

**PREVALENCE AND FACTORS ASSOCIATED WITH
AUTONOMIC NEUROPATHY AMONG DIABETES PATIENTS
AT MOI TEACHING AND REFERRAL HOSPITAL, KENYA.**

BY

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DEGREE OF MASTER OF MEDICINE IN INTERNAL
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DECLARATION

Candidate's Declaration

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DEDICATION

This thesis is dedicated to all patients with Diabetes seeking care at Moi Teaching and Referral Hospital, Kenya.

ABSTRACT

Background: Diabetic autonomic neuropathy (DAN) is a common and serious complication of Type 2 Diabetes Mellitus (T2DM), with reported prevalence ranging from 16% to 70%. It significantly affects quality of life and increases morbidity and mortality. Although key risk factors have been identified, the prevalence and contributing factors in our setting remain unclear. Understanding these would help guide better screening, prevention, and management strategies.

Objectives: To determine the prevalence and factors associated with autonomic neuropathy among patients with (T2DM) at the Moi Teaching and Referral Hospital (MTRH).

Methods: This study was a cross-sectional analysis conducted at the MTRH diabetes outpatient clinic. The study population included 344 adult patients with T2DM from March to August 2024. Diabetic autonomic neuropathy was assessed using the COMPASS-31 questionnaire. A standard interviewer-administered questionnaire was then used to collect socio-demographic and clinical data. The independent variables were age, sex, marital status, level of education, HbA1C, body mass index, statin use, hypertension, dyslipidemia, and creatinine clearance. Categorical variables were summarized using frequency tables, percentages, and bar graphs. Mean, median, and interquartile ranges were used to summarize continuous variables. The association between diabetic autonomic neuropathy and independent variables was assessed using bivariate and multivariate analysis.

Results. The mean age of study participants was 61.0 years (SD 9.8). The mean HbA1c was 9.6 (SD 4.5)%. The median duration of diabetes was 8.62 (IQR 4-12years). Females constituted 65.4% of all study participants. The prevalence of DAN was established to be 53.2% based on the COMPASS 31 questionnaire weighted score. Analysis of autonomic dysfunction according to the domains affected revealed that the most affected domains were the gastrointestinal (65.41%), secretomotor (62.41%), and pupillomotor (53.78%). The orthostatic domain had a prevalence of 53.78%, followed by the vasomotor domain at 48.26%, and the bladder domain had 31.40%.

On multivariable regression models, DAN was inversely correlated with the use of lipid-lowering agents. There was a positive association between DAN and kidney dysfunction as measured by estimated glomerular filtration rate (eGFR).

Conclusion. Our findings revealed a high prevalence of DAN among individuals in outpatient care for T2DM in MTRH indicating a significant clinical problem. There was an inverse correlation between DAN and the use of lipid-lowering agents. There was a positive association between DAN and kidney dysfunction

Recommendation. Assessment of autonomic neuropathy should be integrated in the care of persons with diabetes, given the high prevalence of DAN in this study population and the rising global burden of diabetes.

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ACRONYMS

DAN	Diabetic Autonomic Neuropathy
DOPC	Diabetes Outpatient Clinic
HBA1C	Glycated Hemoglobin
IREC	Institutional Research and Ethics Committee
LDL	Low-Density Lipoprotein
MTRH	Moi Teaching and Referral Hospital
T2DM	Type 2 Diabetes Mellitus

DEFINITION OF TERMS

Composite Autonomic Symptom Score tool (COMPASS-31) – A standardized tool developed to assess the presence and severity of autonomic neuropathy as well as the body systems involved.

Diabetic autonomic neuropathy – this refers to a group of clinical syndromes resulting from impaired functioning of the sympathetic and parasympathetic nerves. This was assessed using the Composite Autonomic Symptom Score tool (COMPASS-31).

Duration of diabetes – this refers to the time period of time in years between time of diagnosis and time of data collection.

HbA1c – this refers to the laboratory measurement of glycated hemoglobin that was carried out at the time of data collection.

Lipid profile levels - this refers to the measurement of low-density lipoprotein, very low-density lipoprotein, high-density lipoprotein and total cholesterol carried out at the time of data collection.

Treatment modality – this refers to the treatment strategy that is employed for the management of a patient with diabetes at the time of data collection.

Type 2 Diabetes Mellitus – this refers to a patient aged >30 years at time of diagnosis and managed on oral antihyperglycemic or insulin and antihyperglycemics; any patient regardless of age managed on oral antihyperglycemic agent without insulin.

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CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Type 2 Diabetes mellitus (T2DM) is a global epidemic (Ginter & Simko, 2012b). Kenya and other developing nations are experiencing a rise in the diabetes disease burden (Ginter & Simko, 2012a; Ruchman et al., 2021). This increase is attributed to a sedentary lifestyle, nutritional transition, and urbanization. Suboptimal control and prolonged disease duration have been associated with life-threatening complications and comorbidities (Tryggestad & Willi., 2015).

Autonomic neuropathy describes a group of clinical syndromes resulting from impaired functioning of the sympathetic and parasympathetic nerves. The autonomic nervous system exerts its control through a broad network of both afferent and efferent nerve fibers. In the setting of persistent hyperglycemia, these nerve fibers are subjected to mechanisms that result in ischemic nerve injury and eventually death. The presentation of autonomic dysfunction in diabetes is diverse, involving the cardiovascular system, thermoregulation, respiration, gastrointestinal urogenital, and pupillomotor functions.

Patients with T2DM are prone to autonomic neuropathy with approximately 50% of them being likely to develop it in their lifetime (ARING et al., 2005). This results in devastating organ dysfunctions and disabilities which negatively affect their quality of life (Rasmussen et al., 2021) and contributes significantly to morbidity and mortality associated with T2DM. Recent studies have shown that the prevalence and severity of diabetes autonomic neuropathy (DAN) is correlated with older age, longer duration of

disease, suboptimal glycemic control, retinopathy, nephropathy, hypertension, obesity, and metabolic dyslipidemia (Benichou et al., 2018).

Early screening of autonomic neuropathy in T2DM can help prevent impairment of function, disability and improve quality of life. The data on risk factors associated with autonomic neuropathy among persons with diabetes would inform strategies for early detection, management, and prevention of DAN (Cernea & Raz, 2021).

1.2 Problem Statement

Diabetic autonomic neuropathy (DAN) is a major yet frequently under-recognized complication of diabetes mellitus, affecting multiple organ systems and contributing substantially to the overall disease burden. The autonomic nervous system is central to the regulation of critical visceral functions including cardiovascular, gastrointestinal, sudomotor, genitourinary, and metabolic processes.

