) were on NPH only and the rest (43.6%) were on both NPH and RI. About two-thirds (68.3%) of patients were on oral hypoglycemic agents with metformin being the commonest (71%). Among the participants, 43.6% were on both insulin and OHA. (Table 4)

Table 4 Medication of the study participants

Variable	**Number**	**Percent**
OHA types	N = 69	
Metformin only	49	71
Glibenclamide only	1	1.4
Metformin + Glibenclamide	13	18.8
Metformin + Glimepiride	2	2.9
Metformin/Vildagliptin	1	1.4

Metformin/Vildagliptin + Glibenclamide	3	4.3
ACEI or ARB therapy		
Yes	50	49.5
No	51	50.5
CCB therapy		
Yes	19	18.8
No	82	81.2
Beta-blocker therapy		
Yes	21	20.8
No	80	79.2
Furosemide therapy		
Yes	13	13
No	88	87
Spironolactone therapy		
Yes	4	4
No	97	96
Statin therapy		
Yes	73	72.3
No	28	27.7
Aspirin therapy		
Yes	34	33.7

No	67	66.3

OHA – oral hypoglycemic agent

5.5 Factors associated with DKD and association of DR with DKD

In this study, based on the p-value of the bivariable analysis, six variables were identified as candidate variables for the multivariable analysis. These are age, retinopathy severity, BMI, type of DM, presence of CVD and duration of DM. The result of multivariable analysis, however, identified severe NPDR to PDR, type 2 DM and presence of CVD as independent risk factors associated with DKD.

After controlling the effect of type of DM, age, BMI status and duration of DM, it was found that having severe NPDR to PDR was 3.97 times more risk for developing DKD compared to mild to moderate NPDR [AOR= 3.97; 95% CI: 1.01 - 15.62]. Similarly, controlling the effect of severity of retinopathy, BMI status, presence of CVD, duration of DM and age, it was found that patients with type 2 DM had 3.74 times higher odds of developing DKD than type 1 DM [AOR= 3.74; 95% CI: 1.29 - 10.75]. Likewise, after controlling the effect of type of DM, age, severity of retinopathy, BMI status, and duration of DM, patients who developed CVD had 3.18 times higher odds of developing DKD than the counterparts [AOR= 3.18; 95% CI: 1.05- 9.59].

Table 5. Bivariable and multivariable logistic regression analysis results of factors associated with DKD

Explanatory variables		DKD by UPCR		**COR 95% CI**	**AOR 95% CI**
		Yes	No		
Age		55.1±11.85	49.03±10.69	1.05(1.009,1.086)	1.003(0.95,1.06)
Retinopathy severity	Mild to moderate NPDR	49(76.6%)	34(91.9%)	1	1
	Severe NPDR to PDR	15(23.4%)	3(8.1%)	3.47(0.93,12.92)	3.97(1.009,15.62)*
BMI status	Normal and below	21(32.8%)	19(51.4%)	1	1
	Overweight and obese	43(67.2%)	18(48.6%)	2.16 (0.94, 4.95)	1.9 (0.77,4.73)
Type of DM	T1DM	8(12.5%)	12(32.4%)	1	1
	T2DM	56(87.5%)	25(67.6%)	3.36(1.22, 9.25)	3.74 (1.29,10.75)*
Presence of CVD	Yes	24(37.5%)	5(13.5%)	3.84(1.32, 11.19)	3.18 (1.05,9.59)*
	No	40(62.5%)	32(86.5%)	1	1
Duration of DM	0-10 years	17(26.6%)	12(32.4%)	1	1
	>10 years	47(73.4%)	25(67.6%)	1.33(0.55, 3.21)	2.05(0.76, 5.5)

* Statistically significant at p value $\leq$ 0.05

6. Discussion

In our study, majority (94.1%) of DR patients had NPDR, 5.9% had proliferative DR and 1% of patients had macular edema. The proportion of NPDR in this study is higher than studies done in Ethiopia at Menelik II hospital (29.2%) and Debre Markos Referral hospital (75.4%). [27, 40] This might be due to the fact that half of our DR patients were diagnosed on the day of study enrolment.

