ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SICENCE

SCHOOL OF NURSING AND MIDWIFERY

Survival Time to Nephropathy and its Predictors Among Type 2 Diabetes Mellitus Patients in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019.

A Thesis Submitted to Addis Ababa University College of Health Science School of Nursing and Midwifery in Partial Fulfillment of the Requirements for the Degree of Master of Science in Adult Health Nursing

Addis Ababa, Ethiopia

June, 2019

ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SICENCE

SCHOOL OF NURSING AND MIDWIFERY

Survival Time to Nephropathy and its Predictors Among Type 2 Diabetes Mellitus Patients in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019.

Investigator:

Kidist Tamru (BSc)

Advisor:

Mr. Fekadu Aga (Assistant Professor, BSc N, RN, MSc, PhD Student)

Sr. Emebet Berehane (MSc, PhD Fellow)

A Thesis Submitted to Addis Ababa University College of Health Science School of Nursing and Midwifery in Partial Fulfillment of the Requirements for the Degree of Master of Science in Adult Health Nursing

ACKNOWLEDGEMENT

I would like to acknowledge Addis Ababa University, College of Health Science, School of Nursing and Midwifery for offering me such chance to conduct this research proposal. I am also very grateful to my advisers Mr. Fekadu Aga (MSc, Assistant. Professor, PhD Fellow) and Sr. Emebet Berehane (MSc, PhD Fellow,) for their valuable academic advising in the process of completing this research thesis.

Lastly but not the least I would also like to thank Tikur Anbessa Specialized Hospital, Endocrine Unit for providing me valuable information to write this research thesis and data collectors.

LIST OF ABBREVIATION AND ACRONYMS

AAU	Addis Ababa University
AHR	Adjusted Hazard Ratio
AOR	Adjusted Odds Ratio
BMI	Body Mass Index
CHR	Crude Hazard Ratio
CHS	College of Health Science
CKD	Chronic Kidney Disease
DM	Diabetes Mellitus
DN	Diabetic Nephropathy
eGFR	Estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
HbA1c	Hemoglobin A1c or Glycated hemoglobin
IDDM	Insulin Dependent Diabetes Mellitus
IDF	International Diabetic Federation
MDRD	Modification of Diet in Renal Disease
NIDDM	Non-Insulin Dependent Diabetes Mellitus
PH	Proportional Hazard
SBP	Systolic Blood Pressure
STPMMC	St. Paul's Millennium Medical College
TASH	Tikur Anbessa Specialized Hospital.
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Introduction: Diabetes is the most common cause of end-stage renal disease in most parts of the world. Kidney involvement both directly and indirectly increases involvement of other organs and increase morbidity and mortality in diabetic patients. However, little is known concerning when nephropathy develops once a person diagnosed with diabetes. **Objective**: The aim of this study is to determine time to nephropathy and its predictors among type 2 diabetic patient attending at Tikur Anbessa Specialized Hospital, 2019. **Methods and materials:** Retrospective cohort study was employed among Type 2 diabetic patients attending their follow up at Tikur Anbessa Specialized Hospital from January 1, 2009 to December 31, 2018. Kaplan-Meier method was used to determine time to nephropathy and log rank test was used to compare time to nephropathy among different covariates in type 2 Diabetes Mellitus patients. Cox proportional hazard model was used to identify factors contributing to nephropathy in type 2 diabetic mellitus patients. **Result:** The overall incidence rate of diabetic nephropathy among newly diagnosed type 2 diabetes was found to be 30.4 per 10,000 person-months follow up. The median time to develop nephropathy was 100.03 months (95% CI, 96.7 – 107). Predictors of nephropathy were being male [HR: 2.7 95%CI; 1.39, 5.23], duration of diabetes [HR: 1.003,95% CI;1.001,1.006], hemoglobin A1c [HR: 1.74, 95% CI; 1.67,3.12], fasting blood sugar [HR: 1.12, 95% CI; 1.03,1.97]. Whereas, high density lipoprotein greater than 40mg/dl [HR: 0.37, 95% CI; 0.16, 0.83] and both oral and injection therapy [HR: 0.07, 95% CI; 0.01, 0.59], were reduced the hazard of nephropathy. **Conclusion:** In this study, the incidence of diabetic nephropathy among type 2 DM patients was relatively high and which is becoming the raising national burden. Being male, longer duration of diabetes, hemoglobin A1c, and one unit increasing of fasting blood sugar were increase the hazard of diabetic nephropathy. On the contrary high density lipoprotein greater than 40mg/dl and those diabetic clients who had received oral and injection therapy were reduced the hazard of diabetic nephropathy.

Key words: Nephropathy, Diabetics, Predictors and Ethiopia.

CHAPTER 1

INTRODUCTION

1.1. Background of the Study

Diabetes mellitus (DM) is chronic non-communicable disease describes a group of metabolic disorders resulting from defects in insulin secretion, insulin action, or both. It is globally an emerging public health problem(1,2). Diabetes can be classified as Type 1, Type 2, Gestational, and other specific types of diabetes mellitus. Type 1 diabetes results from autoimmune beta-cell destruction, usually leading to absolute insulin deficiency while Type 2 occurs due to progressive loss of beta- cell insulin secretion frequently on the background of insulin resistance(3).

Diabetes-related chronic complications make DM the leading cause of morbidity and mortality in the world. Long-term hyperglycemia may contribute to chronic micro-vascular complications; these are kidney disease (nephropathy), eye disease (retinopathy) and neuropathy. Diabetes is also associated with an increased occurrence of macro-vascular complications, including coronary artery disease (myocardial infarction), cerebrovascular disease (stroke), and peripheral vascular disease(4–8).

By the time of diagnosis some patients with type 2 diabetes may already have developed complications like diabetic nephropathy, retinopathy or neuropathy. This is especially worse in low-income countries, where various factors delay the diagnosis compared in high-income nations. Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Ongoing patient self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications. Significant evidence exists that supports a range of interventions to improve diabetes outcomes(9). Diabetic nephropathy is the serious complication which leads to end-stage renal failure and other complication of diabetes mellitus. Diabetic nephropathy and microalbuminuria are also strong predictors of cardiovascular and overall morbidity and mortality in patients of diabetes, and hence vital indicators in the patients(10).

Diabetes is the most common cause of end-stage renal disease (ESRD) in most parts of the world. Kidney involvement both directly and indirectly increases involvement of other organs and increase morbidity and mortality in diabetic patients (11). Diabetic nephropathy (DN), also known as diabetic kidney disease is the chronic loss of kidney function occurring in those with diabetes mellitus(12). Protein loss in the urine due to damage to the glomeruli may become massive, and cause a low serum albumin with resulting generalized body swelling (edema) and result in the nephrotic syndrome. Likewise, the estimated glomerular filtration rate (eGFR) may progressively fall from a normal of over 90 ml/min/1.73m^2 to less than 15, at this point the patient is said to have end-stage kidney disease (ESKD)(13). It usually is slowly progressive over years(14). Diabetic nephropathy is now the most common cause of chronic kidney disease (CKD). Diabetic nephropathy has higher prevalence for type 2 diabetes than type 1, often patients with ESRD have type 2 diabetes(15).

Duration of diabetes is a very important factor in the development of diabetic nephropathy as demonstrated in several studies. In a study of adolescents with a mean duration of disease of 10.9 years, found that the duration of disease was an important factor in the overall severity of glomerulopathy(16). In Tikur Anbessa Specialized Hospital no studies have been done about the time to nephropathy and its predictors. Therefore, this study has the aim to accomplish this task.

1.2. Statement of the Problem

The American Diabetes association estimates diabetes to affect more than 8.5% of the global population. The International Diabetic Federation (IDF) estimated that adults aged 18-99 years (451 million adults) had diabetes mellitus globally in 2017(17). The epidemic of diabetes mellitus and its complication poses a major global health threat. The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease(18). It has been estimated that more than 40% of people with diabetes will develop diabetic nephropathy as a complication.

Diabetic nephropathy is a significant cause of chronic kidney disease and end-stage renal failure globally. A number of researches have been conducted in both basic science and clinical therapeutics, which has enhanced understanding of the pathophysiology of diabetic nephropathy and expanded the potential therapies available(7,9,10,12). End-stage renal disease (ESRD) in patients with diabetes mellitus, particularly type 2 which is much more frequent than type 1 diabetes, has been referred to as a silent epidemic that has not been sufficiently noted by the non-nephrological community. In many countries, diabetic nephropathy in patients with type 2 diabetes be due to diabetic glomerulosclerosis or other causes, has become the single most frequent cause of ESRD. It is increasing all over the world, particularly in the developing countries with their limited financial resources (19).

In Africa the overall prevalence of CKD varied from 11% to 83.7%(20). In Ethiopia the prevalence of microalbuminuria and macro albuminuria for T1DM is 32% microalbuminuria and 15% macro albuminuria and for T2DM 37% microalbuminuria and 20% macro albuminuria(21). Both microalbuminuria and macro albuminuria in individuals with DM are associated with increased risk of cardiovascular disease(22). In Addis Ababa the prevalence of nephropathy was 21% (23) and in Tikur Anbessa Specialized Hospital the prevalence of nephropathy among T1DM was 21% and 15% among T2DM (24).

Individuals with diabetic nephropathy commonly have diabetic retinopathy(25). In a study in Cameroon, T2DM patients are more likely to have nephropathy (26). Studies in Nigeria showed that left ventricular hypertrophy, stroke, myocardial infarction and peripheral arterial disease

were more frequent in T2DM patients with nephropathy, especially those with advanced stages(27,28).