Despite the increasing evidence showing that DAN is associated with heightened morbidity and mortality in individuals with type 2 diabetes mellitus (T2DM), particularly through its contribution to silent ischemia, arrhythmias, and sudden cardiac death. Diabetic autonomic neuropathy remains undiagnosed due to the insidious onset of symptoms, overlap with other comorbidities, and limited use of standardized evaluation tools, especially in resource-constrained settings.

The prevalence as well as factors associated with DAN in our setting remains largely unknown. This leaves a critical yet preventable and treatable factor in T2DM morbidity and mortality unaddressed.

1.3 Justification

The autonomic nervous system mediates the crucial regulation of various organ systems, which include the cardiovascular, gastrointestinal, genitourinary, and

endocrine systems. Type 2 diabetes mellitus has been implicated in the development of various types of neuropathies. Notable among these is DAN which is not only preventable but also potentially treatable. In addition, DAN is implicated in the development of cardiovascular-related morbidity and mortality.

Despite its clinical importance, there is paucity of data on DAN, hence lack of emphasis on systematic screening, timely diagnosis, and structured management of DAN in routine care. This study therefore sought to determine the prevalence of DAN and identify the sociodemographic and clinical factors associated among patients with type 2 diabetes at MTRH.

This study findings will inform improvements in current guidelines, increase awareness, and support targeted interventions for prevention, early detection, and effective management of DAN. Additionally, this finding provides a basis for future research exploring mechanisms, diagnostic strategies, preventive and therapeutic approaches in our set-up.

1.4 Research Questions

- What is the prevalence of autonomic neuropathy among patients with T2DM at MTRH Diabetes Outpatient Clinic?
- What sociodemographic and clinical factors are associated with diabetes autonomic neuropathy among patients with T2DM at MTRH Diabetes Outpatient Clinic?

1.5 Objectives

1.5.1 Broad Objective

To determine the prevalence and factors associated with autonomic neuropathy among patient with T2DM at MTRH Diabetes Outpatient Clinic.

1.5.2 Specific Objectives

- i. To determine prevalence of autonomic neuropathy among patients with T2DM in MTRH Diabetes Outpatient Clinic.
- ii. To describe the sociodemographic and clinical factors associated with autonomic neuropathy among patients with T2DM at MTRH Diabetes Outpatient Clinic.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Burden of Diabetes Mellitus

The International Diabetes Federation (IDF) estimates of the burden of diabetes globally show that approximately 536.6 million individuals are affected, representing 10.5% of the world population (Ogurtsova et al., 2022). These trends are equally alarming with the IDF projecting the prevalence to rise to 12.2% (783.2 million individuals) by 2045 (Ogurtsova et al., 2022).

In Africa, approximately 24 million individuals had diabetes mellitus in 2021 and by 2030 this is projected to rise to 33 million. This would place Africa as the continent with the highest proportional increase in diabetes prevalence by 2020 at 90.5% (Hilawe et al., 2013). This is attributed to the effect of rapid urbanization, nutritional transition, and sedentary lifestyle. In addition, a significant proportion of the adult population is uninformed of their diabetes status with approximately 13 million adult cases of diabetes mellitus undiagnosed (Ogurtsova et al., 2022).

Kenya's prevalence of diabetes mellitus is ranked at number 31 in Africa standing between 3.3% and 4% (Mohamed et al., 2018, Ogurtsova et al., 2022). This prevalence is expected to rise to 4.5% by 2025. In a study conducted in Kenya in the year 2015 only 43.7% of individuals living with diabetes mellitus were aware of their diagnosis with only 20% of these being on treatment (Mohamed et al., 2018). Among those under treatment only 7% had their blood glucose under control (Mohamed et al., 2018).

2.2 Diabetes and Complications

Diabetes is a heterogeneous metabolic disorder associated with abnormal carbohydrate metabolism (Petersmann et al., 2019). It is characterized by inappropriately elevated blood glucose levels resulting from deficiencies in insulin secretion, action, or both. The common categories of diabetes mellitus include Type 1 diabetes (due to autoimmune β -cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes in adults). Type 2 diabetes (due to a nonautoimmune progressive loss of adequate β -cell insulin secretion, frequently on the background of insulin resistance). Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes, diseases of the exocrine pancreas, and drug- or chemical-induced diabetes. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not overt diabetes before gestation or other types of diabetes occurring throughout pregnancy, such as type 1 diabetes (Sapra & Bhandari et al., 2023).

The most common type of diabetes in adults is T2DM, representing over 90 % of diabetes occurrences reported. The disease is characterized by cells resistance to insulin, gradual loss of beta cell insulin secretion, and inadequate compensatory mechanism (Jean-Marie, 2018). . In younger populations, T2DM is becoming more prevalent which is commonly attributed to obesity and overweight (Lascar et al., 2018).

Presentation ranges from predominantly insulin resistance with relative insulin deficiency to predominantly insulin secretory defect with insulin resistance.(Goyal et al., 2023) At least initially, and often throughout their lifetime, these individuals may not need insulin treatment to survive (Coetzee, 2023). Symptoms such as increased

thirst, frequent urination, fatigue, and blurred vision often accompany the condition, although some individuals may remain asymptomatic for a considerable period, leading to delayed diagnosis.

Primary causes and risk factors for developing T2DM include advancing age, obesity, sedentary lifestyle, unhealthy diet, alcohol abuse, and tobacco use (Gudjinu et al 2017). Persons with dyslipidemia, hypertension, polycystic ovarian syndrome (PCOS), and previous gestational diabetes also have an increased risk of developing diabetes (Kyrrou et al., 2020).

Genetic and Environmental Factors: While genetic predisposition plays a role in the development of type 2 diabetes, environmental factors significantly contribute to its onset. Sedentary lifestyles, unhealthy dietary patterns high in processed foods and sugar, and obesity are key environmental determinants driving the escalating prevalence of the disease (Ali, 2013). Additionally, ethnic background and family history of diabetes significantly influence an individual's susceptibility to developing type 2 diabetes (Adeghate et al., 2006).

In some recent studies T2DM has been shown to have genetic predisposition with the risk of developing insulin resistance or diabetes being two to three times higher for individuals with siblings having T2DM in contrast to the general public (Hemminki et al., 2010). The risk is 30-40% higher in individuals with one parent with diabetes and higher at 70% for those with both parents having diabetes (Meigs et al., 2000). Despite these strong genetic associations environmental factors play a big role in the development of diabetes (Kwak & Park, 2016).

