



ASSESSMENT OF THE ASSOCIATION OF KIDNEY FUNCTION
WORSENING AND DIABETIC RETINOPATHY SEVERITY IN
PATIENTS ON FOLLOW UP, AT SAINT PAUL'S HOSPITAL
MILLENNIUM MEDICAL COLLEGE, ADDIS ABABA, ETHIOPIA.

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A THESIS SUBMITTED TO THE DEPARTMENT OF INTERNAL MEDICINE FOR PARTIAL
FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE IN INTERNAL MEDICINE
SPECIALITY; SAINT PAUL'S HOSPITAL MILLENNIUM MEDICAL COLLEGE

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SAINT PAULOS MILLINIUM MEDICAL COLLAGE
DEPARTMENT OF INTERNAL MEDICINE

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SUMMARY

Background: Diabetic nephropathy (DN) and diabetic retinopathy (DR) are both complications of diabetic microangiopathy with similar pathogenesis and clinical relevance. Many literatures have shown the clear association of creatinine and eGFR worsening with presence and severity of retinopathy. There is paucity of evidence if this holds true in African setting and more in Ethiopia

Objective: To assess the association of serum creatinine and estimated GFR worsening with diabetic retinopathy severity among type 2 DM patients on follow up at adult Endocrine, Nephrology and ophthalmology clinic, of St Paul Hospital Millennium Medical College, Addis Ababa, Ethiopia.

Methods: An Institution based cross-sectional study was conducted through chart review among type 2 DM with diabetic retinopathy patients attending adult Endocrine, nephrology and ophthalmology clinic of Saint Paul's Hospital Millennium Medical College. A total of 384 patients were planned and 365 participants were involved making a response rate of 95.1%. Data were collected by structured questionnaire focusing on serum creatinine value and documented diabetic retinopathy severity by chart reviewing. Data was entered and analyzed using SPSS version 26. The result was explained using frequencies of variables, descriptive statistics including mean and standard deviation. Associations between dependent and independent variables were assessed by using binary and multiple logistic regressions using 95%CI and a p-value <0.05 at multivariate logistic regression stated as statistically significant.

Result: - In this study 41.9% of the study participants had proliferative stage of diabetic retinopathy. On the other hand the multivariate logistic regression revealed that male (AOR=2.9, 1.41, 6.01), unstable creatinine (AOR=3.5, 95%CI=1.97, 12.53) and estimated GFR <60 (AOR=29.9, 95%CI=14.38, 62.1) were a significant relation with diabetic retinopathy.

Conclusion and recommendation: - serum creatinine and estimated glomerular filtration rate worsening were a significant association with progression of diabetic retinopathy. This study showed clear/no association between Cr and GFR worsening and severity of DR. it is good to screen for severity of diabetic retinal change just because of Cr and GFR worsening.

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Table of Contents

SUMMARY	3
ACKNOWLEDGMENT	4
ABBREVIATIONS/ ACROMYMS	7
LIST OF TABLES	8
LIST OF FIGURES	1
1. INTRODUCTION.....	2
1.1 Back ground	2
1.2 Statement of the problem	4
1.3 Significance of the study	5
2. LITERATURE REVIEW	6
2.1. Prevalence of Type 2 DM	6
2.2 Prevalence of Diabetic Retinopathy	7
2. Conceptual Framework	10
3. OBJECTIVE	11
3.1 General objective.....	11
3.2 Specific objectives	11
4. METHODS	12
4.1 Study setting.....	12
4.2 Study design.....	12
4.3 Source population.....	12
4.4 Study population	12
4.5 Inclusion criteria for patients	13
Exclusion criteria for patients	13
4.6 Sample size.....	13
4.8 Sampling procedure.....	13
4.9 Study variables	14
4.10 Data collection procedure.....	14
4.11 Data Processing, Management and Analysis.....	15
4.12 Operational definitions	15
4.13 Ethical consideration	15
4.14 Dissemination of findings.....	15
5. Result	16
5.1 Sociodemographic characteristics of the study participants.....	16
5.2 Characteristics of the study participants on Diabetic retinopathy	16
5.3 The study participants characteristics on renal function test.....	17
5.4 The comorbid characteristics of the study participants	17

5.5 The mean value and chi-square association between diabetic retinopathy progression and independent	18
5.6 The determinant factor of diabetic retinopathy progression	19
6. Discussion	21
7. Conclusion	23
8. Recommendation	23
REFERENCE.....	24
ANNEXES.....	26

ABBREVIATIONS/ ACROMYMS

ADA: American Diabetic

AKI: Acute Kidney Injury

CHD: Coronary Heart
Diseases

CKD: Chronic Kidney
Diseases

DCCT: Diabetes Control and
Complication Trial

DM: Diabetes Mellitus

DR: Diabetic Retinopathy

ETB: Ethiopian birr (money)

GFR: Glomerular Filtration
Rate

and Complication trial

IDF: International Diabetic Federation

IGT: Impaired Glucose Tolerance

PAD: Peripheral Arterial Diseases

SPHMMC: Saint Paul's Hospital Millennium
Medical College

SPSS: Statistical Package for the Social Sciences

WHO: World Health Organization

LIST OF TABLES

Table 1. The sociodemographic characteristics of the study participant having diabetic retinopathy at SPMMC, 2023.....	16
Table 2. The study participant characteristics on diabetic retinopathy.....	16
Table 3. The renal function test characteristics of the study participant.	17
Table 5. The mean value and chi-square association between diabetic retinopathy progression and independent	19
Table 6. The bivariate and multivariate logistic regression of association between diabetic retinopathy progression and independent variable among diabetic retinopathic patient in SPMMC, 2023.....	20

LIST OF FIGURES

Figure 1.Schematic presentation of conceptual frame work on factors affecting diabetic retinopathy severity.	10
Figure 1. The list of comorbid disease among diabetic retinopathic patient.	18
Figure 2. The relation between estimated glomerular filtration rate and diabetic retinopathy.	18

1. INTRODUCTION

1.1 Back ground

Type 2 DM is characterized by hyperglycemia, insulin resistance, and also relative impairment in insulin secretion. The presence of insulin resistance explains the strong clinical association of T2DM with obesity and other insulin-resistant states. Impaired insulin secretion has been demonstrated in a variety of studies, which show that patients usually have lost approximately 80 percent of their pancreatic beta cell function before the diagnosis of T2DM. In most cases, the impaired insulin secretion does not appear to be mediated by antibodies against the pancreatic islet cells(1).