Even though studies have been conducted in Ethiopia about the prevalence and incidence rate of diabetic nephropathy no studies have taken to determine the time for the development of diabetic nephropathy, which is important in predicting the time to provide appropriate intervention for better outcome. Therefore, this study aims at estimating the time for the development of nephropathy and its predictors to nephropathy in type 2 diabetic patient.

1.3. Rational of the Study

The global burden of kidney disease due to DM is high in morbidity and mortality. Different study revealed that the burden due to DM is higher among other chronic illness due to spending more money for treating and managing its complication. It is stated in the background of the study diabetic nephropathy has become the major cause of end-stage renal disease (ESRD) in the western world and in the African continent. therefore, in order to go through prevention, it is better if we first know the time to nephropathy and contributing factors for the development of nephropathy, therefore this study will focus on estimating the time for the development of nephropathy(26,29,30).

1.4. Significance of the Study

This study will estimate the time for the development of nephropathy and determine key predictors contributing to diabetes nephropathy among type 2 diabetes mellitus patients at Tikur Anbessa Specialized Hospital. This study will also be significant for patients and society at large to create awareness on diabetic nephropathy and its impact on their health status and to bring better life expectation. In addition, this study will provide health institution of the country to find ways to minimize T2DM related nephropathy, it will also help health care workers to provide timely intervention of diabetic nephropathy, to implement evidence-based practices for nursing education and nursing research. In addition, the study will provide data to researchers for further study at a larger scale.

CHAPTER 2

LITERATURE REVIEW

2.1. Introduction

Diabetic Kidney Disease is a chronic complication of T2DM (insulin resistance and/or decreased secretion of insulin)(31). Diabetic kidney disease develops in approximately 40% of patients with DM and it is the leading cause of CKD worldwide (32,33). The natural history of diabetic kidney disease includes glomerular hyper filtration, progressive albuminuria, declining GFR, and ultimately, ESRD. Metabolic changes associated with diabetes lead to glomerular hypertrophy, glomerulosclerosis, and tubulointerstitial inflammation and fibrosis(33). A study done among native Americans the incidence of ESRD in the diabetic population was higher compared to the non-diabetic population, and relative risks varied from 6.2 in the white population to 62.0 (34)(35).

2.2 Time to Diabetic Nephropathy

A study from St. Paul's Hospital, Addis Ababa, Ethiopia shows that median time to develop CKD was 70.9 months with an interquartile range of (IQR: 41.00–88.73 months). The overall incidence rate of CKD was 2178 (95% CI 12,801, 21,286) cases per 10,000 patient-month with total 28,466.13 patient-months observation. Moreover, the proportion of CKD among newly diagnosed T2DM patients was 14.25%(36).

2.3. Predictors of Time to Nephropathy

2.3.1. Patient Related Factors

Chronic kidney disease complications represent a considerable burden on global healthcare resources and individuals living in Ethiopia have lower socio-economic status. A systematic review among studies shows that individuals of lower socioeconomic status have a higher risk for morbidity and mortality compared with those of higher status (37). Study done in Ethiopia St Paul's hospital showed socio demographic variables like age and sex as a significant risk factors for CKD in T2 DM patients (36). previous study done in tropical African country on features of diabetic nephropathy showed that the frequency of occurrence of diabetic

nephropathy is 28.4% mean age of T2 diabetic patient with nephropathy was 53.4 ± 6.3 years and mean duration of disease was 9.4 ± 4.1 years (38). A study from Indian population showed that DN appears at younger age and genetic factor is more common for the appearance of DN. Similar study from India showed that socio demographic factors like woman gender, Duration of diabetes, family history of kidney disease are associated with DN (39).

2.3.2. Clinical and Laboratory Related Factors

Duration of diabetes is a very important factor in the development of diabetic nephropathy as demonstrated in several studies. Several studies highlighted duration of diabetes as a risk factor for CKD among T2DM patient. For example, previous study showed that as duration increases, there is impairment of renal function as evidenced by increase in blood urea, serum creatinine &micro proteinuria. Statistically significant increase in BP was also observed with increase in duration. Both metabolic & hemodynamic factors play an important role in the development of nephropathy (40). Similar study also showed that duration of disease was an important factor in the overall severity of glomerulopathy. Overt nephropathy caused by glomerulosclerosis first appears 10-15 years after the onset of insulin dependent DM (IDDM)and after 5 to 10 years in patients with non-insulin dependent DM (NIDDM)(41). There is also an even higher prevalence of hypoglycemia due to decreased clearance of anti-diabetic agents or impaired renal gluconeogenesis, and progressive renal dysfunction reduces drug elimination and prolongs exposure to higher drug levels(42).

A study in Southern Ethiopia in Bugarija Hospital Showed that Significant risk factors for CKD in the study subjects when using either the modification of diet in renal disease (MDRD) or C-G equation were older age, longer duration of diabetes, family history of kidney disease, and poor glucose control ($P < 0.05$).Additionally, female sex ($P < 0.008$) and obesity ($P < 0.038$) were independent risk factors for CKD when defined by the MDRD, and type 2 diabetes was when defined by C–G ($P < 0.03$) (43).

A case control study in Ayder Referral Hospital also showed that age of patient (AOR: 1.037 95% CI: 1.01–1.064), duration of diabetes after diagnosis (AOR for one year increase: 1.09 95% CI: 1.036–1.15), not-adhered to blood glucose measurement at home (AOR: 6.81 95% CI: 1.15–40.24), having Systolic Hypertension (AOR;2.13 (1.002–

4.51), poor glycemic control (AOR;2.71 95%CI:(1.49–4.95), being overweight (AOR;2.7(1.47–4.96) were the independent predictors of diabetic nephropathy (44). Similar study from urban Asian-Indian type 2 diabetic patient showed that A1c (odds ratio 1.325 [95% CI: 1.256–1.399], $P<0.001$), smoking (odds ratio 1.464, $P=0.011$), duration of diabetes (1.023, $P=0.046$), systolic blood pressure (1.020, $P < 0.001$), and diastolic blood pressure (1.016, $P = 0.022$) were associated with microalbuminuria. A1C (1.483, $P <0.0001$), duration of diabetes (1.073, $P= 0.003$), and systolic blood pressure (1.031, $P= 0.004$) were associated with overt nephropathy (45).

A study from St. Paul's Hospital, Addis Ababa, shows 62 (14.25%) patients in the sample experienced chronic kidney disease. Old age [adjusted hazard ratio (AHR)= 1.06, 95%CI: (1.03, 1.09)], no diabetic retinopathy[AHR= 0.13, 95%CI: (0.07, 0.24)], high density l ipoprotein cholesterol ≥ 40 mg/dl [AHR= 0.55, 95% CI: (0.31, 0.97)] and high body mass index [AHR= 1.17, 95% CI: (1.1, 1.25)] were common factors for chronic kidney diseases. Therefore, this study shows that the incidence of CKD among type 2 DM patients was moderately growing burdens and seek public concerns. Old age, high BMI, history of diabetic retinopathy and lower levels of HDL cholesterol were risk factors for the development of CKD (36).

A study on features of diabetic nephropathy from Nigeria showed that chronic glomerulonephritis, hypertension, obstructive uropathy, age, sex and duration of disease are common causes of CKD (38). A study on prevalence and risk factors of DN showed that Hypertension, BMI, eGFR, retinopathy was found to be significantly associated with overt DN.

A study from Japan showed that Declines in eGFR were strongly associated with subsequent risk of ESRD in Japanese type 2 diabetic patients. In addition to 30% and 40% declines, a 20% decline in eGFR over 2 years could be considered as a candidate surrogate endpoint of ESRD in diabetic kidney disease (46).

In a study which was based on 100 recently diagnosed diabetics and which divide the patients in to two groups. Group A had 50 patients with at least one risk factor are hypertension, hypercholesterolemia and obesity. Group B had 50 patients without any of the aforementioned factors. Patients were investigated for presence of Diabetic Nephropathy with abnormal serum

Creatinine, creatinine clearance and urinary albumin levels. In this study incidence of diabetic nephropathy is much larger in newly diagnosed cases of T2DM and hypertension, obesity and hypercholesterolemia can contribute to development of nephropathy (68% vs. 18% in those who had the factors vs. those who didn't). Also, urinary micro-albuminuria appears to be much more sensitive than serum creatinine as screening tool(47).