The pathways to β -cell demise and dysfunction are less clearly defined in type 2 diabetes. It is often linked to a strong genetic predisposition or family history in first-

degree relatives, more so than in type 1 diabetes, and in certain racial or ethnic groups (African American, American Indian, Hispanic/Latino, and Asian American)(Meigs et al., 2000).

The associated insulin secretory defects are multifactorial and related to inflammation and metabolic stress, among other causes, including genetic factors(Galicia-Garcia et al., 2020). Insulin resistance, characterized by reduced responsiveness of cells to insulin especially in muscle, liver, and adipose tissue is a key pathophysiological feature of type 2 diabetes. At the same time, pancreatic beta cells struggle to produce enough insulin to compensate for this resistance, resulting in insufficient insulin secretion and worsening hyperglycemia(Courtney & Olefsky, 2023).

Obesity, especially visceral fat, plays a major role in causing insulin resistance and the development of type 2 diabetes(Blüher, 2009). Dysfunction in adipose tissue leads to the release of inflammatory cytokines and adipokines, which further impair insulin action(Kahn et al., 2006). Sedentary lifestyles worsen this condition, as physical activity is essential for maintaining glucose balance and insulin sensitivity. It is also more common in women who have had gestational diabetes mellitus (GDM), as well as in those with hypertension or dyslipidemia(Kim et al., 2002).

Clinical Presentation of Type 2 Diabetes Mellitus.

The progression from normal glucose metabolism through pre-diabetes to overt diabetes is marked by distinct clinical presentations, each carrying significant clinical implications for both individuals and healthcare providers(Elsayed et al., 2023). Understanding the clinical presentation of T2DM from pre-diabetes to advanced stages is essential for timely intervention and effective management. Each stage presents unique opportunities for preventive strategies and tailored interventions

aimed at reducing the risk of complications and improving long-term outcomes for individuals affected by type 2 Diabetes (“2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024,” 2024).

Pre-diabetes: Type 2 diabetes mellitus diagnosis is frequently preceded by a long latent period of pre diabetes and goes undiagnosed for many years because hyperglycemia develops gradually and, at earlier stages, is often not severe enough for the patient to notice the classic diabetes symptoms. Pre-diabetes represents an intermediate stage in the progression towards T2DM and is characterized by higher-than-normal blood glucose levels but not meeting the criteria for diabetes. Clinical indicators of pre-diabetes include impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or elevated HbA1c levels of 5.7–6.4% Clinical presentations of pre-diabetes may include subtle symptoms such as fatigue, increased thirst, and mild weight gain. However, it is often asymptomatic, making routine screening crucial. American Diabetes Association recommends consideration for testing for pre-diabetes and/or T2DM in asymptomatic adults of any age with overweight or obesity and one or more additional risk factors for diabetes (“2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024,” 2024)

The clinical significance of identifying pre-diabetes lies in its role as a precursor to T2DM. Pre-diabetes is also associated with presence of traditional risk factors for cardiovascular disease which include; obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.(Vistisen et al., 2019) Individuals with pre-diabetes are at an increased risk for developing micro-vascular and macro-vascular complications including cardiovascular disease (CVD) due to the long pre-diabetic period and clustering of these risk factors(Drobek et al., 2021).

Pre-diabetes is potentially a reversible state. ADA recommends early interventions at this stage including; lifestyle modifications such as adopting a healthy diet, weight management and increased physical activity to reduce the risk of progression to overt diabetes, potentially revert to normo-glycemia and mitigate this risk of cardiovascular disease(Mai et al., 2021)

Early Stage Type 2 Diabetes: In the early stages of type 2 diabetes, patients may exhibit mild or nonspecific symptoms such as increased thirst, frequent urination, unexplained weight changes, fatigue, and blurred vision(Wilmot & Idris, 2014). However, many individuals might remain asymptomatic during the initial phase, making early detection challenging(Duan et al., 2021). Diagnosis is typically made through routine screening or when patients present with complications associated with sustained elevated blood glucose levels(PIPPITT et al., 2016).

The ADA emphasizes the importance of early diagnosis through regular screenings, especially for individuals with risk factors such as obesity, family history, or sedentary lifestyles. Early diagnosis and intervention in type 2 diabetes are crucial for preventing complications. At this stage, lifestyle changes remain foundational, but pharmacological interventions might also be initiated as per ADA guidelines to achieve glycemic control reduce the risk of cardiovascular events. Regular monitoring of blood glucose levels, blood pressure, lipid profile, and kidney function becomes imperative to prevent or delay the onset of complications. Regular monitoring and patient education are crucial to achieving treatment goals.

Advanced Stage Type 2 Diabetes: As type 2 diabetes progresses, symptoms become more pronounced and complications may arise(Chao & Hirsch, 2018). Clinical presentations may include severe hyperglycemia, recurrent infections, slow wound

healing, and peripheral neuropathy. Patients might also experience severe fatigue, persistent thirst and frequent urination. Additionally, complications such as diabetic retinopathy, nephropathy, and cardiovascular diseases become more prevalent (Maraschin et al., 2025).

The clinical implications of advanced T2DM are profound, with an increased risk of macro-vascular and micro-vascular complications (Farmaki et al., 2020). Intensive glycemic control remains a key focus. ADA recommends a multidisciplinary approach involving healthcare professionals from various specialties and stresses the importance of personalized treatment plans, considering individualized glycemic targets, addressing comorbidities and managing associated complications. Management extends beyond glycemic control to encompass comprehensive care targeting cardiovascular risk reduction, kidney protection, vision preservation, and neuropathy management (Lower Your Risk of Diabetes Complications | ADA, n.d.).

2.3 Screening and Diagnosis of Diabetes

Patients with T2DM may initially be asymptomatic owing to the insidious onset of the disease and for most, the diagnosis is made long after the pre-diabetic phase has elapsed (Duan et al., 2021). Early diagnosis and screening are paramount in reducing morbidity and premature mortality associated with overt diabetes and concomitant complications. The American Association of Clinical Endocrinologists and American College of Endocrinology advocates for screening of diabetes in adults over 35 years or earlier for individuals with risk factors for future diabetes. If the screening test is negative it is repeated at 3-year interval or earlier if symptoms develop or if there is a change in the risk profile for diabetes (Rodbard et al., 2007).