The prevalence of NPDR in the present study is in line with a meta-analysis in China (93.8%) and a study done in Armenia (90.2%).[56, 68] This is higher than studies in Khartoum (51.7%), Bangladesh (63.3%) and in Iran (70.9%).[12, 21, 69] These variations might be due to quality of care for DM patients, diagnostic methods, genetic differences and majority (51.5%) of our DR patients were newly diagnosed patients. A study conducted in Israel showed that Ethiopian Jews immigrants were prone to T1DM. [76] A study by Siraj et al. revealed that Ethiopians with T1DM had less prevalence of islet cell autoantibodies as compared to Caucasians. [77]

Previous studies showed that increased age, poor glycemic control, HTN, duration of diabetes and dyslipidemia were significantly associated with presence of DR,[33, 55, 59] but these factors were not evaluated in the present study.

In this study, we found that the proportion of DKD among DR patients was 70.3% and the DR severity was identified as one of the associated risk factors of DKD. The odds of developing DKD was 3.97 times higher among patients with Severe NPDR to proliferative DR compared to mild to moderate NPDR [AOR= 3.97; 95% CI: 1.01 - 15.62]. Previous studies have revealed that both the presence and severity of DR were associated to lower eGFR and more severe proteinuria, which might be explained by similar pathological mechanisms underlying the development of microvascular damage in the retina and kidneys.[17, 22, 70]

In this study, in addition to DR severity, T2DM and CVDs were found to be independently associated with DKD. It was found that patients with T2DM had 3.74 times higher odds of developing DKD than T1DM [AOR= 3.74; 95% CI: 1.29 - 10.75]. Few prior studies have compared rates of diabetic kidney disease according to diabetes type.[71,72] In a systematic review of diabetes patients, annual incidence of albuminuria was slightly higher among type 2 diabetes (3.8 to 12.7% per year) compared with type 1 diabetes (1.3 to 3.8% per year).[71] A large population-based study in the United Kingdom found that, among those with preserved eGFR (≥60 mL/min/1.73 m^2), the prevalence of increased albuminuria (urine ACR ≥30 mg/g) was similar (18%) in patients with type 1 and type 2 diabetes and the prevalence of decreased eGFR (<60 mL/min/1.73 m^2) was less common in type 1 (14%) than in type 2 diabetes (25%).[72] In a study at Ayder Referral hospital, type of diabetes was not independent predictor of DKD.[28] These discrepancies might be due to variations in sample size, duration of diabetes, diagnostic methods and care of diabetes patients.

In the present study, 28.7% of patients had cardiovascular diseases. Patients with CVD had 3.18 times higher odds of developing DKD than patients with no CVD [AOR= 3.18; 95% CI: 1.05-9.59]. This finding is supported by previous studies in Ethiopia, in Saudi Arabia and a study in Western countries.[31, 73, 74]

On the other hand, older age, HTN, poor glycemic control, longer duration of diabetes, dyslipidemia, obesity, smoking and family history of kidney disease were not associated with DKD in this study. These results are inconsistent with previous studies which have shown that poor glycemic control, DM duration and HTN are risk factors for DKD. [6, 21] These variations might be due to small sample size and majority of our patients had poor glycemic control and HTN in the current study which might mask the comparisons.

Therapy with ACEIs/ARBs was not associated with lower proportions of DKD in our study, although it has been demonstrated in previous studies.[65, 66] This might be partly due to small sample size in the present study.

No significant association was found between DR severity and eGFR level in the present study. The lack of association with the eGFR level was probably due to the small sample size in this cross-sectional study.

Strengths and limitations of the study

The strengths of this study are the use of well validated grading of DR and to the best of our knowledge, this is the first study in Ethiopia that assessed the association of DR and DKD.

This study also has some limitations. First, this study is a single center, hospital-based study which was conducted with small sample size due to budget constraints. Second, we defined DKD using a single measurement of the eGFR based on the CKD-EPI equation and of proteinuria by spot UPCR, but ideally DKD should not be diagnosed on the basis of single measurements of serum creatinine and proteinuria. Third, transient proteinuria might have been inadvertently included as it was a single spot urine measurement of proteinuria.