2.3.3. Comorbidity Condition

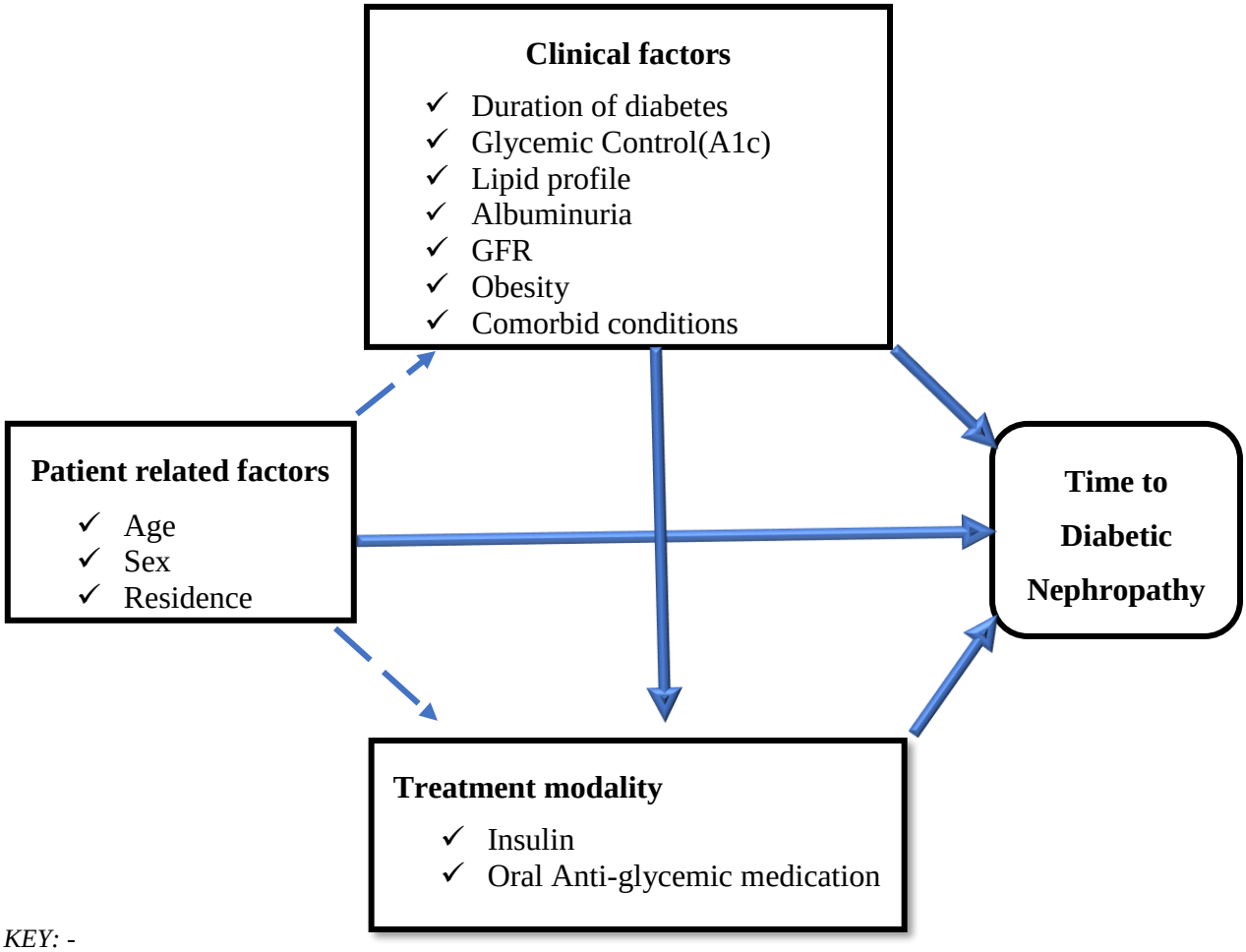
Diabetic patients with CKD are suffering from multiple comorbidity who have an increased risk of complications, such as hypertension, anemia, malnutrition, bone and mineral disorders, retinopathy and neuropathy(43). A study done on tropical African population showed that coronary heart disease is also another types of comorbidity in diabetic patient with CKD (38). A study on risk factors of DN showed that CKD in individuals with DM are associated with increased risk of cardiovascular disease like coronary artery disease (CAD), peripheral arterial disease (PAD), cerebrovascular disease (39).

2.3.4. Treatments Related Factors

The principle of treatment of diabetic nephropathy is based on tight control of hyperglycemia, tight control of blood pressure and glomerular pressure, control of dyslipidemia, restriction of protein intake and smoking withdrawal(48).

2.4. Conceptual Frame Work

This conceptual frame work is developed from Clinical Practice Guideline and different literatures (43,47,49,50). This frame work shows the relationship between Diabetic nephropathy with patient related factors, clinical factors, treatment modalities. Patient related factors have both direct and indirect effect on the diabetic nephropathy. Those independent variables are operated into proximal (clinical and treatment factors and distal (patient related) factors to the outcome variable (diabetic nephropathy).



KEY: -

→ Direct relationship

⋯► sociodemographic variables have a relationship with the clinical factors and treatment modalities

Figure 1. Conceptual Frame work for the study on survival time to Nephropathy and its predictors among T2 DM patientsat TASH Addis Ababa, Ethiopia, 2019.

CHAPTER 3

OBJECTIVES

3.1 General Objective

- To assess the survival time to nephropathy and its predictors among type 2 diabetes mellitus patient attending at Tikur Anbessa Specialized Hospital, 2019.

3.2 Specific Objectives

- To determine time to nephropathy among 2 diabetes mellitus patients attending at Tikur Anbessa Specialized Hospital, 2019.
- To identify its predictors to diabetic nephropathy among type 2 diabetes mellitus patients attending at Tikur Anbessa Specialized Hospital, 2019.

CHAPTER 4

METHODS AND MATERIALS

4.1. Study Area

Addis Ababa is the largest city in Ethiopia, with a population of around 3,384,569 according to the 2007 population census. Population in the near future is expected to grow to exceed 6.5 million residents. The annual growth rate of the city has been estimated in recent years to be 3.8% (51). Its area is estimated to be 527 Km2 with altitudes ranging from 2200 to 3000 meter above sea level, average temperature of 22.8°C and average rainfall of 1,180.4 mm. Tikur Anbessa Specialized Hospital has established in the year 1963 and situated at the heart of the capital city on Churchill Avenue. It is the largest teaching hospital in Ethiopia and provides a tertiary level referral treatment with 24 hours' emergency services and it has different specialty clinic which give follow up service, among this diabetic follow up clinic will be selected as study unit for this study. The unit has the largest referral clinic of DM in the country regularly more than 200 individuals visited per week for service provision.

4.2. Study Design and Study Period

Retrospective cohort study was employed to assess time to nephropathy and its predictors T2DM patients presented at TASH. The study period was from April 29 to May 20,2019.

4.3. Source Population

The sources population of the study was all T2DM patients presented at TASH Diabetic Unit.

4.4. Study Population

T2DM Patients' card reviewed during data collection time at TASH from January, 2009 to December 31, 2018

4.5. Eligibility Criteria

4.5.1. Inclusion criteria

All T2DM patients attending at TASH from January, 2009 to December 31, 2018

4.5.2. Exclusion Criteria

- Incomplete patient charts
- Patient card whose diagnose year or month missing
- Patient who referred from another facility and their diagnosis time differ from study period
- patients who have history of nephropathy from other underlying causes

4.6. Sample Size and Sampling technique

Sample size was determined by using double population proportion using past research as a reference (36). By using the variable retinopathy with the percentage of an outcome in unexposed group 48.38%, the percentage of an outcome in exposed group 11.6%, 95% confidence interval of certainty ($\alpha = 0.05$) and 90% power the sample size was found to be 72. Using the variable HDL cholesterol with the percentage of an outcome in unexposed group 8.67%, the percentage of an outcome in exposed group 22.5%, 95% confidence interval of certainty ($\alpha = 0.05$) and 90% power the sample size was found to be 314. Therefore, the total sample size was calculated for this study is found to be 314. Where, $\alpha = 0.05, \beta = 0.10$ (power = 90%). Based on this information, sample size estimation for the assessment of time to nephropathy development under the cox-proportional hazard model was computed using Epi info. The total sample size of three hundred forty-six with adding 10 % contingency rates for an incomplete chart has been determined. Study participants were filtered first from the database according to their entry time to DM clinic then patients' cards were filtered using eligibility criteria. The samples were proportionally allocated to each year according to their total population and the data was collected by using simple random sampling from the sampling frame.

Table 1. Proportional allocation of study subject for each year at TASH, Addis Ababa, Ethiopia, 2019.

Year	Year 2009	Year 2010	Year 2011	Year 2012	Year 2013	Year 2014	Year 2015	Year 2016	Year 2017	Year 2018	Total
Source Population =N	184	156	186	253	502	456	352	400	617	580	N=3,683
Study population =n	17	15	17	24	47	43	33	38	58	54	n=346

4.7. Study Variables

Dependent Variable: Time to nephropathy

Independent Variables:

Socio demographic variables: Age, gender, residence,

Clinical variables: Diabetic duration, obesity, systolic blood pressure, diastolic blood pressure, HbA1c, dyslipidemia, Fasting blood glucose, Lipid profile

Treatment Modality: A prescribed medication used to treat health problem of diabetic patient. (Insulin, oral antidiabetic agent, or both)

4.8. Operational Definition

Time to Nephropathy: is the time starting from the date the patient is confirmed as T2DM diabetic patient to the happening/development of nephropathy.

Diabetic duration: The time between the patients confirmed as diabetic and the date of last contact with the health facility.

Glycemic control: The regulation and maintenance of blood glucose levels within normal reference range which measured by glycated hemoglobin or HbA1c.

Incomplete charts: A patient chart which miss patient height, weight, systolic blood pressure, diastolic blood pressure, HbA1c

Censored: Those patients include who lost their follow up, transferred to other health facilities, not develop nephropathy until end of study period.

Starting date: The date that a patient diagnosed and starting their follow up January 1, 2009.

Ending date: The patient follows up until end of study period December 31, 2018

Body Mass Index (BMI) is a measurement of a person's weight in kilograms (kg) divided by his or her height in meters squared and it is key index for relating weight to height.

Underweight: -BMI; is a measurement of a person's weight in kg divided by height in meters which is less than 18.5 Kg/m2.