The criteria for the diagnosis of diabetes (Rodbard et al., 2007):

- Fasting blood glucose (Fasting is defined as no caloric intake for at least 8 hours P) equal to or more than 7.0 mmol/L (126mg/dL) **OR**
- 2-hour postprandial glucose test (following ingestion of 75-g glucose load) equal to or more than 11.1 mmol/l (200mg/dl) **OR**
- Patients with classic symptoms of hyperglycemic crisis: Random plasma glucose in symptomatic patient equal to or more that 11.1 mmol/L (200mg/dL)
OR
- A HbA1c level equal to or more than 6.5% (48mmol/L). (Test should be performed in a laboratory using methods that are certified and standardized to the Diabetes Control)

An oral glucose tolerance test (OGTT) is still a crucial diagnostic tool recommended by American Diabetes Association (ADA). During the procedure 75-gram oral glucose load is ingested and two hours later, plasma glucose levels are measured as part of the OGTT, which evaluates the body's capacity to metabolize glucose. It detects abnormalities in glucose metabolism that may not be apparent with fasting glucose or HbA1c tests alone. The test is helpful in also in detecting impaired glucose tolerance (IGT) and diagnosing diabetes. people with borderline or ambiguous fasting glucose readings.

One notable limitation of certain glucose monitoring tests, such as the oral glucose tolerance test (OGTT), is the need for patient preparation, which can be time-consuming and may contribute to poor reproducibility of results. Patients must fast for at least 8 hours and follow specific dietary instructions before the test, which can be inconvenient and challenging to adhere to consistently. Additionally, factors such as stress, illness, or variations in carbohydrate intake prior to testing can affect glucose metabolism, leading to variability in results between tests.

Current ADA guidelines highlight the increasing role of continuous glucose monitoring (CGM) devices for glucose monitoring and potential diagnostic use, especially in type 1 diabetes and insulin-treated type 2 diabetes. CGM provides real-time glucose data, enabling patients and clinicians to detect glycemic excursions, reduce hypoglycemia and hyperglycemia, and improve time-in-range metrics. This leads to better glycemic control, reduced complications, and enhanced quality of life. CGM is recognized not only as a monitoring tool but also as a means to personalize therapy, improve outcomes, and empower patients. Clinicians are encouraged to integrate CGM early and utilize standardized data reporting, including ambulatory glucose profiles and weekly summaries, to facilitate clinical interpretation and optimize treatment decisions.

Although, Continuous Glucose Monitoring (CGM) devices, offer real-time glucose data and reduce the need for frequent finger pricks, proper sensor insertion and site preparation are required. Patients need to clean and prepare the skin area (usually the abdomen or back of the arm) carefully to ensure sensor adhesion and accurate readings. While CGM reduces some burdens of traditional glucose monitoring, it still requires patient education and adherence to device maintenance protocols to optimize accuracy and reliability.

Ongoing studies aim to further validate CGM's benefits in non-insulin-treated T2D populations, including its role in guiding medication adjustments and lifestyle changes. The ADA acknowledges the need for more data but supports CGM use based on emerging evidence and patient-centered care principle. Recent policy changes and pharmacy benefit manager (PBM) coverage expansions are facilitating broader CGM access for T2D patients not on insulin, aligning with ADA's

recommendations. This is expected to increase CGM adoption and integration into routine care.

2.4 Management of Type 2 Diabetes

The major principles for management of diabetes are to improve quality of life, control comorbidities and prevent long-term complications. Diabetes associated complications are often of gradual onset and are largely irreversible. Prevention thus remains the best strategy for management. Important recommended preventive strategies for diabetes mellitus include dietary modification, regular physical exercise, appropriate glycemic control and early appropriate management of complication (Galaviz et al., 2018)

The American Diabetes Association recommend extensive diabetes education on lifestyle modification in prevention of diabetes and concomitant complications for patients at risk or diagnosed with the disease (Rodbard et al., 2007). In a study conducted on patients at risk of developing diabetes under the Diabetes Prevention Program, participants were divided into with one group receiving metformin daily and the other group managed on lifestyle modification with target of 2.5 hours of vigorous exercise every other week to achieve at least 7% reduction in weight. The study illustrated a 58% reduction of incidence of diabetes in the lifestyle modification cohort compared to 31% in the metformin cohort(WC et al., 2002)

Initiating and sustaining lifestyle changes constitute a cornerstone in the prevention of Diabetes Mellitus (DM) and complications. Among these pivotal changes, a reduction in calorie intake emerges as a crucial strategy, especially for individuals with DM, to effectively lower excessive body weight. The significance of this approach lies not only in addressing weight concerns but also in mitigating the risk factors that

contribute to the progression and exacerbation of diabetes (Schulze & Hu, 2005). A dietary pattern that has attracted significant attention for its cardiovascular benefits is the Mediterranean diet. When supplemented with olive oil and/or nuts, this dietary regimen has shown a remarkable ability to reduce the incidence of major cardiovascular events in individuals with DM. Incorporating heart-healthy fats from olive oil and nuts, along with the rich variety of fruits, vegetables, whole grains, and lean proteins typical of the Mediterranean diet, creates a synergistic effect that promotes overall cardiovascular health (Ley et al., 2014).

Regular physical activity such as walking, moderate endurance, and aerobics exercise enhances overall cardiovascular performance and decreases the activation of mechanisms leading to diabetes complications. The use of bariatric surgery to promote weight loss in severely obese T2DM patients has been associated with improved blood pressure control, as well as better cardiovascular and autonomic function. This reduces cardiovascular-related morbidity and mortality (Ma & Han, 2020). However, bariatric surgery has also been linked to autonomic neuropathy in patients who do not receive vitamin B12 supplementation after surgery (Punchai et al., 2017).

Smoking is a risk factor for developing T2DM and increases the risk of developing atherosclerotic cardiovascular disease, microvascular disease, premature death and worsen glycemic control (Chen et al., 2021). Diabetes patients should be informed on these effects of smoking and advised on interventions to support them quit tobacco use (Y. S. Yang & Sohn, 2020)

Strict glycemic control is regarded as an important aspect in preventing chronic complication in patients with T2DM. The American Diabetes Association (ADA) has

recommended adoption of the Diabetes Control Complication Trial standards of tight glycemic control in patients with diabetes notably a peak post prandial plasma glucose level less than 10.0mmol and A1C value of less than 7.0%(Rodríguez-Gutiérrez & Montori, 2016)

Glycemic control with insulin sensitizers such as metformin and thiazolidinediones act significantly to reduce risk of developing complication compared to insulin providing therapies (sulfonylureas, glinides and incretin-related drugs such as dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists). Insulin sensitizers alter body composition, decrease circulating free fatty acid levels and decrease production and action of circulating proinflammatory cytokines.

In some instances, insulin may be beneficial when started early especially if there is continuous weight reduction, hyperglycemia symptoms, HBA1C levels more than 10% (86mmol/mol) or glucose levels >16.7mmol/l(300mg/dl) (Aschner et al., 2020).