Type 2 diabetes is an impairment in the way the body regulates and uses sugar (glucose) as a fuel. This long-term (chronic) condition results in too much sugar circulating in the bloodstream. Eventually, high blood sugar levels can lead to disorders of the circulatory, nervous and immune systems(2).

The countries with the greatest number of individuals with diabetes in 2019 were China (116.4 million). India (77 million).the United States (31 million),Pakistan (19,4 million). Brazil (16.8 million) and Mexico (12.8 million). The prevalence of type 2 DM and its harbinger, IGT, is highest in certain pacific islands and the middle east and intermediate in countries such as India and the United States. This variability is likely due to genetic behavioral and environmental factors(1).

According to World Health Organization (WHO), diabetes is a major cause of blindness, kidney failure, heart attack, stroke and lower limb amputation. Between 2000 and 2019, there was a 3%increase in diabetes mortality rates by age. In 2019, diabetes and kidney disease due to diabetes caused an estimated 2 million deaths(3). In Ethiopia prevalence of DM was 6.5%(2).

Diabetic kidney disease" is a clinical diagnosis based upon the presence of albuminuria, decreased estimated glomerular filtration rate (eGFR), or both, in patients with diabetes. Notably, diabetic kidney disease (DKD) does not indicate the specific pathological phenotype of kidney damage due to diabetes. Rather, the designation DKD (or "CKD in diabetes") is used to clarify that the underlying pathologic phenotype is unknown in most cases. The likelihood that diabetic

glomerulopathy is the underlying pathology of DKD varies widely depending upon the clinical circumstances. It is highly likely that diabetic glomerulopathy is the pathologic phenotype of diabetic kidney disease in type 1 diabetes of five or more years duration with albuminuria, but the frequency can vary widely in type 2 diabetes. Only a kidney biopsy can confirm with certainty that diabetic kidney disease is due to diabetic glomerulopathy, but biopsies are infrequently performed for clinical purposes in such patients (4).

Diabetic retinopathy (DR) is one of the most important causes of visual loss worldwide and is the principal cause of impaired vision in patients between 25 and 74 years of age. Visual loss from DR may be secondary to macular edema (macular edema; retinal thickening and edema involving the macula), hemorrhage from new vessels, retinal detachment, or neovascular glaucoma. DR is often asymptomatic until the very late stages. Because the rate of progression may be rapid and therapy can be beneficial for visual improvement, prevention of further visual loss, and reduction in the rate of disease progression, it is important to screen patients with diabetes regularly for the development of retinal disease. Diabetic retinopathy (DR) is divided into two major forms: non-proliferative and proliferative, respectively named for the absence or presence of abnormal new blood vessels emanating from the retina. DR can be further classified by severity. Diabetic macular edema (ME) may develop at any point along the spectrum of mild non-proliferative disease to proliferative diabetic retinopathy. These designations have been useful for analysis of treatment efficacy in the literature and general indicators for treatment strategies. However, each patient with DR has a unique combination of findings, symptoms, and rate of progression, which necessarily requires an individualized approach to treatment in the effort to preserve vision (5).

The International Diabetes Federation (IDF) estimated the global population with diabetes mellitus (DM) to be 463 million in 2019 and 700 million in 2045. In Ethiopia, a systemic review with meta-analysis done on 2019 the overall prevalence of retinopathy was 19.48% (95% CI: 15.95, 23.01) Based on the subgroup analysis the prevalence of retinopathy was 12.48% in SNNPR, 24.8% in Oromia, 19.99% in Amhara, and 16.29% in Addis Ababa(6).

1.2 Statement of the problem

Diabetes related complications affect many organ systems and are responsible for the majority of morbidity and mortality associated with the diseases for many years in the United States, diabetes is the leading cause of blindness in adults, renal failure and non-traumatic lower extremity amputations. diabetes associated micro vascular complications usually do not appear until the second decade of hyperglycemia(1, 7).

The vascular complications of DM are further subdivided into micro vascular (retinopathy, neuropathy, nephropathy) and macro vascular complications (CHD, peripheral arterial disease [PAD], cerebrovascular disease). Micro vascular complications are diabetes specific, whereas macro vascular complications have additional Pathophysiologic features that are shared with the general population(1, 7, 8).

The DCCT done in 1981 at USA phase demonstrated that improvement of glycemic control reduced non proliferative and proliferative retinopathy (47% reduction), albuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction). Improved glycemic control also slowed the progression of early diabetic complications(3). DM is the leading cause of blindness between the ages of 20 and 74 in the United States. Severe vision loss is primarily the result of progressive diabetic retinopathy, which leads to significant macular edema and new blood vessel formation(1, 8, 9). Previous studies have consistently demonstrated the association of worse kidney function with increased risk of DR among T2DM patients(2).

There is no study conducted on the association of serum creatinine and estimated GFR variability in Ethiopia so this study to fill the knowledge gap and pave the way for further research. Therefore, assessment association of serum creatinine and estimated GFR variability with diabetic retinopathy among diabetic patients attending adult Endocrine, Nephrology and ophthalmology clinic at Saint Paul's Hospital Millennium Medical College (SPHMMC), Addis Ababa, Ethiopia, which is one of the country's largest tertiary hospitals, will help identify creatinine and estimated GFR variability is a risk factor for diabetic retinopathy progression.

1.3 Significance of the study

The finding of this study was important to determine the association of serum creatinine and estimated GFR worsening with diabetic retinopathy at SPMMC in type 2 DM. When there is minor AKI with recovery injuries factors like inflammatory burden may accumulate and contribute to DR. It also used to have screening measures in place and treat them in the future, and to improve quality of treatment

Furthermore, the result was assisting other governmental and non-governmental organizations in collaboration with Ministry of Health to be aware of the gaps & strength and formulate strategies which can be implemented nationally. The end result of this study can also be used as a baseline data for further large studies.

2. LITERATURE REVIEW

2.1. Prevalence of Type 2 DM

Diabetes mellitus is prevalent in 11.3% of world's population and from those 95% of patients are Type 2 DM. Type 2 DM is a rapidly evolving global issue. The prevalence of Type 2 DM is raising more rapidly presumably because of dietary changes and increased obesity, reduced physical activity levels as the countries becomes more industrialized and aging of the population(1).

The countries with the greatest number of individuals with diabetes in 2019 were China (116.4 million). India (77 million). the United States (31 million), Pakistan (19,4 million). Brazil (16.8 million) and Mexico (12.8 million). The prevalence of type 2 DM and its harbinger, IGT, is highest in certain pacific islands and the middle east and intermediate in countries such as India and the United States(6).