Healthy weight: - is a measurement a person's weight in kg divided by height in meters giving a result ranging 18.5 to 24.9 Kg/m2. The lower and upper boarder are included in the category.

Overweight: -is a measurement a person's weight in kg divided by height in meters giving a result rangingbetween25 to 29.9 Kg/m2. The lower and upper boarder are included in the category.

Obese: - is a measurement of a person's weight in kg divided by height in meters which is 30Kg/m2 or higher.

Comorbidity:- the presence of one or more additional conditions co-occurring with a primary condition.

4.9. Data collection tools and procedures

4.9.1. Data collection tools

The data extraction checklist was adopted from the World Health Organization (WHO) Guidelines (52). A standard checklist was used for recording information extracted from patient cards. The checklist was containing three parts including the general information. The 1st part contain questions which measure the socio demographic characteristics of the patient, the 2nd part contain questions which measure the clinical and laboratory characteristics of the patient and the 3rd part the treatment modalities. The data collectors fill the responses for the question in the data abstraction form from the medical records of patients.

4.9.2. Data collection procedures

Data was collected from medical records of T2DM patient attending their follow up at TASH. The data was collected by four experienced DM clinic nurses who were trained on diabetic care and data collection was supervised by trained supervisors.

4.10. Data Quality Assurance

Training to data collectors were given for 2 days prior to the actual data collection period. Pretest was carried out at STPMMC before 2 weeks. Supervision of the data collectors and close monitoring was done every day. The supervisor was random evaluate the filled checklist for data completeness. Computer frequencies and data sorting were used to check for missed variables, outliers or other errors during data entry

4.11. Data Processing and Analysis

Data was cleaned, edited, coded and then entered using epi data version 3.1 and then transferred into Stata version 14 for analysis. Basic descriptive analyses were done in terms of central tendency and dispersion value for continuous data and frequency distribution for categorical data based on the nature distribution. The outcome variables were dichotomized into nephropathy and censored. Survival table was used to estimate probabilities of survival after diagnosis of type 2 diabetes mellitus at different time intervals. Kaplan Meier survival curve

together with the log-rank test was done to estimate the survival curve and for the presence of a difference in survival among explanatory variables.

The necessary assumptions for the model was checked by scheonfeld residual test and variables having P-value >0.05 was considered as fulfilling the assumption and all variable was fulfilling the assumption. Bivariable cox regression was fitted and those independent variables which become significant on the bivariable regression less than or equal to 0.25 level of significance was included in the multivariable analysis(53). Multiple cox regression was done at 0.05 level of significance to determine the net effect of each explanatory variable on time to nephropathy after diagnosis of type 2 diabetes mellitus. The P value less than 0.05 in the multivariable analysis was considered as statically significant. The results of these models were expressed as hazard ratios (HRs) with 95% confidence interval and p-values are used to measure the strength of association and to identify statistically significant factors.

4.12. Ethical Consideration

Ethical clearance and approval were obtained from the Institutional Review Board (IRB) of the College of Health Sciences of Addis Ababa University. Official letters were obtained from School of Nursing and Midwifery to TAH. After obtaining ethical clearance data was collected from patient chart using check list, code was used for the purpose of confidentiality. The extracted checklist was being stored and locked at the separate place. The entered data was locked by Computer password. The data was utilized by the principal investigator.

4.13. Dissemination of Results

The results of this study will be presented and summited to AAU, CHS, school of nursing and midwifery and submitted to Endocrinology department (diabetic unit). In addition, the final result document will be presented to responsible bodies working in the area (service providers and other accessible concerned stake holders) and the findings of the study will be published through peer reviewed journals.

CHAPTER 5

RESULT

5.1. Baseline sociodemographic characteristics

In the current study a total of 346 participants were included in the analysis. The mean age of the participant at the time of newly diagnosis of type 2 diabetes was 56.70 with SD ± 10.48 years. About slightly more than half, 178(51.45%) of the study participants were male. Concerning their residential status, majority 279(85.85%) of the participants were urban (table 2).

Table 2. Baseline sociodemographic characteristics of diabetic patients at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019(N=346).

Variable	**Category**	**Frequency**	**Percentage (%)**
Gender	Male	178	51.45
	Female	168	48.55
Age	Mean =56.70 with SD ± 10.48 years.		
Residence	Urban	279	85.84
	Rural	49	14.16
Comorbidity	Yes	258	74.6
	No	88	25.4

5.2. Clinical and treatment characteristics of study subjects

According to this study more than two third, 235(67.92%) of the study participant had hypertension and about nearly one third 103(30.03%) of the study participants had dyslipidemia. More than half, 199(57.5%) of the participant their Hemoglobin A1c were less than 7, and most, 273(78.9) of them were their total cholesterol less than 200mg/dl. On the other hand, regarding high density lipoprotein most, 250(72.25%) of them were less than 40mg/dl and similarly about nearly two third, 213(61.5%) of the study participant were their low density lipoprotein less than 100mg/dl. Regarding the treatment type most 250(72.25%) of the study participant were used oral hypoglycemic agent (table3).

Table 3. Clinical and treatment characteristics of diabetic patients at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019(N=346).

Variable	**Category**	**Frequency**	**Percentage (%)**
Hypertension	Yes	235	67.92
	No	111	32.08
Peripheral neuropathy	Yes	53	15.32
	No	293	84.68
Diabetic retinopathy	Yes	20	5.78
	No	326	94.22
Dyslipidemia	Yes	103	30.03
	No	240	69.97
Duration of diabetic (in years)	Mean =5.63 with SD ± 2.96 years		
Body mass index(kg/m^2)	<18.5	11	3.18
	18.5-24.9	62	17.92
	25-29.9	144	41.62
	>30	129	37.28
HbA1c	<7	199	57.51
	≥7	147	42.49
Total cholesterol, mg/dl	<200	273	78.9
	≥200	73	21.1

Triglyceride, mg/dl	<150	246	71.1
	≥150	100	28.9
High density lipoprotein, mg/dl	<40	250	72.25
	≥40	96	27.75
Low density lipoprotein, mg/dl	<100	213	61.56
	≥100	113	38.44
Systolic bp,mmHg	Mean =132.91with SD ± 17.7mmhg		
Diastolic bp,mmHg	Mean = 80with SD ± 9.4 mmhg		
Fasting blood sugar(mg/dl)	Mean =170.26 with SD ± 57 mg/dl		
Type of DM medication	Oral	250	72.25
	Injection	45	13.01
	Mixed	51	14.74

5.3. Time to diabetic nephropathy

The overall incidence rate of diabetic nephropathy in the cohort during the 22,417 person-month of observation (PMO) was found to be 30.4 per 10,000 person-months follow up. Similarly, the cumulative incidence of diabetic nephropathy was nearly19.65% over ten year follow up. In the present study, diabetic clients were followed up for a total of 120 months, with a median time to develop nephropathy was100.03 months (95% CI, 96.7 – 107). The estimated survival rate was 97.6%, 93.2%, 83.5%, and 49.7% at 1, 3, 7, and 10 years respectively.

The Kaplan Meir curve for time to diabetic nephropathy, the probability of developing nephropathy was increase as the follow-up time increases (**Figure 2**).

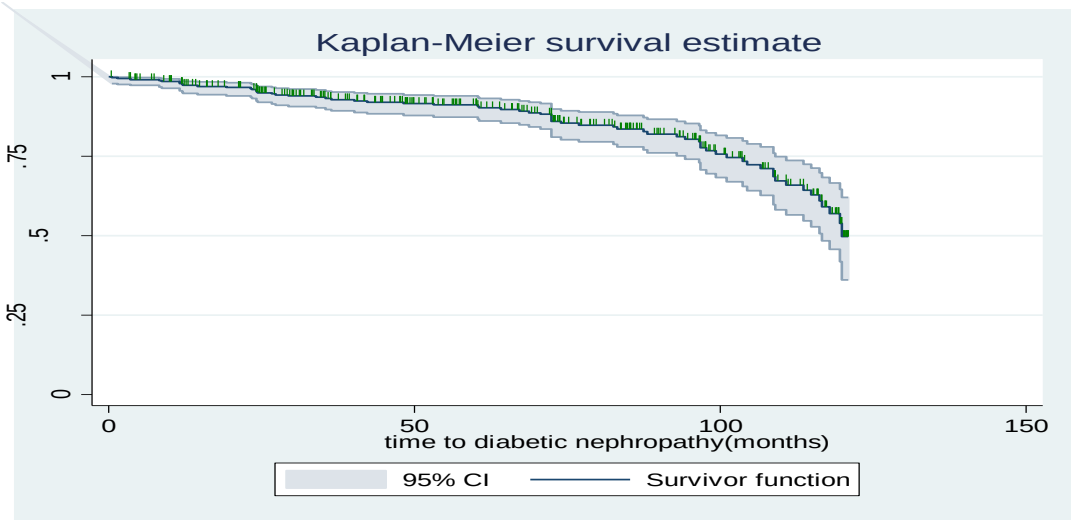


Figure 2. Overall Kaplan-Meier analysis of nephropathy-free survival of diabetic clients at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019(N=346).

5.4. Life table on cumulative estimation of time to diabetic nephropathy

The actuarial life table analysis showed that about 9(13.2%) of diabetic nephropathy occurred from 100-120 months. The cumulative proportion of free from any diabetic nephropathy up to 20 months was 95.7%. The cumulative proportion of free from diabetic nephropathy up to 120 months was 49.74%. Similarly, a total of 12.5% (8/68) develop nephropathy in their first 10 months of newly diagnosis of diabetic mellitus, 7.3% (5/68) develop nephropathy between 60 and 70 months newly diagnosis of diabetic mellitus, and 10.9% (7/64) develop diabetic nephropathy between 90 and 100 months newly diagnosis of diabetic mellitus(table 4).