Statins are highly effective in preventing complications and reducing mortality, showing a favorable safety profile with few adverse events. Given the increased risk in patients with Diabetes Mellitus (DM), intensive statin therapy is recommended on a personalized, case-by-case basis(Hirano, 2018). Currently, statins remain the primary treatment for lipid lowering in patients with DM. The addition of ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, either with a statin or as an alternative for those with documented statin intolerance, further helps lower low-density lipoprotein cholesterol (LDL-C) levels in patients with DM. This comprehensive approach not only improves LDL-C reduction but also plays a key role in enhancing overall outcomes and decreasing mortality(Sorouch et al., 2024).

For patients with diabetes classified as being very high risk for cardiovascular complication, the recommended target for LDL-C is <1.4 mmol/L (<55 mg/dl), with a minimum LDL-C reduction of 50%. Similarly, for those at high risk for cardiovascular complication the target LDL-C is <1.8 mmol/L(<70 mg/dL), accompanied by a reduction of atleast 50%. In cases where DM patients have a moderate cardiovascular risk, the goal is to achieve an LDL-C target of <2.6 mmol/L (100mg/dL)(Yun et al., 2022). These target values and reduction percentages serve as critical benchmarks in tailoring lipid management strategies to the specific risk profiles of individuals with DM, thereby optimizing their cardiovascular health outcomes(Chait et al., 2024)

The blood pressure (BP) goals is to target systolic BP (SBP) to 130mmHg in patients with diabetes and <130 mmHg if tolerated but not <120 mmHg in older adults(aged >65 years) the SBP range of 130-139mmHg. The diastolic BP (DBP) target is <80 mmHg but not <70 mmHg(Mei et al., 2021). Optimal BP control reduces risk of micro and macro vascular complications. Guidance on lifestyle changes must be provided for patients with DM and hypertension. Evidence strongly supports the inclusion of angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) in patients who are intolerant to ACEI. BP control often requires multiple drug therapy with a renin–angiotensin–aldosterone system (RAAS) blocker, and a calcium channel blocker or diuretic. Dual therapy is recommended as first-line treatment. The combination of an ACEI and an ARB is not recommended(B. Singh et al., 2025). In pre-diabetes, the risk of new onset diabetes is lower with RAAS blockers than with beta-blockers or diuretics. Patients 50 with diabetes on combined antihypertensive treatments should be encouraged to self-monitor BP(W. Wang et al., 2025).

There is evidence that initiating sodium glucose cotransporter 2 (SGLT2) inhibitor and glucagon like peptide (GP1) receptor agonist in T2DM patients reduce cardiogenic risk in patients with at higher risk of developing atherosclerotic cardiovascular disease, heart failure and chronic kidney disease (Bethel et al., 2018). Studies have also shown that Glucagon like peptide (GP1) receptor agonist confers greater efficacy, prolonged effect of treatment, consistent weight loss and decrease risk of hypoglycemia benefit when used with insulin (Maiorino et al., 2017).

Smoking damages endothelial function and increases sympathetic activity. Quitting smoking lowers cardiovascular risk and enhances autonomic balance. Engaging in stress-reduction and mind-body techniques, such as Tai chi, yoga, meditation, and mindfulness, has been shown to improve the quality of life for cardiovascular patients, reduce blood pressure, and decrease sympathetic overdrive. They are believed to enhance parasympathetic activation and may improve autonomic function. Proper sleep hygiene and sufficient restorative sleep improve heart rate variability, reduce sympathetic tone, and promote better autonomic function.

2.5 Complications of diabetes

Diabetes mellitus can cause both acute and long-term devastating and life-threatening complications. The acute disorders of diabetes include hyperosmolar hyperglycemic state, diabetic ketoacidosis, and hypoglycemia (Rodbard et al., 2007). The long-term complications result from metabolic effects on the vasculature and can be classified according to size of blood vessels affected as either “microvascular complications” with small blood vessels affected or “macrovascular complications” with major arteries involved.

The presence of long-term complications of diabetes have been associated with higher morbidity and mortality with most deaths resulting from cardiovascular diseases (Balakumar et al., 2016). Studies have shown that about 90% of patients with diabetes will have at least one complication or comorbidity at the time of diagnosis. In individuals with T2DM, as high as 52% of deaths are due to cardiovascular causes, while figures of 44% have been reported in type 1 diabetes. People with diabetes have a 2- to 6 times increased risk of cardiovascular morbidity and mortality than non-diabetics. When compared to age-matched controls, the cardiovascular mortality rate is much higher in diabetes patients, even those without risk factors like hypertension or hypercholesterolemia.

The macro-vascular complications include coronary artery disease, cerebrovascular disease, and peripheral vascular disease. Microvascular complications commonly involve the eyes, kidney and nerves and are referred to as diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy, respectively. Poor glycemic control, hypertension, obesity, smoking, male gender, dyslipidemia, increasing age and genetic factors have been associated with increased risk of developing these microvascular conditions in diabetes. (Karatas et al., 2018).

2.5.1 Diabetes nephropathy

A third of patients with diabetes have nephropathy and is considered a major cause of end stage renal disease globally (Erek et al., 2007). Diabetic nephropathy is characterized by glomerular hypertrophy, transient hyperfiltration, persistent proteinuria, renal fibrosis and gradual decrease in glomerular filtration rate (Wolf & Ritz, 2003).

According to the American Diabetes Association recommendations, screening for diabetic nephropathy should be carried out in all T2DM patients at diagnosis and annually thereafter (Kowalski et al 2014). The disease has a slow progression and takes 10-20 years for overt clinical symptoms to manifest (Byberg et al., 2021). Diabetes nephropathy can aggravate high blood pressure and cardiovascular disease, and ultimately if untreated can lead to uremia, organ failure, and eventually death.

2.5.2 Diabetic Retinopathy

Another common microvascular complication is diabetes retinopathy, a major cause of preventable blindness among adults aged 20–74 years (Melo et al., 2018). Diabetic retinopathy is characterized by structural changes in the retina which include increased vascular permeability, capillary microaneurysms, capillary degeneration, and excessive formation of new blood vessels. Early in the disease there is intramural pericyte death and thickening of the basement membrane which leads to alteration of the blood-retinal barrier and vascular permeability. As the disease progresses into proliferative phase, ischemia leads to degeneration of capillaries and accumulation of fluid within the retina which contribute to the visual disturbance. Some patients might have severe cases with distortion of retinal architecture, bleeding and detachment of retina (Duh et al., 2017). Several studies have shown that diabetes retinopathy is associated with long duration of disease, persistent hyperglycemia and hypertension (Hong et al., 2021). Early diagnosis and screening diabetic retinopathy can allow timely institution of measures directed at slowing progression of disease.