DM prevalence also varies among different ethnic populations within a given country, with indigenous of diabetes than the general population of the country.DM in the United States (age>20; 2017-2018) was 7.5% in non-Hispanic whites ,9.2 in Asian Americans,11.7% non-Hispanic blacks,12.5% in Hispanics but it exceeds 14% in American Indian and Alaskan native populations(10). In Asia the prevalence of diabetes is increasing rapidly, with an onset at a lower body mass index (BMI) and younger age, greater visceral adiposity, and reduced insulin secretory capacity(9).

Diabetes is the major cause of mortality.in recent years diabetes has been listed as the seventh leading cause of death in the United States, but several studies indicate that diabetes-related deaths are likely under reported(1, 2, 11). In 2019, data from the IDF suggest that diabetes was responsible for nearly 4.2 million deaths worldwide accounting for 11.3% of global all-cause mortality in adults aged 20-79 years Diabetes also has important economic implications. In 2019, it was estimated that \$760 billion of health care expenditures worldwide were spent on diabetes (a range of 8–19% of total expenditures across regions). Up to 75% of individuals with diabetes live in low- or middle-income countries(1).

In Ethiopia, a systemic review with meta-analysis forty studies done in November 2021 from the pooled prevalence of DM was 6.5%. The sub-group analysis revealed that the highest prevalence of DM was found in Dire Dawa city administration (14%), and the lowest prevalence was observed in Tigray region (2%). The pooled prevalence of DM was higher (8%) in studies conducted in health facility. Factors like: Age $\geq$ 40 years, Illiterate, Cigarette smoking, Body mass index (BMI) $\geq$ 25 kg/m², family history of DM, history of hypertension and physical inactivity were significantly associated with type-2 DM in Ethiopian population(6).

New onset of diabetes mellitus was noted as the commonest comorbidity in the COVID-19 pandemic, which contributed to a worse prognosis. Existing evidence showed that new-onset diabetes is associated with increased mortality compared to nondiabetic and known diabetic patients in the COVID-19 era. SARS-CoV-2 virus can worsen existing diabetes; at the same time, it can trigger new-onset diabetes that eventually worsens patient outcomes. Thus, this study is aimed at determining the prevalence and factors associated with new onset of diabetes mellitus among COVID-19 patients(12).

Institution-based retrospective cross-sectional study design was conducted by reviewing 244 patient's records in the Addis Ababa COVID-19 care center done 2022. A significant proportion of COVID-19 patients had been diagnosed with new onset of diabetes mellitus, and new-onset type 2 diabetes mellitus is the most common diabetes mellitus type. Being male, obesity, having a pulmonary embolism, family history of hypertension, and hyperkalemia were independently associated with new onset of diabetes mellitus among COVID-19 patients. Therefore, focused interventions need to be strengthened towards the identified factors(12).

2.2 Prevalence of Diabetic Retinopathy

DM is the leading cause of blindness between the ages of 20 and 74 in the United States. Sever vision loss is primarily the result of progressive diabetic retinopathy, which leads to significant macular edema and new blood vessel formation. The International Diabetes Federation (IDF) estimated the global population with diabetes mellitus (DM) to be 463 million in 2019 and 700 million in 2045(8).

A study done on the relationship between renal function and diabetic retinopathy in patients with type 2 diabetes revealed Abnormal renal profiles (including low levels of eGFR and high levels of MAU) were associated with the progression of DR, but not with the development of DME.

Diabetic patients with renal impairment may be likelier to be required to be closely monitored for DR to detect and intervene in the progression of DR at an early stage (13).

In Ethiopia, a systemic review with meta-analysis done on 2019 the overall prevalence of retinopathy was 19.48% (95% CI: 15.95, 23.01) Based on the subgroup analysis the prevalence of retinopathy was 12.48% in SNNPR, 24.8% in Oromia, 19.99% in Amhara, and 16.29% in Addis Ababa(6).

The true prevalence and incidence of CKD and kidney failure is from diabetes is impossible to know, because kidney biopsies (the gold standard for diagnosis of diabetic kidney diseases are in frequently performed in patients diabetes and CKD(2, 11).

A study done in Australia on The Association of Estimated Glomerular Filtration Rate age- and sex-adjusted models, lower levels of eGFR were associated with DR (odds ratio [OR], 1.54; 95% confidence interval [CI], 1.16–2.05; $P = 0.003$ per SD decrease in eGFR. compared to individuals with normal renal function, those with impaired renal function and CKD were more likely to have DR (OR, 2.97; 95% CI, 1.12–7.87; $P = 0.028$ and OR, 3.77; 95% CI, 1.28–11.1; $P = 0.016$, respectively) after multivariable adjustments. lower levels of eGFR were associated with severe DR (OR, 1.75; 95% CI, 1.11–2.76; $P = 0.036$, per SD decrease in eGFR). CKD was associated with moderate DR (OR, 5.83; 95% CI, 1.44–23.5), severe DR (OR, 4.91; 95% CI, 1.26–19.0) (12).

A study done in Asians revealed that diabetic retinopathy have higher adjusted-serum creatinine-standard deviation than non-diabetic retinopathy [9.1 (4.9–21.6) vs 5.4 (3.4–10.1) μ M, $p < 0.001$]. After multivariable adjustment, adjusted-serum creatinine-standard deviation was associated with diabetic retinopathy [odds ratio=1.47, 95% confidence interval (1.02–2.10), $p = 0.04$]. The area under the curve increased significantly after adding adjusted-serum creatinine-standard deviation [0.70 (0.65–0.75) vs 0.72 (0.68–0.77), $p < 0.03$]. Proliferative diabetic retinopathy have higher adjusted-serum creatinine-standard deviation than non-proliferative diabetic retinopathy [15.5 (6.6–39.7) vs 7.47 (4.52–17.8) μ M, $p < 0.001$]. After adjustment, adjusted-serum creatinine-standard deviation remained associated with non-proliferative diabetic retinopathy [1.48 (1.04–2.12), $p = 0.03$] and proliferative diabetic retinopathy [2.43 (1.34–4.39), $p = 0.003$; $p\text{-trend} = 0.002$]. Similar findings were observed for estimated glomerular filtration rate variability(14).

a study done in China on the Relationship between Estimated Glomerular Filtration Rate and

Diabetic Retinopathy statistically significant differences were detected for age ($P = 0.003$), family history of DM ($P = 0.036$), duration of DM ($P < 0.001$), FBG and 2hPG ($P < 0.001$), HbA1c ($P = 0.003$), TC ($P < 0.001$), HDL-C ($P = 0.013$), LDL-C ($P = 0.002$), SBP ($P < 0.001$), DBP ($P = 0.033$), eGFR ($P < 0.001$), and SCR ($P < 0.001$). There were significant associations between DR and age ($P < 0.001$), DM duration ($P < 0.001$), HbA1c ($P = 0.007$), HDL-C ($P = 0.024$), SBP ($P < 0.001$), DBP ($P = 0.007$), and eGFR ($P = 0.010$). According to the severity of the disease, DR patients were divided into 3 groups: nondiabetic retinopathy (NDR), non-proliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR) groups. The mean value of eGFR was 106.27 ± 23.37 , 100.12 ± 30.85 , and 83.33 ± 33.77 (mL/min) for the NDR, NPDR, and PDR groups, respectively(15).