Table 4. The actuarial life table cumulative estimation of time to diabetic nephropathy among Type 2 diabetes mellitus at Tikur Anbessa Specialized Hospital, Ethiopia, 2019(N=346).

Interval start time, mo	Number entering interval	Number of nephropathy	Number of censored	Cumulative Proportion Surviving at end of Interval, %	Standard error of proportion surviving at end of interval	Confidence interval(95 %CI)
0 - 10	346	8	17	97.63	0.008	0.953,0.988
10-20	321	6	15	95.76	0.011	0.929, 0.975
20-30	300	8	28	93.08	0.014	0.897,0.954
30-40	264	3	19	92.0	0.015	0.883,0.945
40-50	242	3	27	90.78	0.017	0.868,0.935
50-60	212	1	18	90.33	0.017	0.863,0.932
60-70	193	5	19	87.87	0.020	0.833,0.912
70-80	169	7	27	83.91	0.024	0.785,0.880
80-90	135	4	26	81.16	0.027	0.752,0.858
90-100	105	7	23	75.09	0.034	0.678,0.809
100-110	75	7	18	67.12	0.041	0.583,0.745
110-120	60	9	41	49.74	0.067	0.360,0.620

mo; months

5.5. Time to nephropathy among different groups of diabetes patients

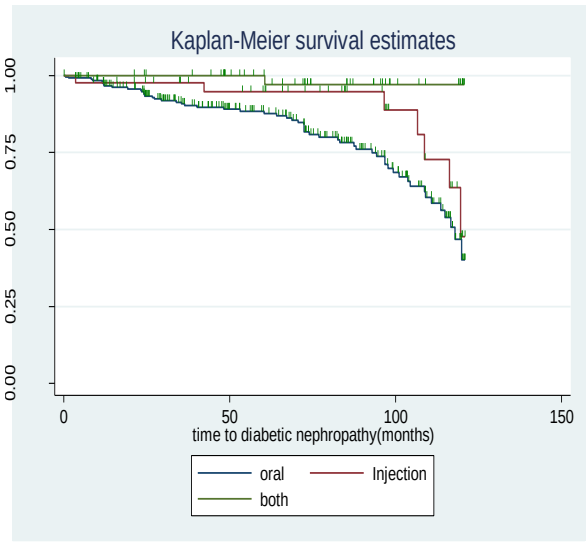
In the present study log-rank test was performed to test equality of nephropathy free survival curves for the presence of any significant differences in time to nephropathy among various levels of the categorical variables. In this study, it is found that the median time to develop nephropathy for those who had hemoglobin A1c less than 7 had a longer survival than hemoglobin A1c greater than 7 (116.7 months). This difference was statistically significant with (p-value = 0.002). On the other hand, the 10-year overall nephropathy-free survival after newly diagnosis of diabetes was 84.6% for patients whose high density lipoprotein greater than 40mg/dl and 42.6% for those their high density lipoprotein less than 40mg/dl. Likewise, for those their low density lipoprotein higher than 100mg/dl was 35.5% which is lower than for those low density lipoprotein less than 100mg/dl. This difference was statistically significant with (p-value = 0.031) (Table 4 and figure3).

Table 5. Nephropathy free overall survival rates and median time to nephropathy during 10-year of follow-up (Kaplan-Meier method) of diabetic patients, at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019 (N=346).

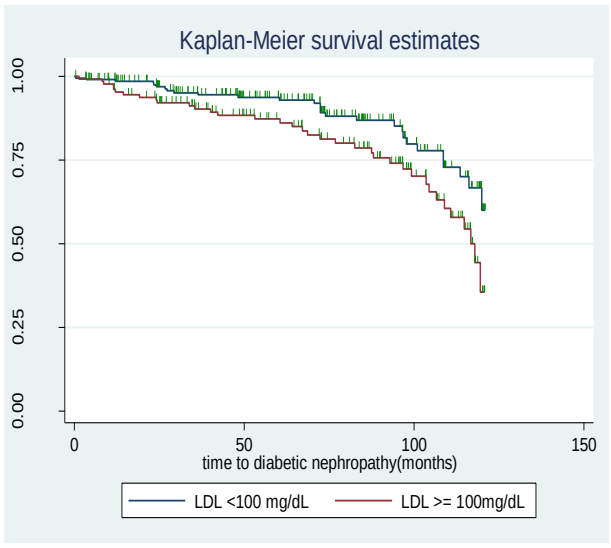
Variable	**Category**	**Median time to nephropathy (95% CI)**	**Overall 10-year NFS (%)**	**P –value with log rank**
Gender	Male	116.19(101.02,118.7)	36.03	0.000
	Female	----	75.50	
Residence	Urban		55.8	0.246
	Rural	116.69(92.85,120)	0	
Hypertension	Yes	----	50.78	0.500
	No	119.57(110.84-.--)	47.91	
Peripheral neuropathy	Yes	119.57(117.95---)	47.97	0.800
	No	119.94(114.84---)	49.6	
Diabetic retinopathy	Yes	114.84(97.75,120)	0	0.124
	No	------	53.1	
Dyslipidemia	Yes	-----	56.25	0.505
	No	119.94(109.02)	46.1	
Body mass index(kg/m^2)		40.13(40.13,69.6)		
	<18.5	---	50	
	18.5-24.9	---	50.33	0.247
	25-29.9	114.84(108.66,118.9)	72.26	

	>30		31.79	
HbA1c	<7	---	62.22	0.002
	≥7	116.69(108.66,119.2)	35.51	
Total cholesterol, mg/dl	<200	119.94(116.19--)	49.34	0.995
	≥200	---	59.35	
Triglyceride, mg/dl	<150	----	60.81	0.158
	≥150	117.95(106.61---)	33.06	
High density lipoprotein, mg/dl	<40	117.95(110.84,120)	42.58	0.014
	≥40	---	84.62	
Low density lipoprotein, mg/dl	<100	-----	59.97	0.031
	≥100	116.69(109.02,119.5)	35.49	
Type of DM medication	Oral	117.95(109.02,119.6)	40.41	
	Injection	119.57(108.66, --)	47.72	0.005
	mixed	----	97.06	

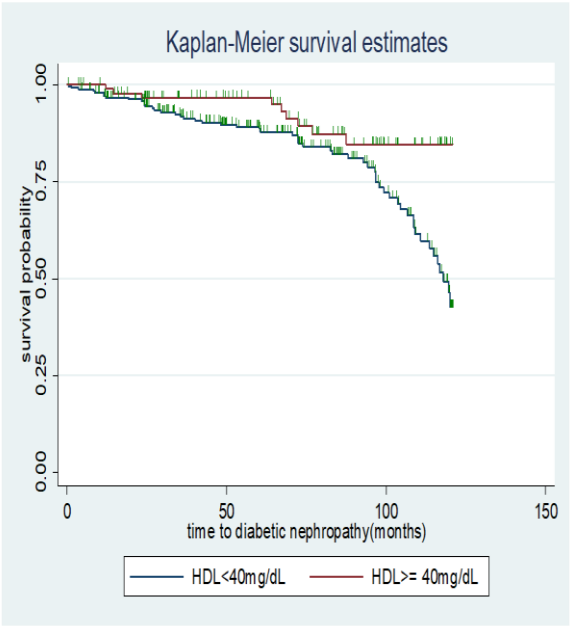
N.B: NFS; nephropathy free survival.



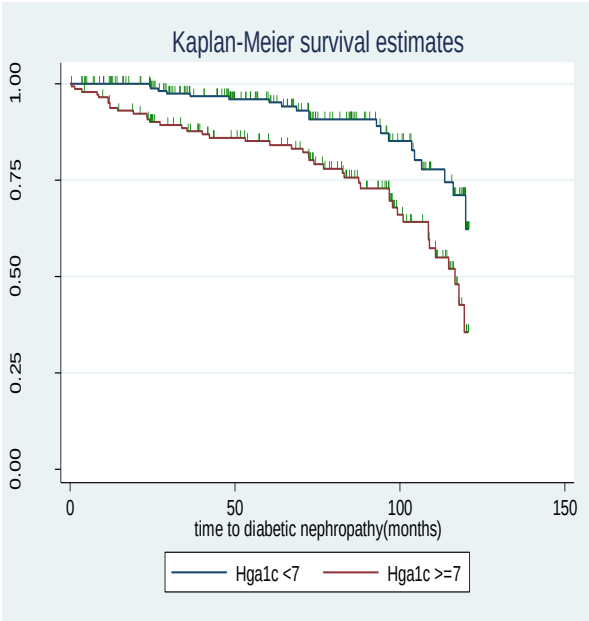
A



B



C



D.

Figure 3. Kaplan-Meier nephropathy free survival function among different groups of diabetic patients by type of diabetic medication (A), Low density lipoprotein (B), High density lipoprotein (C) and Hemoglobin A1c (D), in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019 (N=346).

5.6. Predictors of diabetic nephropathy

In Bivariate cox proportional hazard regression model, age, gender, duration of diabetic, hemoglobin A1c, high density lipoproteins, low density lipoprotein, systolic blood pressure, fasting glucose level, and type of medication were significantly associated with diabetic nephropathy($P<0.05$). Likewise, those variables with p-value <0.25 in the bivariable analysis were included in multivariable cox regression analysis.