2.5.3 Diabetic Autonomic Neuropathy

Diabetic neuropathy refers to derangement in the functioning of nerves among individuals living with diabetes mellitus. Patients with T2DM have a higher prevalence at 28% as compared to T1DM at 7% (M. J. Young et al., 1993). The derangement may involve various nerves or groups of nerves notably autonomic nerves, peripheral nerves, cranial nerves and splanchnic nerves among others.

A classification of diabetes neuropathy based on etiology, pathological/topographic features and clinical manifestation was initially presented by Peter Thomas and is still the preferred classification for diabetic neuropathy. It has four main groups(Bodman et al., 2024)

- Rapidly reversible
 - hyperglycemic neuropathy
- Generalized symmetrical polyneuropathies
 - Chronic sensorimotor
 - Acute sensory
 - Autonomic
 - Prediabetic or impaired glucose tolerance neuropathy
- Focal and multifocal neuropathies
 - Cranial
 - Thoracolumbar radiculoneuropathy
 - Focal limb

- Proximal motor (eg, amyotrophy)
- Superimposed chronic inflammatory demyelinating neuropathy

Diabetic autonomic neuropathy, the focus of this thesis, is a form of diffuse neuropathy involving the sympathetic and parasympathetic nerves and is discussed subsequently.

2.6 Prevalence of Autonomic Neuropathy Among Diabetic Patients: global

Diabetic autonomic neuropathy (DAN) is a common long-term complication of diabetes mellitus associated with high morbidity and mortality (Vinik, 1999). The prevalence of autonomic neuropathy among individuals with diabetes varies greatly depending on the population, diagnostic criteria, and diabetes duration. Studies report prevalence rates ranging from 20% and 65% (Spallone et al., 2011; Vinik & Ziegler, 2020).

Cardiovascular autonomic neuropathy (CAN), a well-researched type of DAN, affects approximately 30% of patients with type 1 diabetes and up to 60% of those with type 2 diabetes, depending on disease duration (Pop-Busui et al., 2017). In Oxford, England, a community-based population study on diabetic neuropathy found that 16.7% of participants had autonomic neuropathy as indicated by abnormal heart rate variability testing. A study by Vinik et al., (2007) on the prevalence of cardiac autonomic neuropathy (CAN) among 1171 persons with diabetes conducted in Germany, Austria, and Switzerland revealed a DAN prevalence of 25.3% among the type 1 diabetes group and 34.3% in the type 2 diabetes study group. These patients were found to have abnormal findings in two of the six autonomic function tests conducted (Vinik & Ziegler, 2007). A similar study in North American studies report figures close to 50% in specialized settings (Tesfaye et al., 2020).

2.7 Prevalence of Diabetic Autonomic Neuropathy in Sub-Saharan Africa and Kenya

In sub-Saharan Africa, data on the prevalence of diabetic autonomic neuropathy remain limited due to scarce diagnostic resources and underreporting. However, available studies indicate rising rates of DAN alongside the increasing diabetes burden. A study in Nigeria found that 25.8% of patients with diabetes exhibited symptoms consistent with autonomic dysfunction (Ogunsemi et al., 2019). According to a study in South Africa, the prevalence of autonomic neuropathy was 32% among Africans with insulin-dependent diabetes (Tuch et al., 1994). In Kenya, research specifically focusing on DAN is limited. Kioy et al. conducted a study on 31 diabetes mellitus patients to examine neurological complications of diabetes and found that autonomic neuropathy was present in 15% on clinical examination and 35% on electrophysiological testing. Recent studies on diabetic complications at facilities like Kenyatta National Hospital reveal high levels of undiagnosed neuropathies. These trends indicate a significant, yet often overlooked, burden of DAN in Kenya.

2.7.1 Pathogenesis of Diabetic Autonomic Neuropathy

Several pathophysiological mechanisms are involved in the development of diabetic autonomic neuropathy. These include hyperglycemia, metabolic damage to nerve fibers, neurovascular insufficiency, autoimmune damage, and neuro-hormonal growth factor deficiency mechanisms (Apfel et al., 1994).

Persistent hyperglycemia is a main factor in the pathophysiology of DAN. Hyperglycemia leads to hyperactivity of the polyol pathway, excess formation of advanced glycation end product, increased oxidative stress and free radical production, activation of protein kinase C (PKC), and activation of genes involved in

humoral damage. In addition, hyperglycemia-induced mitochondrial dysfunction and endoplasmic reticulum stress promote reactive oxygen species (ROS) accumulation. The excess ROS interacts with deoxyribonucleic acid (DNA) and proteins causing cellular injury (Yang et al., 2023). This is demonstrated in Figure 1 below.