A study conducted in China on the relationship between renal function and diabetic retinopathy in patients with type 2 diabetes revealed that Low eGFR levels at baseline were associated with the development of DR (HR, 1.044 per 1-SD decrease; 95% CI, 1.035–1.053; $P < 0.001$). Compared to the participants with eGFRs >90 mL/min/1.73 m², the participants with eGFRs of 60–90 mL/min/1.73 m² (HR, 1.649; 95% CI, 1.094–2.485; $P = 0.017$) or < 60 mL/min/ 1.73 m² (HR, 2.106; 95% CI, 1.039–4.269; $P = 0.039$) had a higher risk of DR progression. Increasing MAU tertiles were associated with progression of DR (Tertile 2: HR, 2.577; 95% CI, 1.561–4.256; $P < 0.001$; Tertile 3: HR, 3.135; 95% CI, 1.892–5.194; $P < 0.001$). No significant relationship was found between renal function and the development of DME ($P > 0.05$)(16).

2. Conceptual Framework

The conceptual framework is adapted from different literatures. It assesses factors such as, socio-demographic, disease characteristics, serum creatinine, estimated GFR, worsening dyslipidemia, hypertension affects the severity of diabetic retinopathy (fig. 1).

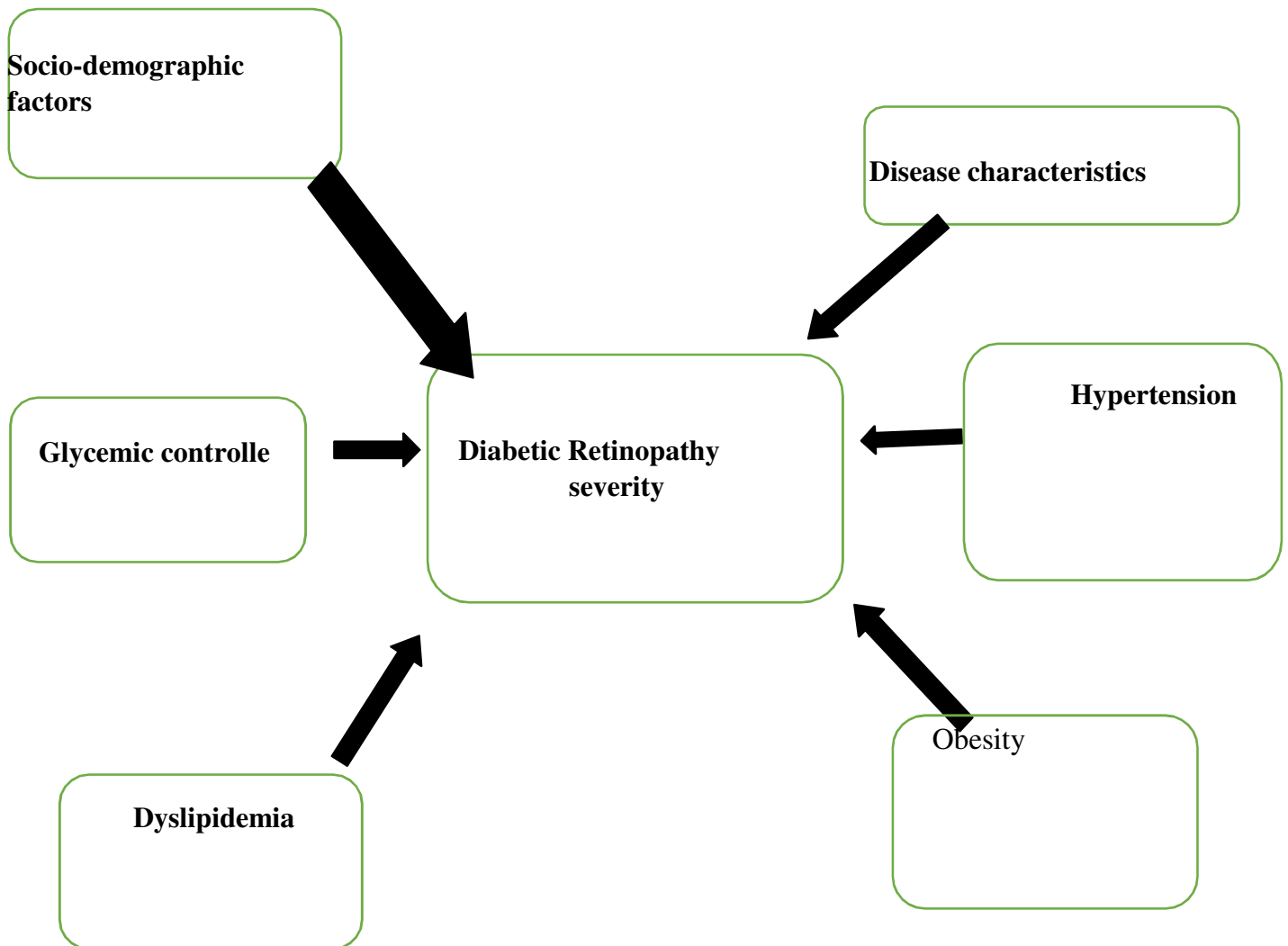


Figure 1. Schematic presentation of conceptual frame work *on factors affecting* diabetic retinopathy severity.

3. OBJECTIVE

3.1 General objective

To assess the association of serum creatinine and estimated GFR worsening with severity of diabetic retinopathy in Type2 DM patients on follow up at Endocrine, Nephrology and ophthalmology clinic, at St Paul Hospital Millennium Medical College, Addis Ababa, Ethiopia.

3.2 Specific objectives

- I. Determine association of potential risk factors for diabetic retinopathy Type2 DM patients on follow up at Endocrine, Nephrology and Ophthalmology clinic, at St Paul Hospital Millennium Medical College, Addis Ababa, Ethiopia
- II. To determine the diabetic retinopathy progression.