The finding of the present study revealed that being male was found to be 2.7 times more likely to develop nephropathy as compared to those with female (AHR: 2.7, 95% CI: 1.39,5.23). Similarly, those clients whose duration of diabetic increase by one year showed 0.3% increasing the risk of diabetic nephropathy (AHR: 1.003, 95% CI: 1.001,1.006). Those patients whose hemoglobin A1c level greater than 7 were found to be 1.74 times higher hazard of developing diabetic nephropathy compared to those having hemoglobin A1c level less than 7 at time of diagnosis (AHR: 1.74, 95% CI:1.67,3.12). On the other hand, clients who had high density lipoprotein greater 40mg/dl were 67% less hazards to develop nephropathy as compared to their counterparts (AHR: 0.37, 95% CI:0.16, 0.83). Furthermore, participant who had been used both type of antidiabetic therapy (oral and injection) during the follow up time were reduced the hazards of nephropathy by 93% compared to those who had used oral hypoglycemic agent (AHR: 0.07, 95% CI: 0.01, 0.59) (table 5).

Table 6. Results of the bivariable and multivariable cox regression analysis of diabetic patients at Tikur Anbessa Specialized hospital, Addis Ababa, Ethiopia, 2019(n=346).

Variable	**Category**	**nephropathy status**		**CHR (95% CI)**	**AHR (95% CI)**
		Event	censored		
Gender	Male	55	123	3.91(2.12,7.20) *	2.70(1.39,5.23) *
	Female	13	155	1	1
Residence	Urban	57	240	1	1
	Rural	11	38	1.48(0.75,2.93)	0.91(0.42, 1.97)
Age				1.02(1.001,1.05) *	0.99(97, 1.02)
Hypertension	Yes	52	183	1.21(0.68,2.14)	
	No	16	95	1	
Peripheral neuropathy	Yes	11	42	0.92(0.48,1.76)	
	No	57	236	1	
Diabetic retinopathy	Yes	9	11	1.78(0.84,3.76)	1.01(.43,2.33)
	No	59	267	1	1
Dyslipidemia	Yes	22	81	0.83(0.48,1.42)	
	No	45	195	1	
Duration of diabetic (in years)				1.00(1.002,1.004) *	1.003(1.001,1.006) *
Body mass index(kg/m^2)	<18.5	1	10	1	

	18.5-24.9	10	52	0.51(0.06,4.11)	
	25-29.9	21	123	0.50(0.06,3.85)	
	>30	36	93	0.83(0.11,6.24)	
HbA1c	<7	22	177	1	1
	≥7	46	101	2.62(1.54,4.47) *	1.74(1.67,3.12) *
Total cholesterol, (mg/dl)	<200	53	220	1	
	≥200	15	58	1.01(0.55,1.82)	
Triglyceride, (mg/dl)	<150	43	203	1	1
	≥150	25	75	1.43(.86,2.37)	1.61(0.91,2.88)
High density lipoprotein, (mg/dl)	<40	58	192	1	1
	≥40	10	86	0.42(0.20,0.86) *	0.37(0.16,0.83) *
Low density lipoprotein, (mg/dl)	<100	30	183	1	1
	≥100	38	95	1.85(1.12,3.04) *	1.67(0.94,2.96)
SBP, (mmHg)				1.01(1.006,1.027) *	0.99(0.98, 1.01)
DBP, (mmHg)				1.02(0.99,1.05)	1.02(0.99,1.05)
FBS (mg/dl)				0.98(0.97,0.99) *	1.12(1.03, 1.97) *
Type of DM medication	Oral	58	192	1	1
	Injection	9	36	0.54(0.24,1.82)	0.53(0.23,1.21)
	mixed	1	50	0.06(0.008,0.45) *	0.07(0.01, 0.59) *

N.B; *** p-value less than 0.05 both at Bivariable and multivariable cox regression analysis; 1** shows the reference group of different variables, CHR; crude hazard ratio, AHR; adjusted hazard ratio.

5.7. Test of proportional-hazards assumption

A cox regression model was used to evaluate the effects of sociodemographic, clinical and treatment characteristics of study participants in time to nephropathy. The following predictor variables were included in the mode like age, gender, duration of diabetic, hemoglobin A1c, high density lipoprotein, low density lipoprotein, systolic blood pressure, fasting sugar level, and type of medication. Along with it, schoenfeld residual test was conducted to assess the proportional hazard (PH) assumptions of the cox model for given predictor variables. As a result, the findings indicated that all variable included in the model were satisfy PH assumptions (p-value>0.05) (**table5**).

Table 7. Test of proportional-hazards assumption among different covariate of diabetic patients at Tikur Anbessa Specialized Hospital, Ethiopia, 2019(N=346).

Variables	rho	chi2	df	P-value
Gender	-0.15043	1.64	1	0.200
Residence	0.19701	3.01	1	0.0828
Age	0.09798	0.71	1	0.4003
Retinopathy	-0.00082	0.00	1	0.9944
Hga1c	-0.18384	2.43	1	0.1194
Triglyceride	0.05440	0.20	1	0.6519
HDL	0.01248	0.01	1	0.9137
LDL	-0.03640	0.10	1	0.7562
Systolic BP	0.24359	5.74	1	0.166
Diastolic BP	0.01780	0.03	1	0.8697
Fasting sugar	-0.05788	0.39	1	0.5311
Injection	0.07557	0.33	1	0.5632
Both	-0.03209	0.07	1	0.7858
Duration	0.13519	1.36	1	0.2443
Global test		16.71	14	0.2720

CHAPTER 6

DISCUSSION

The main aim of this research was to estimate time to nephropathy and its predictors among diabetic patients. In line with this objective, the finding of the current study revealed that the incidence rate of nephropathy was found to be 30.4 per 10,000 person-months observation among diabetic clients and the overall cumulative incidence of nephropathy among newly diagnosed diabetes clients was 19.65% over ten years follow up. This finding is much lower than a study conducted in St. Paul's Hospital which is 2178 per 10,000 person-months observation.

This gap could be those patients know their diabetes status might be delayed in case of St. Paul's Hospital and other explanation could be in TASH clients might have good treatment adherence and other behavioral modification.

In this retrospective follow up study, the overall nephropathy free survival rates at 1, 3, 7 and 10 years were, 97.6%, 93.2%, 83.5% and 49.7% respectively. According to the current study, the overall median time to develop nephropathy was found to be100.03 month (95% CI, 96.7 – 107). Our results were higher than the previous studies done in St. Paulo's hospital with median time to develop nephropathy was 70.9 months with an interquartile range of (IQR: 41.00–88.73 months). This difference might be early diagnosis, treatment and those who attend follow up at TASH may have good health seeking behavior.

This study found that clients who had male gender were 2.7 times, higher hazard of developing nephropathy than their counter part. This finding is in line with a study conducted in Nigeria (38). On the other hand, our finding is in contrary with the study done in India (39) and southern Ethiopia Bugarija (43). To discover the scientific justification behind this difference further research is needed. In the current study those clients whose duration of diabetic increase by one year showed 0.3% increasing the hazard of diabetic nephropathy. This finding is consistent with a study conducted in different area of the globe (39, 40, 43-45).

According to this study finding those participants whose hemoglobin A1c level greater than 7 was found to be 1.74 times higher hazard of developing diabetic nephropathy compared to those

having hemoglobin A1c level less than 7 at time of diagnosis. Our study finding is in line with a study done southern and northern region of Ethiopia (43, 44) and southern India (45). The current study showed that participants who had high density lipoprotein greater 40mg/dl were 67% less likely to develop nephropathy as compared to those counterparts. This finding is in line with a study done in St. Paul's hospital Ethiopia (36). The scientific rational behind to this reflects that among those type 2 diabetes patients might be primarily involved in the reverse cholesterol transport and in a number of other non-cholesterol dependent effects, including anti-oxidant, and anti-inflammatory.

The current study revealed that participant who had used both oral and injection type of antidiabetic therapy during the follow up time were reduced the hazards diabetic nephropathy by 93% compared to those who had taken oral hypoglycemic agent. Despite previous studies would not support our evidence, we would recommend further researcher could investigate the possible effect of each therapy on the incidence of nephropathy. Furthermore, in the present study, we found that, there was nearly 12%, increase the hazard of diabetic nephropathy for every 1mg/dl increasing fasting blood sugar level.

LIMITATION AND STRENGTH OF THE STUDY

Limitations

Due to the retrospective nature of the study, selection bias is possibly introduced during secondary data collection because patients with incomplete records were excluded. Other limitation also, lack of data on some sociodemographic factors like education, marital status and smoking prevented us from analyzing the role of them to time to diabetic nephropathy. In addition, we were unable to consider wider risk factors in depth due to incomplete data. Despite these limitations, conducting this study for 10 year follow up would provide adequate number of events. Data were collected by nurses who were trained on diabetic client care has an important role in the quality of the data.

Strength

Despite the above potential limitations, the study has the following strengths. The study was conducted for a long follow up (ten years) period which increases period of observation, and enabled to know the long-term impact of chronic kidney disease care. Data were collected by nurses who have been trained in diabetic care and this has an important role in the quality of data.