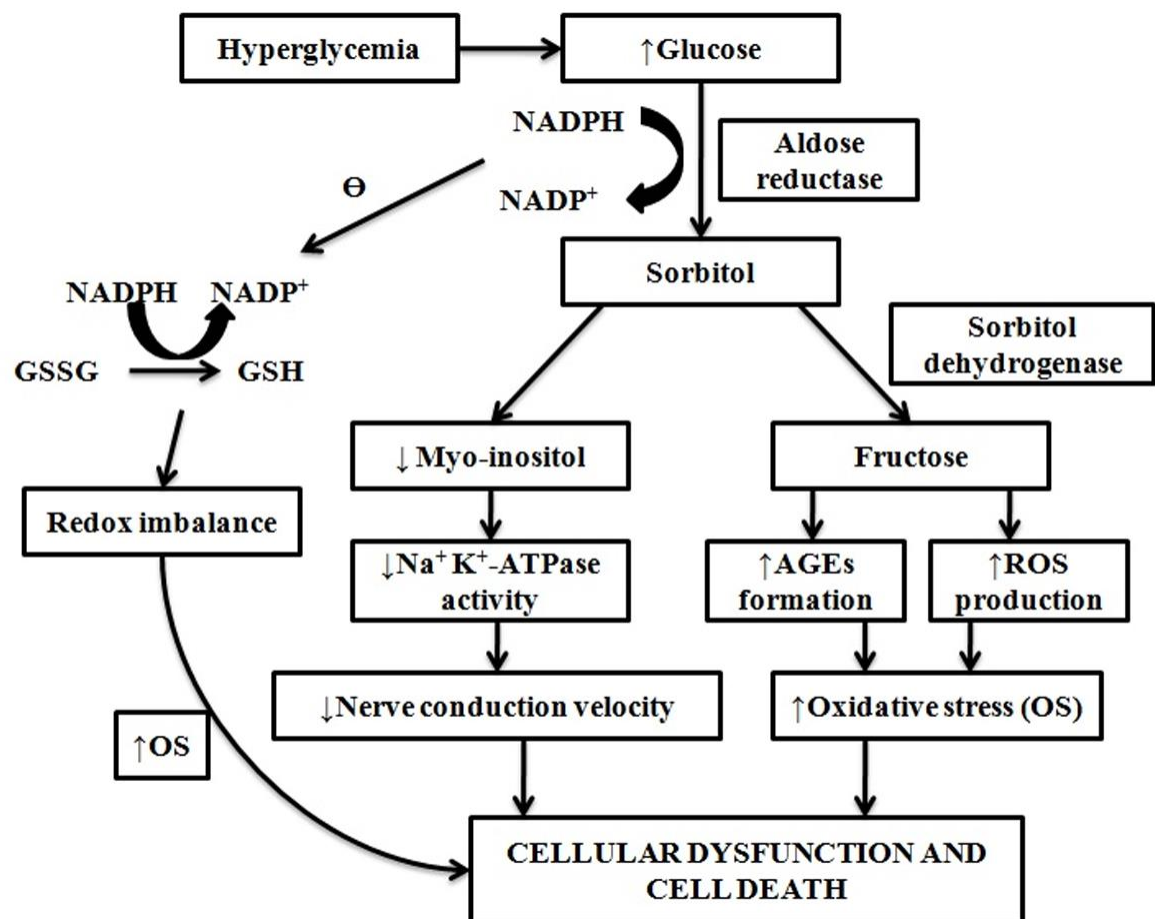


Figure 1: Pathogenesis of Diabetic Autonomic Neuropathy: Polyol Pathway

AGE = advanced glycation end products, ROS = reactive oxygen species, GSH = glutathione, GR = glutathione reductase, GSSG = glutathione disulfide, NADPH = nicotinamide adenine dinucleotide phosphate

Adopted from (Kaur, 2014)

Activation of the Polyol pathways results in a buildup of products such as sorbitol and alteration of NAD:NADH ratio causing decrease in blood supply to nerve and direct nerve damage. The excess ROS also interacts with deoxyribonucleic acid (DNA) and leads to the modification of amino acids. (Low et al., 1997) There is also activation of protein kinase C which induces vasoconstriction and eventually a reduction in neuronal blood flow (Dunlop et al., 2000).

Advance glycation end products are products of a non-enzymatic complex combination of glucose to amino acid particles. These cause disruption in the normal functioning of nerves by interfering with receptor functioning, disrupting enzymatic activity, and altering their molecular conformation (Forbes et al., 2008). Accumulation AGES, reduction of neurotropic growth factors, and deficiency of essential fatty acid in endoneurial blood vessels also cause a reduction of endoneurial blood flow, nerve hypoxic damage and dysfunction (Wada et al., 2005). Other processes may activate poly ADP ribosylation depleting ATP resulting in cell necrosis and activation of genes responsible for neuronal damage (Stefano et al., 2016).

It has also been established that inflammation is also a main factor in the pathogenesis and advancement of DAN. Diabetes and hyperglycemia creates a proinflammatory microenvironment resulting in an increase in circulating pro-inflammatory markers notably cytokine C-reactive protein, interleukin (IL)-6, IL-8, tumor necrosis factor alpha (TNF) and endothelin 1 (Muller et. al., 2002). This subsequent cytokine overproduction, phagocytic cells infiltration and innate immune activation lead to neuronal death and vascular damage.

Studies have shown that patients with DAN have genes that predispose them to oxidative stress and increase risk for neuropathy from oxidative enzymes such as superoxide dismutase, glutathione peroxidase and catalase. (Chen et al., 2023)

2.7.2 Clinical Presentations of Diabetic Autonomic Neuropathy

Diabetic autonomic neuropathy is heterogenous presents with diverse signs and symptoms owing to the several control functions of the autonomic nervous system. This is highlighted below based on the different body systems involved.

2.7.2.1 Cardiovascular Autonomic neuropathy

Cardiovascular autonomic neuropathy (CAN) refers to the damage of nerve fibers that supply the heart and blood vessels resulting in abnormalities in heart rate control and vascular dynamics (Agashe & Petak, 2018). Diabetes associated CAN is a serious complication that affects approximately one third of patients with T2DM resulting in a five-fold rise in risk of developing cardiovascular conditions and associated deaths (AS & H, 2015). Several studies have illustrated varying prevalence and incidences of CAN in diabetes ranging from 1.6% in well controlled patients and 90% in those with poor control and of longer duration of disease (Panackal et al., 2022).

In a study conducted in neighboring Uganda, the prevalence of CAN was shown to be 52.2%. This is comparable to other studies done in middle- and low-income countries that illustrated prevalence ranging between 45% to 60% (Migisha et al., 2020). This prevalence of CAN is much higher compared to recent studies from higher income countries (Canada, United States, Germany and England) that showed an estimated prevalence ranging between 15 to 34% (Jaiswal et al., 2018). These differences in prevalence could be attributed to poorer glycemic control and late diagnosis of diabetes in our setup.

The signs and symptoms of cardiac autonomic neuropathy are varied and include an elevated resting heart rate, orthostatic hypotension and syncope, low exercise tolerance, anesthesia cardiac liability, and silent myocardial ischemia.

Heart rate abnormalities are a common manifestation of CAN. Initially, most patients are asymptomatic with later progression into resting tachycardia (90-130 bpm) then a persistent elevated heart rate often unresponsive to moderate exercise, stress, and sleep (Fisher & Tahrani, 2017). Indeed, Hillis et. al. demonstrated a strong link between resting tachycardia and an increase in the risk of death and cardiovascular complications among T2DM patients (Hillis et al., 2012).

Exercise intolerance in CAN is due to defective sympathetic regulation leading to impaired adjustment of cardiac function to adapt to the exercise demands. Individuals with CAN showed a decreased response in heart rate and blood pressure during exercise (Didangelos et al., 2014). A similar study elucidated lower cardiac output in response to physical exercise in persons with CAN (Khandelwal et al., 2011).

Orthostatic hypotension, another manifestation of CAN, refers to a drop in blood pressure $>20\text{mmHg}$ systolic or $>10\text{mmHg}$ diastolic experienced during postural adjustment (Freeman et al., 2011). Gravity affects blood flow during change of posture from sitting/lying to standing with significant blood pooling the vessels of lower extremities. In healthy individuals their cardiovascular system and autonomic nervous system rapidly responds by adjusting the heart rate and redirecting blood supply from lower limbs and abdomen by causing the vessels to constrict hence maintaining blood pressure to the brain. Damage to the efferent sympathetic vasomotor fibers is associated with orthostatic hypotension in diabetes patients. Patient will often report dizziness, lightheadedness, weakness, fatigue visual

disturbance, and neck discomfort (Shibao et al., 2013). Patients with severe forms of orthostatic hypotension may experience syncopal events due to the severe drop in blood pressure.