Conclusion

In conclusion, in this study DR severity, T2DM and CVDs were strongly associated with DKD.

Recommendations

The primary diabetes care providers should make a timely referral of diabetics to eye care services and they should follow regularly the renal function and proteinuria. When a primary diabetes care provider finds proteinuria and/or renal function dysfunction, early referral to a nephrologist should be considered.We recommend further prospective, cohort, population-based studies with larger sample size to reproduce and confirm our study findings.

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Annex I: Questionnaire

Part I – Socio-demographic characteristics:

1.1 Age (in yrs) ……

1.2 Sex - Male ☐ Female ☐

1.3 Marital status – Single☐ Married☐ Divorced☐ Widowed☐

1.4 Religion – Orthodox Christian☐ Muslim☐ Protestant Christian☐ Others☐ (Specify)……..

1.5 Place of residence- Urban☐ Rural☐

1.6 Educational status:

No formal education☐ Primary (Grade 1-8)☐ Secondary (Grade 9-12)☐ College/University☐

1.7 Job status – Having job ☐ Not having job ☐

1.8 Smoking status – Never☐ Current smoker☐ Ex-smoker☐

1.9 If he/she is current/ex-smoker:

how many cigarettes a day (average estimate) …… and for how long (in yrs) ……

1.10 If he/she was ex-smoker in the above question, when did he/she quit smoking?..... (Years back)

1.11 Weight (kg) …….

1.12 Height (cm) …….

Part II: Clinical characteristics:

2.1 Type of diabetes

T1DM ☐ T2DM ☐ Other ☐(specify) …….

2.2 Duration of diabetes:

New☐ < 5 yrs ☐5-10 yrs ☐10-15 yrs ☐15-20 yrs ☐ > 20 yrs ☐

2.3 Type of Retinopathy

mild background/NPDR ☐ moderate background/NPDR ☐ severe background/NPDR (Pre-proliferative DR) ☐ proliferative DR ☐ Diabetic macular edema ☐ 2.4 Duration of retinopathy (in yrs) ……

2.5 History of laser therapy – Yes ☐ No ☐

2.6 History of intravitreal injection treatment – Yes ☐ No ☐

2.7 History of DR related surgical treatment – Yes ☐ No ☐

2.8 Family history of diabetic kidney disease – Yes ☐ No ☐

2.9 History HTN? Yes ☐ No ☐

2.10 If yes in the above question:

. Duration of HTN (in yrs) …….

. Current BP (mmHg)…….

2.11 Is he/she on antihypertensive drugs? Yes☐ No☐

2.12 Does the patient have cardiovascular diseases – Yes ☐No ☐

2.13 If yes in the above question, the patient has:

Ischemic heart disease☐ Heart failure☐ Hypertensive heart disease☐ Peripheral arterial disease☐ Stroke☐ others (specify) ☐ ……

Part III: Laboratory measurements:

3.1 Creatinine (mg/dL) ……...

3.2 Urea (mg/dL) …….

3.3 FBS (mg/dL):

Current FBS (at the time of data collection)……

Average FBS ……(If the patient has > 1 value in the past 6 mo)

3.4 HbA1C (%) …… (If it was determined in the past 6 mo)

3.5 Lipid profile (mg/dL):

Cholesterol – Total …… HDL …… LDL……

Triglycerides……

3.6 Random urine protein (mg/dL) …….

3.7 Random urine creatinine (m/dL)…….

3.8 Urine dipstick:

Current proteinuria – Trace ☐ +1 ☐ +2 ☐ ≥ +3 ☐

Proteinuria (If urinalysis done 6 weeks – 6 months ago)

Trace ☐ +1 ☐ +2 ☐ ≥ +3 ☐ Not done☐

3.9 24 –hours urine protein (g/day) [If it was done] …….