CONCLUSION AND RECOMMENDATION

Conclusion

In current study, the incidence of diabetic nephropathy among DM patients was relatively high and which becomes the raising national burden. Being male, longer duration of diabetes, hemoglobin A1c greater than 7, and one unit increasing of fasting blood sugar were increase the hazard of diabetic nephropathy. On the contrary high density lipoprotein greater than 40mg/dl and those diabetic clients who had received both oral and injection therapy were reduced the hazard of diabetic nephropathy.

Recommendation

Based on the finding of the present study the following recommendation is forwarded: -

To the Federal Minister of Health: -

- ✓ Could expand clinical early screening programs to diabetic nephropathy among diabetic clients throughout the nation.
- ✓ Improve information dissemination in collaboration with public media about the major complication of diabetes particularly to diabetic nephropathy is crucial.

To Tikur Anbessa Specialized Hospital and health care professional: -

- ✓ Enhance awareness to have good glycemic control is vital to reduce the incidence of diabetic nephropathy.
- ✓ Could give special emphasize to those who had longer duration of follow up, their high density lipoprotein lower than 40mg/dl and high fasting blood sugar at the time of diagnosis.
- ✓ Even though, there is the need to have further study, provide treatment using both oral and injection regimens is encouraged.

To further researchers: -

- ✓ Further prospective follow up study and randomize control trial could be conducted by incorporating important predictors of diabetic nephropathy like the effect of treatment adherence, biological and molecular variable.

Reference

1. Ahn JH, Yu JH, Ko S, Kwon H, Kim DJ, Kim JH, et al. Prevalence and Determinants of DiabeticNephropathy in Korea: Korea National Health and Nutrition Examination Survey Study population. DIABETESMET ABOLISM J. 2014; 38(2):109±19.
2. Effective health care program. Evidence based Practice Center Systematic Review Protocol Projecttitle: Behavioral Programs for Diabetes Mellitus. AHRQ. 2014;1±27.
3. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes care 2014;37(Suppl. 1):S81-S90/https://doi.org/10.2337/dc18-S002.
4. Hove MN, Kristensen JK, Lauritzen T, et al. The prevalence of retinopathy in an unselected population of type 2 diabetes patients from Arhus County, Denmark. Acta Ophthalmol Scand 2004; 82: 443–8.
5. Seki M, Tanaka T, Nawa H, et al. Involvement of brain-derived neurotrophic factor in early retinal neuropathy of streptozotocininduced diabetes in rats: therapeutic potential of brain-derived neurotrophic factor for dopaminergic amacrine cells. Diabete.
6. Huang C, Kim Y, Caramori MLA, et al. Cellular basis of diabetic nephropathy: II. The transforming growth factor-beta system and diabetic nephropathy lesions in type 1 diabetes. Diabetes 2002; 51: 3577–81.
7. Looker HC, Fagot-Campagna A, Gunter EW, et al. Homocysteine as a risk factor for nephropathy and retinopathy in type 2 diabetes. Diabetologia 2003; 46: 766–72.
8. Svensson M, Eriksson J. Glycemic control, age at onset, and development of microvascular complications in childhood-onset type 1 diabetes: a population-based study in northern. Diabetes2004; 27: 955–62.
9. American Diabetes Association. Introduction: Standards of Medical Care in Diabetes. Diabetes Care 2018;41(Suppl. 1):S1-S2/ https://doi.org/10.2337/dc18-SINT01.
10. Vitan Patel, MinalShastri, Nisha Gaur, PruthaJinwala, Abhishek Y. Kadam. A study in prevalence of diabetic nephropathy in recently detected cases of type 2 diabetes mellitus as evidenced by altered creatinine clearance, urinary albumin and serum creat.
11. Diabetic kidney disease; review of the current knowledge.,HeshmatollahShahbazian 1 ,* and Isa Rezaii. 2013. Journal of JRIP.
12. Kittell F (2012). “Diabetes Management”. In Thomas LK, Othersen JB. Nutrition Therapy for Chronic Kidney Disease. CRC Press. p. 198.

13. Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J (2013). Harrison's manual of medicine (18th ed.). New York: McGraw-Hill Medical. p. 2982. ISBN 978-0-07-174519-2.
14. Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, de Boer IH (August 2016). "Clinical Manifestations of Kidney Disease Among US Adults With Diabetes, 1988-2014". JAMA. 316 (6): 602–10. doi:10.1001/jama.2016.10924. PMID 27532915.
15. Rabkin R. Diabetic nephropathy. Clin Cornerstone. 2003;5:1–11. [PubMed].
16. Rudberg S, Qsterby R, Dahlquist G, Nyberg G, Persson B. Predictors of renal morphological changes in the early stage of microalbuminuria in adolescents with IDDM. Diabetes Care 1997; 20: 265.
17. International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation, 2017.
18. Bertoni AG, Krop JS, Anderson GF, Brancati FL. Diabetes-related morbidity and mortality in a national sample of U.S. elders. Diabetes Care 2002; 25:471–75.
19. Ritz E, Rychlik I, Locatelli F, Halimi S. End-stage renal failure in type 2 diabetes: a medical catastrophe of worldwide dimensions. Am J Kidney Dis1999; 34: 795808.
20. Jean Jacques N Noubiap, Jashira Naidoo, Andre P Kengne. Diabetic nephropathy in Africa: A systematic review. world Journal of diabetes. 2015 June 10; 6(5): 759-773. DOI: 10.4239/wjd.v6.i5.759.
21. Rahlenbeck SI, Gebre-Yohannes A. Prevalence and epidemiology of micro- and macroalbuminuria in Ethiopian diabetic patients. J Diabetes Complications 1997; 11: 343-349 [PMID: 9365876].
22. Vijay V, Seena R, Lalitha S, Snehalata C, Jayaraman M, Ramachandran A: Significance of microalbuminuria at diagnosis of type 2 diabetes. Int J Diab Dev Countries 18:5– 6, 1998.
23. Feleke Y, Enquselassie F. An assessment of the health care system for diabetes in Addis Ababa, Ethiopia. Ethiop J Health Dev 2005; 19: 204–10.
24. Gizaw M, Harries AD, Ade S, et al. Diabetes mellitus in Addis Ababa, Ethiopia: admissions, complications and outcomes in a large referral hospital. Public Health Action 2015; 5: 74–8.
25. Mohan V, Meera R, Premalatha G, Deepa R, Miranda P, Rema M: Frequency of

proteinuria in type 2 diabetes mellitus seen at a diabetes centre in southern India. Postgrad Med J 76:569 –573, 2000.

26. Choukem SP, Dzudie A, Dehayem M, Halle MP, Doualla MS, Luma H, Kengne AP. Comparison of different blood pressure indices for the prediction of prevalent diabetic nephropathy in a sub-Saharan African population with type 2 diabetes. Pan Afr Med J 2012;
27. Alebiosu CO, Odusan O, Familoni OB, Jaiyesimi AE. Cardiovascular risk factors in type 2 diabetic Nigerians with clinical diabetic nephropathy. Cardiovasc J S Afr 2004; 15: 124-128 [PMID: 15258622].
28. Alebiosu CO, Odusan O, Jaiyesimi A. Morbidity in relation to stage of diabetic nephropathy in type-2 diabetic patients. J Natl Med Assoc 2003; 95: 1042-1047 [PMID: 14651370].
29. Parving HH, Gall MA, Skøtt P, Jørgensen HE, Løkkegaard H, Jørgensen F, et al. Prevalence and causes of albuminuria in non-insulin-dependent diabetic patients. Kidney Int. 1992;41:758–62. [PubMed].
30. Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, et al. Nephropathy in diabetes. Diabetes Care. 2004;27(Suppl 1):S79–83. [PubMed].
31. Piccoli GB, Grassi G, Cabiddu G, Nazha M, Roggero S, Capizzi I. et al. Diabetic Kidney Disease: A Syndrome Rather Than a Single Disease. Rev Diabet Stud. 2015;12:87–109. [PMC free article] [PubMed].
32. Huang R, Feng Y, Wang Y, Qin X, Melgiri ND, Sun Y, et al. (2017) Comparative Efficacy and Safety of Antihypertensive Agents for Adult Diabetic Patients with Microalbuminuric Kidney Disease: A Network Meta-Analysis. PLoS ONE 12 (1): e0168582. doi:10.1371/j.
33. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. CJASN. 2017;13.
34. Levey AS, Coresh J, Balk E, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease:evaluation, classification, and stratification. AnnIntern Med 2003;139:137–147.
35. Narres M, Claessen H, Droste S, Kvitkina T, Koch M, Kuss O, et al. (2016) The Incidence of EndStage Renal Disease in the Diabetic (Compared to the Non-Diabetic) Population:

A Systematic Review. PLoS ONE 11(1): e0147329. doi:10.1371/journal. pone.0147329.