4. METHODS

4.1 Study setting

St. Paul Hospital Millennium Medical College (SPHMMC) is the second largest public hospital in Ethiopia. It is located in Gullele Sub City in Addis Ababa and built by Emperor Haile Selassie in 1969 with the mission to provide preventive, promotive, curative, and rehabilitative health care service in the country. It has 2800 clinical, academic and administrative and support staffs that provide medical specialty services to patients who are referred from all over the country, teaching medicine and nursing students and doing basic and applied researches. While the inpatient capacity is more than 700 beds, The College sees an average of 1200 emergency and outpatient clients daily and has a catchment population of more than 5 million. Adult endocrine, Nephrology and ophthalmology clinics are sub specialty outpatient clinics that provide care to patients with Endocrine, Renal and Eye disease every activity (5 times per week), (3 times per week) and (5 times per week) respectively

4.2 Study design

An Institution based cross-sectional study was carried out

4.3 Source population

All patients on follow up at adult Endocrine, Nephrology and Ophthalmology clinic in St Paul Hospital Millennium Medical College in Addis Ababa, Ethiopia.

4.4 Study population

All patients on follow up at adult Endocrine, Nephrology and Ophthalmology clinic in St Paul Hospital Millennium Medical College in Addis Ababa, Ethiopia. The study population for physicians includes all physicians working at adult Endocrine, Nephrology and Ophthalmology clinic

4.5 Inclusion criteria for patients

- Age ≥ 30
- Type 2 DM and patients serum creatinine is greater than 1.2 with two or more determination and diabetic retinopathy
- Patients who have proteinuria

Exclusion criteria for patients

- Patients who have other kidney diseases
- Type 1 DM
- Patients who took non-steroidal anti-inflammatory drugs or steroid

4.6 Sample size

For the participating patients there is no similar previous research conducted so the p value is 50%. With 95% confidence level and 0.05 margin of error a sample size is calculated by using single proportion formula:

$$n = \frac{(Z\alpha/2)^2(p)(1-p)}{d^2} = \frac{(1.96)^2(0.5)(1-0.5)}{(0.05)^2}$$

$$= 384.16 \approx 384$$

4.8 Sampling procedure

Data from the Health Management Information System (HMIS) showed that around 35 – 40 patients per day were seen at adult Endocrine, Nephrology and ophthalmology clinic, in the past 1 year, out of which 8- 12 of them were Type 2 DM with diabetic retinopathy. Most diabetic retinopathy on follow up were appointed within 4- 6 months. So, taking the above information into consideration in order to attain our sample size the study period should span 5 months. Therefore, diabetic retinopathy coming to the 3 clinics during the study period & fulfilling the inclusion criteria will be included in the study. Data collection was stopped once the sample size is achieved.

4.9 Study variables

Dependent variable: severity of Diabetic Retinopathy

Independent variable

- ✓ Age
- ✓ Sex
- ✓ Smoking history
- ✓ Hypertension
- ✓ Duration of illness
- ✓ Type 2 DM burden and risk factors
- ✓ Serum creatinine level

4.10 Data collection procedure

Data were collected through patient chart review using a structured questionnaire comprising socio-demographic characteristics, disease characteristics, serum creatinine value worsening in each visit, estimated GFR variability in visit, hypertension, dyslipidemia and documented diabetic retinopathy severity.

All the questionnaire were in English language and data collectors were trained on how to effectively gather information from the patients during their visits to adult endocrine, nephrology and ophthalmology clinic. Pretest in 5% of the sample size were undertaken on the questionnaire before the actual data collection starts. The collected data was checked by investigator for incompleteness and/or inconsistency.

4.11 Data Processing, Management and Analysis

Data was entered analyzed by SPSS version 26 software package for analysis. Different statistical analyses were used including frequencies of variables, descriptive statistics including mean and standard deviation. Associations between dependent and independent variables were assessed by using binary and multiple logistic regressions.

4.12 Operational definitions

DM: FBS>125mg/dl or HgA_{1c} or those who started treatment of DM.

DR: a diabetic complication that affects the eyes.it is caused by damage to blood vessels of light sensitive tissue at the back of the eye (retina).

Stable serum Creatinine: The creatinine level during follow up does not vary with greater than 0.3 mg/dl or 2.0 fold increase in serum creatinine level with in 6 months

Estimated GFR: It is a measure of how well your kidneys are working it is an estimated on a blood taste age, sex, body type and race.

Renal function worsening: - The creatinine level during follow up increased by 0.3mg/dl from the previous value.

Severity: -diabetics retinopathy classified based on funduscopy examination non proliferative and proliferative by assessing retinal bleeding abnormal beading abnormal vascular findings like intraretinal microvascular anomalies and abnormal blood vessels grow in the surface of the retina.

Dyslipidemia: Total cholesterol greater than 200mg/dl and TG greater than 200mg/dl

Hypertension: blood pressure greater than or equal to 140/90 or patients who started treatment are considered as hypertensive.

4.13 Ethical consideration

Before starting the actual data, approval letter and authority permission from the institutional review board of SPHMMC was received. The purpose of the study, the right to participate and refuse was told to the study participants. written consent from the study participants were obtained. Confidentiality of the information were guaranteed.

4.14 Dissemination of findings

The result of this research report will be provided for St Paul Hospital Millennium Medical

College. If any need arises for this study to be used as reference it can be presented to any authority.

5. Result

5.1 Sociodemographic characteristics of the study participants

In this study 365 study participants were involved making a response rate of 95.1%. Majority of the study participants were in the age group of 41-60 years with mean and SD of 53.2 ± 12.29 respectively. majority (58.6%) of the study participants were male and 41.4% were female.

Table 1. The sociodemographic characteristics of the study participant having diabetic retinopathy at SPMMC, 2023.

Variable	frequency	Percent
Age of the study participants		
20-40	47	12.9
41-60	195	53.4
≥ 61	123	33.7
Sex of the study participants		
male	214	58.6
female	151	41.4

5.2 Characteristics of the study participants on Diabetic retinopathy

The mean duration of diabetic retinopathy was 3.13 years with a major (83.8%) duration of <5 years. Fifty-eight percent of the participants diabetic retinopathy were non-proliferative and 41.9% of the retinopathy were in the proliferative stage. Thirty-four percent of the study participants had protein urea and from those having protein urea, 30.6% had +1 level of protein urea.