Part IV: Medications:

4.1 Is he/she on Insulin? –Yes☐ No☐

4.2 If yes, he/she is on insulin: NPH only☐ RI only☐ Both NPH & RI☐ others (specify) ☐……..

4.3 Is he/she on oral antidiabetic drug? –Yes☐ No☐

4.4 If the answer is yes in the above question, he/she is on (more than choice is possible):

Metformin☐ Sulfonylureas☐ (specify)…… Others☐ (specify)……

4.5 ACE or ARB – Yes☐ No ☐

4.6 Calcium channel blockers – Yes☐ (Specify)……. No☐

4.7 β-blocker – Yes☐ No ☐

4.8 Furosemide – Yes☐ No☐

4.9 Spironolactone – Yes☐ No ☐

4.10 Statin – Yes☐ No☐

4.11 Aspirin - Yes☐ No ☐

Annex II

Information sheet in English version

We want to do research that will try to see if your diabetes related eye problem has any relationship with the diabetes affecting your kidneys. The information you give us will be used to provide people living with diabetes a better medical care. The research needs your urine sample to see your kidneys status. There is no harm of participating in this study. Your decision to take part in this study is voluntary. Your responses will be kept confidential. Your information may be directly accessible for monitoring by advisors, Institutional Review Board or by regulatory agencies. Collected information will be coded and the result will be sent for publication. If you do not want to participate in this research that will not have any impact on the medical care we give you. If you have questions, you can ask the data collector nurse. If you decide to take part, we ask you to help us by answering the following questions.

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በአማርኛ የጥናቱ መረጃ

ይህ ጥናት የስኳ ር በሽታ ዓይን ላይ የ ሚ ያመጣው ተፅዕኖ፣ ኩላሊት ላይ ያለውን ግንኙነት የሚያጠና ነው፡፡ ጥናቱ ከስኳር በሽታ ጋር የሚኖሩ ሰዎችን ጤና ለማሻሻል የሚረዳ ነው፡፡ ጥናቱ በጤናዎ ላይ የሚያመጣው ችግር አይኖርም፡:: በጥናቱ ተሳታፊ ሲሆኑ ሽንት ምርመራ ይደረግልዎታል፡፡ የሚሰጡት መረጃ በፈቃደኝነት የተመሰረተ ሲሆን መረጃው ጥናቱን ከሚቆጣጠር አካል ውጭ ምስጢራዊነቱ ይጠበቃል፡፡ የጥናቱ ውጤት የእርስዎን ማንነት በማያሳውቅ ሁኔታ ለህትመት የሚበቃ ይሆናል፡፡ በጥናቱ ለመሳተፍ ፈቃደኛ ባይሆኑም በምንሰጠው አገልግሎት ላይ የሚያጣው ለውጥ አይኖርም፡፡

ጥያቄ ካለዎት መረጃ የሚሰበሰበውን ባለሞያ መጠየቅ ይችላሉ፡፡

ጥናቱን የሚያጠናው: ዶ/ር ወዳጆ መንገ ሻ

በአዲስ አበባ ዩኒቨርሲቲ የመጨረሻ ዓመት የውስጥ ደዌ ህክምና ተማሪ
ስልክ ቁጥር: +251936744127
e-mail: wodme.2020@gmail.com

Annex III

Consent form in English version

I have read the information or it has been read to me by the nurse and I am aware of the purpose and significance of the study. I have agreed to participate in the research voluntarily.
Thank you for giving us your permission.
Study participant's signature ……
ICare Number…….. Date …….

Nurse's Name …….. Signature …….. Date ……..

አማርኛ የጥናቱ ፈቃድ መስጫ

የጥናቱን መረጃ አንብቤ ወይም ባለሞያ አንብቦልኝ ተረድቻለሁ፡፡ በጥናቱ በፈቃደኝነት ለመሳተፍ ወስኛለሁ፡፡

በጥናቱ ለመሳተፍ ፈቃደኛ ስለሆኑ እናመሰግናለን፡፡

የጥናቱ ተሳታፊ ፊርማ _____

የጥናቱ ተሳታፊ አይኬር ቁጥር _____

ቀን _____

መረጃውን የሰበሰበው ባለሞያ ስም _____

ፊርማ _____ ቀን _____