36. Alemayehu Hussen Geletu, Alemayehu Shimeka Teferra, Malede Mequanent Sisay and Destaw Fetene Teshome. (2018). Incidence and predictors of chronic kidney diseases among type 2 diabetes mellitus patients at St. Paul's Hospital, Addis Ababa, Ethiopia. Jornal.
37. ElHafeez SA, Bolignano D, D'Arrigo G, Evangelia Dounousi GT, Zoccali C. Prevalence and burden of chronic kidney disease among the general population and high-risk groups in Africa: a systematic review. 2018. Jornal of BMC. Volume 8.
38. Olutayo Christopher Alebiosu. Clinical Diabetic Nephropathy in a Tropical African Population. 2003·Research Gate. Vol 22, No 2. DOI: 10.4314/wajm.v22i2.27938.
39. Vimalkumar VK, Anand Moses CR, Padmanaban S. 2011. Prevalence & Risk Factors of Nephropathy in Type 2 Diabetic Patients. International Journal of Collaborative Research on Internal Medicine & Public Health. Vol. 3 No. 8.
40. JijiInassi, VijayalakshmyR.Role of duration of diabetes in the development of nephropathy in type 2 diabetic patients. Volume 3 ▏Issue 1 ▏Jan – March 2013. national journal of medical research.
41. Tung P, Levin SR. Nephropathy in NIDDM. American Journal of Medical sciences. 1988; 85: 131.
42. Grandfils N, Detournay B, Attali C, Joly D, Simon D, Vergès B, et al. Glucose Lowering Therapeutic Strategies for Type 2 Diabetic Patients with Chronic Kidney Disease in Primary Care Setting in France: A Cross-Sectional Study. Int J Endocrinol [Intern.
43. Temesgen Fiseha, Mehidi Kassim and TilahunYemane. Prevalence of chronic kidney disease and associated risk factors among diabetic patients in southern Ethiopia. 2014; 2(4): 216-221. doi: 10.11648/j.ajhr.20140204.28. American Journal of Health Research.
44. Hintsa S, Dube L, Abay M, Angesom T, Workicho A. Determinants of diabetic nephropathy in Ayder Referral Hospital, Northern Ethiopia: Acase-control stud. Plosone. 2017;
45. Ranjit Unnikrishnan, Mohan Rema, Rajendra Pradeepa, Mohan Deepa, Coimbatore Subramaniam Shanthirani, Raj Deepa And Viswanathan Mohan. 2007. Prevalence and Risk Factors of Diabetic Nephropathy in an Urban South Indian Population. Journal of Epid.

46. Oshima M, Toyama T, Haneda M, Furuichi K, Babazono T, Yokoyama H. Estimated glomerular filtration rate decline and risk of end-stage renal disease in type 2 diabetes. PLoS One. 2018;13(8).
47. Yadav SCB. Glycemic control in diabetic kidney disease patients. Clin Queries Nephrol. 2012 Apr;1(2):111–4.
48. Chaturvedi N, Bandinelli S, Mangili R, Penno G, Rottiers RE, Fuller JH. Microalbuminuria in type 1 diabetes: rates, risk factors and glycemic threshold. Kidney Int. 2001;60:219–227. [PubMed].
49. McGovern AP, Rusholme B, Jones S, Vlymen JN van, Liyanage H, Gallagher H, et al. Association of chronic kidney disease (CKD) and failure to monitor renal function with adverse outcomes in people with diabetes: a primary care cohort study. BMC Nephrol.
50. Solomon Hintsa, Lamessa Dube, Mebrahtu Abay, Teklit Angesom Abdulhalik Workicho. (2017) Determinants of diabetic nephropathy in Ayder Referral Hospital, Northern Ethiopia: Acase-control stud. Journal of Plos|one.
51. http://worldpopulationreview.com/world-cities/addis-ababa/.
52. WHO. Guidelines for the prevention, management and care of diabetes mellitus; 2006. p. 32.
53. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. BioMed Central. 2008;3: 17.

APPENDIX

Annex 1: Subject Information Sheet English Version

Title of the Research proposal: Survival Analysis of Time to Nephropathy among Type 2 Diabetes Mellitus Patients in Tikur Anbesa Specialized Hospital, Addis Ababa, Ethiopia, 2019 retrospective follow up study.

Name of Investigator: Kidist Tamru, BSc

Name of the Organization: Addis Ababa University, College of Health Science, School of Nursing and Midwifery

Name of the Sponsor: Addis Ababa University

Purpose of the Research Project: To determine survival time to nephropathy development and contributing factors among T2 Diabetic patient from 2009-2018G.C follow up in TASH, Addis Ababa, Ethiopia, 2019

Procedure: In order to achieve the above objective, information which is necessary for the study will be taken from medical record forms by the aid of data extraction tool and patients enrolled during January 1st, 2009 to December 30th, 2018G.C will be selected.

Risk and /or Discomfort: Since the study will be conducted by taking appropriate information from the medical chart, it will not inflict any harm on the patients. The name or any other identifying information will not be recorded on the questionnaire and all information is taken from the chart will be kept strictly confidential and in a safe place. The information retrieved will only be used for the study purpose.

Benefits: The research has no direct benefit for those whose document/ record is included in this research. However, the indirect benefit of the research for the participant and other clients in the program is clear. This is because if program planners are preparing a predicted plan, there is a benefit for clients in the program of getting appropriate care and treatment services for the Type 2 Diabetic patients. Of all, the research work has a paramount direct benefit for health care

planners and managers, especially for those type 2 diabetic patient program planning and management**.**

Confidentiality: To reassure confidentiality the data on the chart will be collected without the name of the clients and the information collected from this research project will be kept confidential and will be stored in a file cabinet. In addition, it will not be revealed to anyone except the investigator and it will be kept in a key and locked system with computer pass ward.

Person to contact: This research project will be reviewed and approved by the institutional review board of school of nursing and midwifery, college of health sciences, Addis Ababa University. If you have any question you can contact any of the following individuals (Investigator and Advisors) and you may ask at any the time you want.

Kidist Tamru, BSc: Addis Ababa University, College of Health Sciences, School of Nursing and Midwifery

Cell phone: +251911860965, E-mail: ktamru@gmail.com

Mr. Fekadu Aga, MSc, Assistant. Professor, PhD Fellow: Addis Ababa University, College of Health Sciences, School of Nursing and Midwifery

Sr. Emebet Berhanu, MSc, PhD Fellow: Addis Ababa University, College of Health Sciences, School of Nursing and Midwifery.

Annex 3: Data Extraction Check List

Topic: Survival Analysis of Time to Nephropathy among Type 2 Diabetes Mellitus Patients in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019

Instruction: Dear data collector this is a data abstraction form designed to collect data of patients started the treatment in public health facilities of TASH diabetic clinic. Please try to fill all the requested fields that are prepared in the section of the data abstraction form.

The form has three sections:

The first section: General information

The second section: the socio-demographic characteristics of the patient

The third section: The clinical and laboratory characteristics of the patient

Part I General information

001. Date: _____

002. Name of the health facility _____

003. Code given for the chart_____

004. Name of the data collector_____

005. Name of the supervisor_____

Part I Baseline Socio demographic characteristics of T2DM patient

Code	Characteristics	Coding classification
101	Gender	1. Male

		2. Female
102	Age	_____years
103	Place of residence	1. Urban 2. Rural

Part II Baseline clinical and laboratory characteristics of T2DM patients

201	Date the patient confirmed as T2 Diabetic patient	dd/mm/yy_____/_____/_____
202	Hypertension	0. Absent 1. Present
203	Myocardial infarction	0. Absent 1. Present
204	Congested heart Failure	0. Absent 1. Present
205	Peripheral disease	0. Absent 1. Present
206	Cerebrovascular disease	0. Absent 1. Present
207	Chronic pulmonary disease	0. Absent 1. Present
208	Liver Disease	0. Absent 1. Present

209	HIV AIDS	0. Absent 1. Present
210	Connective tissue Disease	0. Absent 1. Present
211	Peptic ulcer disease	0. Absent 1. Present
212	Retinopathy	0. Absent 1. Present
213	Leukemia	0. Absent 1. Present
214	Lymphoma	0. Absent 1. Present
215	Tumor	0. Absent 1. Present
216	Dyslipidemia	0. Absent 1. Present
216	Wt. (Kg) _____ Ht. (m) _____ BMI _____	_____kg/m^2
217	Glycemic Control measured by hemoglobin A1c	_____%

218	Lipid profile Total cholesterol(mg/dl) _____ Triglyceride(mg/dl) _____ HDL (mg/dl) _____ LDL (mg/dl) _____	
219	Systolic Blood Pressure	_____ mmhg
220	Diastolic blood pressure	_____ mmhg
221	Fasting serum glucose	_____mg|dl
222	Diabetic duration (for how long the patient live as T2 diabetic patient)	_____month

Pat III Treatment related factors

301	Types of medication	1.oral 2.injection 3.both
302	Status of patients at last contact	Censored Nephropathy
303	If last contact is “censored”	1 Transferred out 2 Lost to follow up

		3 No nephropathy 4 Unknown
304	If the answer to Q305 is Nephropathy date confirmed to Nephropathy	dd/mm/yy_____/____/____
305	Last date of contact	dd/mm/yy_____/____/____

STATEMENT OF DECLARATION

By my signature below, I declare and affirm that this thesis is my own work. I have followed all ethical principles of scholarship in the preparation, data collection, data analysis and completion of this thesis. All scholarly matter that is included in the thesis has been given recognition through citation. I affirm that I have cited and referenced all sources used in this document. Every effort has been made to avoid plagiarism in the preparation of this thesis.

This thesis is submitted in partial fulfillment of the requirement for a graduate degree from the Addis Ababa University at College of Health Sciences, School of Nursing and Midwifery. The thesis is deposited in the Addis Ababa University Digital Library and is made available to local, national and international scientific community. I solemnly declare that this thesis has not been submitted to any other institution anywhere for the award of any academic degree, diploma or certificate.

Kidist Tamru _____ _____

Signature Date

Research advisors:

Mr Fekadu Aga (Assistant Professor) _____ _____

Name Rank Signature Date

Sr. Emebet Berehane (MSc, PhD Fellow) _____ _____

Name Rank Signature Date