Table 2. The study participant characteristics on diabetic retinopathy

Variable	frequency	Percent
Severity of diabetic retinopathy		
Non proliferative	212	58.1
Proliferative	153	41.9
Duration retinopathy in years		
<5	306	83.8
≥ 5	59	16.2
Patient have protein urea		
no	241	66.0
yes	124	34.0
Level of protein urea (n=124)		
Trace	32	25.8
+1	38	30.6
+2	28	22.6
+3	24	19.4
+4	2	1.6

5.3 The study participants characteristics on renal function test

Most of (94.2%) the participants had three or more renal function test and from those having RFT, 63.9% of them had stable creatinine and 36.1% had creatinine worsening. More than half (51.5%) of the study participants had an estimated glomerular filtration rate of ≥ 60 and 55.3% of the participants had < 7 HgA1c and 8.2% had a 24hours urine protein and from those of having 24 urine protein, 53.3% had > 1000 mg/dl.

Table 3. The renal function test characteristics of the study participant.

variable	frequency	Percent
Does the patient have 3 or more renal function test		
yes	344	94.2
no	21	5.8
Stability of the creatinine(n=344)		
Stable	220	63.9
Worsened creatinine	124	36.1
Estimated GFR		
≥ 60	188	51.5
30-59	113	31.0
15-29.9	56	15.3
≤ 14.9	8	2.2
HgA1c during follow up less than 7		
no	163	44.7
yes	202	55.3
Have 24hours urine protein		
no	335	91.8
yes	30	8.2
The amount of 24hours urine protein (n=30)		
< 500	7	23.3
500-1000	7	23.3
> 1000	16	53.3

5.4 The comorbid characteristics of the study participants

In this study 54.2% of the study participants had comorbid disease and from those having comorbid disease, 85.4% (n=169) had hypertension followed by dyslipidemia (n=30), stroke (n=14), ischemic heart disease (n=13) and heart failure. More than half (52.9%, n=193) of the study participants had uncontrolled BP with the mean systolic and diastolic blood pressure of 131.29 & 77.55 respectively.

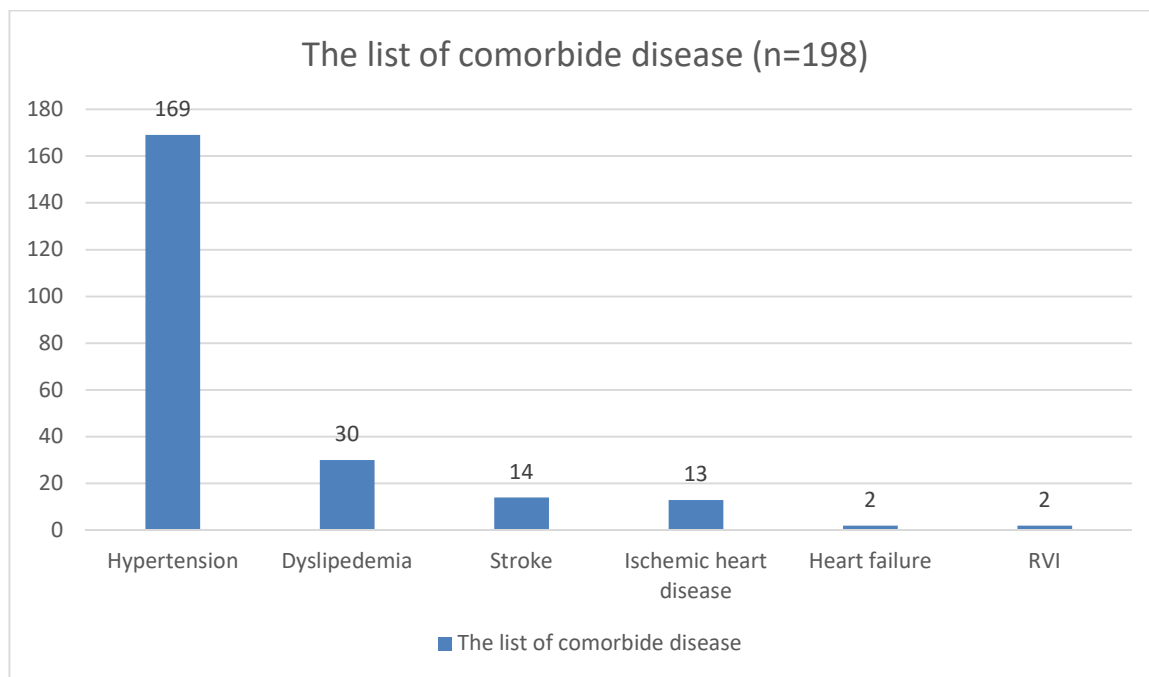


Figure 2. The list of comorbid disease among diabetic retinopathic patient.

The relation between diabetic retinopathy with estimated glomerular filtration rate

From those having a GFR of >60ml/min, 91.4% of them had non proliferative diabetic retinopathy, while those having a GFR <15ml /min had developed 100% of proliferative diabetic retinopathy as shown in the figure below.

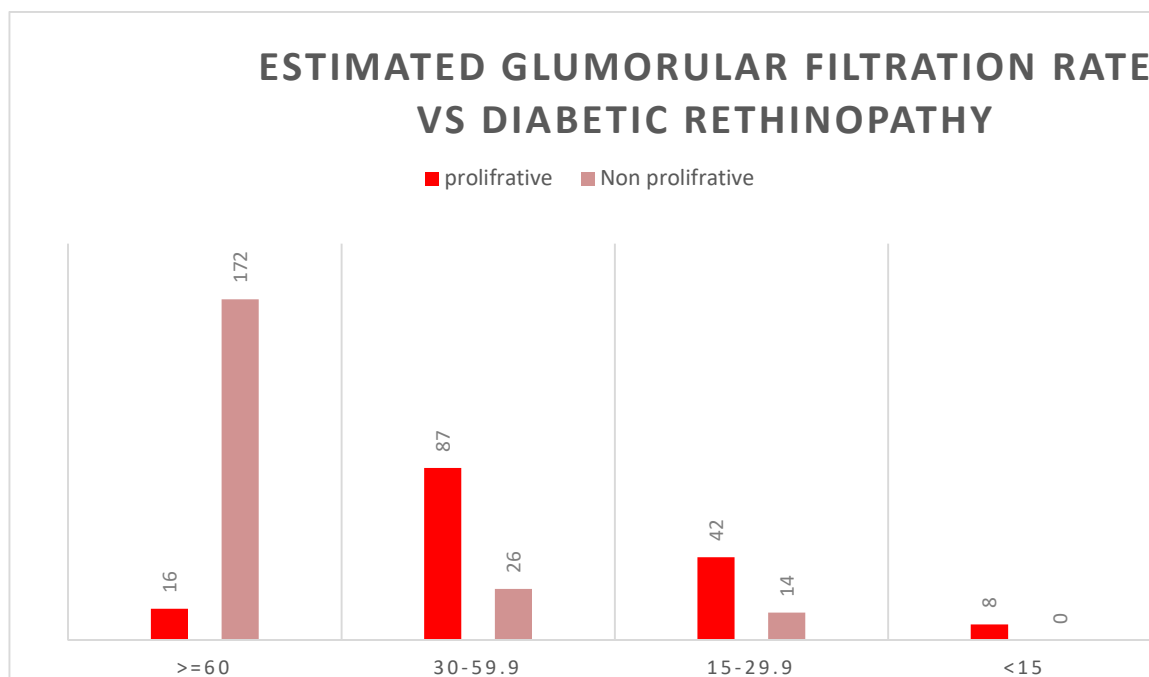


Figure 3. The relation between estimated glomerular filtration rate and diabetic retinopathy.

5.5 The mean value and chi-square association between diabetic retinopathy progression and independent

In this study age of the study participants (p-value <0.001), duration of diabetic retinopathy (p-value <0.001), estimated GFR (p-value <0.001), Systolic blood (p-value <0.001) and diastolic blood pressure (p-value <0.001) were a statistically significant using χ^2 -test for progression of diabetic retinopathy at p-value <0.001.

Table 4. The mean value and chi-square association between diabetic retinopathy progression and independent

variable	Mean value diabetic retinopathy		X2-value	p-value
	Non-proliferative	proliferative		
Age	52.76	53.83	103.9	0.000
Duration of diabetic retinopathy	2.78	3.62	37.42	0.000
Estimated GFR	73.64	40.49	269.9	0.000
Systolic blood pressure	131.64	131.22	137.1	0.000
Diastolic blood pressure	76.72	78.70	72.5	0.000

5.6 The determinant factor of diabetic retinopathy progression

The strength of association was measured using odd ratio and 95%CI. Accordingly, sex, duration of retinopathy, creatinine stability, estimated GFR and Presence of proteinurea were an association with progression of retinopathy by using bivariate logistic regression. The multivariate logistic regression revealed that study participant having male sex were 2.9 folds increase its proliferative stage of DR compared to female (AOR=2.9, 1.41, 6.01) and study participant who haven't stable creatinine were 3.5 increase its DR progression compared to its opposite compartment (AOR=3.5, 95%CI=1.97, 12.53). The study participant having <60 estimated GFR had 29.9 folds increase its proliferative DR compared to those of having ≥ 60 estimated GFR (AOR=29.9, 95%CI=14.38, 62.1).

Table 5. The bivariate and multivariate logistic regression of association between diabetic retinopathy progression and independent variable among diabetic retinopathic patient in SPMMC, 2023.

variable	Diabetic retinopathy		p-value	COR with 95%CI	p-value	AOR with 95%CI
	proliferative	Non-proliferative				
Age						
20-40	18	29	1		1	
41-60	81	114	0.685	1.1(0.59, 2.20)	0.431	0.65(0.22, 1.91)
≥61	54	69	0.109	1.3(0.63, 2.51)	0.847	1.1(0.37, 3.34)
Sex						
Male	106	108	0.000	2.2(1.40, 3.36)	0.004	2.9(1.41, 6.01)
female	47	104	1		1	
Duration of retinopathy in years						
<5	116	190	1		1	
≥5	37	22	0.001	2.8(1.55, 4.90)	0.240	1.8(0.68, 4.56)
Stability of creatinine						
Yes	45	175	1		1	
no	96	28	0.000	13.3(7.82, 22.73)	0.044	3.5(1.97, 12.53)
Estimated GFR						
<60	137	40	0.000	16.8(9.77, 68.56)	0.000	29.9(14.38, 62.1)
≥60	16	172	1		1	
Presence of protein urea						
No	84	157	1		1	
yes	69	55	0.000	2.3(1.51, 3.65)	0.266	1.5(0.73, 3.17)
Presence of comorbid disease						
No	62	105	1		1	
yes	91	107	0.089	1.4(0.95, 2.19)	0.462	0.74(0.33, 1.66)
Blood pressure						
Controlled	77	95	1		1	
uncontrolled	76	117	0.218	0.8(0.53, 1.22)	0.203	1.6(0.29, 1.29)

6. Discussion

In this study age of the study participants was a statistically significant using χ^2 -test for progression of diabetic retinopathy at p-value <0.001 . this finding was in line with the study done in Australia and China(12, 15). This was may be due to the longer a person has diabetes, the higher the risk of developing diabetic retinopathy. As age often correlates with the duration of diabetes, older individuals may be more prone to diabetic retinopathy progression. Age often comes with other health conditions that may impact the progression of diabetic retinopathy. Conditions such as hypertension can exacerbate the vascular changes in the retina, leading to more severe diabetic retinopathy.

duration of diabetic retinopathy was a statistically significant using χ^2 -test for progression of diabetic retinopathy at p-value <0.001 . This finding was congruent with the study done in China(15). This was due to the fact that Prolonged exposure to high blood sugar levels can lead to microvascular changes in the retina's blood vessels. These changes may include weakening of the vessel walls, microaneurysms, and the formation of abnormal blood vessels. The risk of progression from mild to severe stages of diabetic retinopathy increases with the duration of diabetes. Long-term exposure to elevated blood sugar levels can contribute to the development of more advanced stages of the disease, such as proliferative diabetic retinopathy

estimated GFR (p-value <0.001) was a statistically significant using χ^2 -test for progression of diabetic retinopathy at p-value <0.001 . This finding was congruent with the study done in China (16). This was may be due to diabetic retinopathy and diabetic nephropathy share common risk factors, primarily long-term exposure to high blood sugar levels. As a result, individuals with diabetes are at an increased risk of developing diabetic retinopathy.

Systolic blood was a statistically significant using χ^2 -test for progression of diabetic retinopathy at p-value <0.001 . the finding was supported by the study done in study done in China on the Relationship between Estimated Glomerular Filtration Rate and Diabetic Retinopathy(15). diastolic blood pressure was a statistically significant using χ^2 -test for progression of diabetic retinopathy at p-value <0.001 . the finding was in line with the study done in study done in China on the Relationship between Estimated Glomerular Filtration Rate and Diabetic Retinopathy(15). hypertension can contribute to changes in the blood vessels, including the small vessels in the eyes. Elevated blood pressure can damage the delicate blood vessels in the retina, leading to complications such as microaneurysms, hemorrhages, and other abnormalities characteristic of diabetic retinopathy.

study participant having male sex were 2.9 folds increase its proliferative stage of DR compared to female (AOR=2.9, 1.41, 6.01). this finding was in line with the study done in Australia(12).

study participant who hasn't stable creatinine were 3.5 increase its DR progression compared to its opposite

compartment (AOR=3.5, 95%CI=1.97, 12.53). this finding was supported by the study done in Australia, study done in Asian,(12, 14) . This was may be due to creatinine levels are typically used as a marker of kidney function rather than a direct indicator of diabetic retinopathy progression. However, there is a connection between kidney disease, diabetes, and diabetic retinopathy. Both diabetic retinopathy and diabetic nephropathy (kidney disease) are microvascular complications of diabetes, and they often share common risk factors. while creatinine levels are not directly linked to diabetic retinopathy, the broader context of kidney function and the systemic effects of diabetes are important considerations. It's crucial for individuals with diabetes to manage their blood sugar levels, blood pressure, and other cardiovascular risk factors to reduce the risk of both diabetic retinopathies.

The study participant having <60 estimated GFR had 29.9 folds increase its proliferative DR compared to those of having ≥ 60 estimated GFR (AOR=29.9, 95%CI=14.38, 62.1). This finding was congruent with the study done in Australia, Asian and China(12, 14, 16). This was may be due to the severity of diabetic retinopathy and the presence of diabetic nephropathy. Individuals with more advanced stages of diabetic nephropathy may be at a higher risk of developing severe diabetic retinopathy.

This study has limitations which include first,serum creatinine and estimated GFR levels can be affected by factors such as laboratory assay variability and dietary factors(protein) .Second this study has small sample size and our study was based on patients on tertiary hospital whose conditions may be different from diabetes patients at the national level.

7. Conclusion

In this study 41.9% of the study participants had proliferative stage of diabetic retinopathy. Using chi-square test age, duration of diabetic retinopathy, estimated GFR and blood pressure were a significant relation with progression of diabetic retinopathy. On the other had the multivariate logistic regression revealed that male (AOR=2.9, 1.41, 6.01), worsened renal function (AOR=3.5, 95%CI=1.97, 12.53) and estimated GFR <60 (AOR=29.9, 95%CI=14.38, 62.1) were a statistically significant relation with diabetic retinopathy.

8. Recommendation

serum creatinine and estimated glomerular filtration rate worsening were a significant association with progression of diabetic retinopathy. there for the recommendation will be

Regular Monitoring: -Healthcare providers should emphasize regular monitoring of serum creatinine levels and eGFR in individuals with diabetes. An integrated care approach involving both ophthalmologists and nephrologists can enhance patient outcomes.

Lifestyle modifications: -Encourage lifestyle modifications, such as maintaining a healthy diet, regular exercise, and avoidance of smoking, as they contribute to overall cardiovascular health and can impact diabetic complications.

Blood pressure: -the study participants better to monitor their blood pressure and if its elevated better to consulted with their doctor.

Early Intervention: -Early intervention in cases of declining kidney function or the onset of diabetic retinopathy is critical. Timely medical intervention, such as medication adjustments or additional treatments, may help prevent or slow the progression of complications.

For doctors: - better to search the underlining cause of serum creatinine worsening or worsening of renal function test and treat the underline cause as national guideline.

Patient Education: -Patients should be educated about the relationship between diabetes, kidney function, and retinopathy. Understanding the importance of regular check-ups, adherence to medications, and lifestyle modifications empowers patients to actively participate in their healthcare

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ANNEXES

Annex I

Participants Information Sheet and Informed Voluntary Consent Form for physicians participated in the Study

My name is_____I am working as data collector for the study being conducted in S; I kindly request you to lend me your attention to explain you about the study.

Study Title: the association serum creatinine and estimated GFR with diabetic retinopathy patients
Attending St. Paul's Hospital Millennium Medical College, Ethiopia

Purpose: -The study will be helpful to assess the association of serum creatinine and estimated GFR with diabetic retinopathy.

Procedure and duration: There are about 41 questions to be answered where I fill the questioner by interviewing you. The interview will take around 30 minutes.

Risks and benefits: - The risk of being participating in this study is very minimal, except taking some minutes, for the interview, there is no other risk that you will be experienced. By participating in this study, you will not get direct benefit but the outcome of this study will be useful tool for decision makers **Confidentiality:** - The information, which you provide us, will be confidential. There will be no information that will identify you. The finding of study will be general for the study population and will not reflect any thing particular of individual person. The questionnaire will be coded to exclude showing names; no references will be made in oral or written reports that could link participants to the research.

Right: - Participation in this study is voluntary. You have the right to declare not to participate in this study. If you decide to participate first, you have the right to withdraw from the study at any time and this will not result in you for any loss of benefit, which you otherwise are entitled. You do not have to answer any question that you do not want to answer.

Contact address: -If you have any questions or enquiries at any time about the study or the procedures, please contact and communicate with Principal investigator: - Dr. Amare Tibebu:- +251938512661, amaretibebu2123@gmail.com,

Participant questionnaires

questionnaires

			Remark
1	Age	_____ (years)	
2	Sex	1-Male	
		2-Female	
3	How long is it since the patient have been diagnosed with diabetic retinopathy.	_____ (years)	
4	What is the severity of diabetic retinopathy	1.Non proliferative 2.proliferative	
5	Does the patient have 3 or more renal function test	1. Yes 2. No	
6	If question number 5 is yes is the renal function test stable	1.Yes 2.no	
7	What is the Estimated GFR during follow up?	1.specify	
8	Does the patient have proteinuria with dipistick ?	1.Yes 2.No	
9	If question number 8 is yes specify	1. Trace 2. +1 3. +2 4. +3 5. +4	
10	If the patient have 24 hour proteinuria	Specify	
11	is the patients HgA1c during follow up less than 7	1.Yes 2.No	

12	Does the patient have comorbidity?	1. Yes 2. No	
13	What is the Blood pressure during follow up ?	Specify	

Name of data collector: _____ Signature_____

Name of Supervisor: _____ Signature_____

Date:_____

Thank You!!!

Annex II

Annex II

Assurance of Investigator

I the undersigned resident agree to accept all responsibilities for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the Research and Publication Directorate and /or Department of Public Health of St. Paul's Hospital Millennium Medical College.

Name of the Resident: _____

Signature: _____

Date: _____

Approval of Advisors

Name of Public Health Advisor: _____

Signature: _____

Date: _____

Name of Clinical Advisor: _____

Signature: _____

Date: _____