Several studies that evaluated the association between CAN and the development of silent myocardial ischemia with the consistent findings of a significant relationship putting individuals with CAN at increased risk for silent myocardial ischemia (Gupta & Pandit, 1992). Sensation of angina is impaired in T2DM patients compared to healthy individuals. The alteration involving myocardial sensory afferent fibers is one of the suggested mechanisms leading to silent myocardial infarction. A comparative study done in India revealed that heart rate variability is reduced in diabetes with silent ischemia when compared to individuals without diabetes with myocardial ischemia (Gupta & Pandit, 1992).

2.7.2.2 Gastrointestinal Autonomic Neuropathy

Gastrointestinal autonomic neuropathy is common in patients with diabetes mellitus compared to the general population with the prevalence of gastrointestinal autonomic neuropathy in patients with diabetes mellitus being as high as 70% in some communities compared to the general population (Maleki et al., 2000). These gastrointestinal symptoms are frequently seen in females compared to males which has been associated with higher psychological stressors in females (B. E. Young et al., 2020). In a community-based study involving more than 1000 persons, symptoms were twice as frequent in those with depression and anxiety (Talley et al., 2001).

Esophageal gastropathy, gastroparesis, diarrhea, constipation, fecal incontinence, and gallbladder atony are common manifestations of gastrointestinal autonomic

neuropathy. Esophageal disturbance is due to abnormal peristalsis and dysfunction of the lower esophageal sphincter and commonly presents with heartburn and dysphagia.

Gastroparesis disorder affects close to 50% of T2DM patients with a 10 year-cumulative frequency of 1% (Wang et al., 2008). It is characterized by delay in gastric emptying of mostly solid food with no apparent mechanical gastric outlet obstruction (von Arnim, 2015). Gastroparesis in diabetes is often asymptomatic although some patients may experience early satiety, anorexia, nausea, vomiting, epigastric discomfort, belching and bloating (Khoo et al., 2009). Hyperglycemia and enteric neuromuscular inflammation and injury are some of the pathophysiological changes seen in gastroparesis (Bharucha et al., 2019).

Diarrhea associated with DAN is present in 20% of diabetes patients and is associated with advance disease (Frías et al., 2016). Diarrhea is caused by dysfunctional motility of the small intestine, overgrowth of microorganisms and disturbance of water and electrolyte transport. This type of diarrhea is intermittent with more than 20 episodes of bowel movements witnessed in a day (Careyva et al., 2016).

Fecal incontinence is also common and is mostly due to impaired anal sphincter tone, abnormal rectal sensation, or impaired external sphincter. Patients with fecal incontinence will report loss of control over the passage of stool or gas emission. This condition is often embarrassing and rarely reported by patients (Alavi et al., 2015).

2.7.2.3 Diabetic Genitourinary Autonomic Neuropathy

Diabetic autonomic neuropathy also affects the genitourinary system resulting in various complications. These conditions include bladder dysfunction, retrograde ejaculation, erectile dysfunction (ED), and dyspareunia (Hill et al., 2008). A study conducted on patients with diabetes revealed that symptoms of genitourinary

dysfunctions may be present in up to 50 percent of patients. The same study highlighted the importance of early diagnosis of genitourinary autonomic dysfunctions because of the potential detrimental effects on renal function (Kebapci et al., 2007).

Diabetes patients often experience early onset and severe urological disorders. Bladder dysfunction in diabetes is due to damage to autonomic afferent bladder innervation which leads to decreased ability to sense a full bladder and infrequent bladder emptying (Al Qurabiy et al., 2022). Symptoms commonly reported include dysuria, frequency, urgency, nocturia, poor stream, hesitancy in initiating micturition, recurrent cystitis, and stress and urge incontinence. These abnormalities increase the individual's risk of recurrent urinary tract infections and overflow incontinence (Lin et al., 2012).

Erectile dysfunction (ED) is the inconsistent inability to attain and sustain an erection sufficient for sexual intercourse. Studies have shown that ED is the more prevalent sexual dysfunction in T2DM males aged above 40 years (Kouidrat et al., 2017). A large comparative study involving men aged 53-90 with and without diabetes demonstrated a strong association between diabetes and ED. In yet another similar study, there was a fourfold increase in ED in diabetes patients compared to healthy individuals (Yafi et al., 2016).

Pathogenesis of Diabetes associated ED complex and result from atherosclerosis and changes in the corporal erectile tissue. Proposed mechanisms leading to ED include smooth muscle degeneration, abnormal collagen deposition, endothelial cell dysfunction and dysfunction of autonomic neurotransmission control involving the cavernosal and detrusor smooth muscle of the penile shaft (Pop-Busui et al., 2015).

In addition to T2DM, age, dyslipidemia, hypertension, cardiovascular disease, obesity, metabolic syndrome, lack of exercise, and smoking increase the risk of ED (Defeudis et al., 2022). Erectile dysfunction is also common in individuals with underlying vascular disease, endocrine disorders, psychogenic disturbance, and poor nutrition. Moreover, it is a strong predictor of poor quality of life among males with diabetes (Nutalapati et al., 2020).

Sexual dysfunction is also seen commonly in diabetes females with metabolic syndrome, dyslipidemia, and advanced age. The common manifestations include decreased sexual desire and dyspareunia (Imprialos et al., 2021).

2.7.2.4 Peripheral Sudomotor and Vasomotor Neuropathy

Sudomotor dysfunction refers to damage to the small unmyelinated C-fibers that innervate sweat glands and is often an early sign of diabetic autonomic neuropathy. Sudomotor dysfunction is commonly observed in prediabetic stages and manifests before large fiber neuropathy. It results from hyperglycemia-induced metabolic and vascular insults, leading to degeneration of sudomotor fibers, decreased sweating, and dry skin. Patients with sudomotor neuropathy are at increased risk for infections, diabetic foot ulcers, and fissures due to decreased sweating, which also impairs thermoregulation and skin hydration. The gold standard for diagnosing sudomotor dysfunction is skin punch biopsy, but its routine use is limited by its invasiveness (Sun et al., 2006).

The Vasomotor neuropathy is characterized by abnormal vasoconstriction or vasodilation in peripheral arteries due to autonomic nerve dysfunction that affects vascular smooth muscle regulation. Recent research shows that diabetic neuropathy causes medium-sized arteries, such as the brachial artery, to have impaired

sympathetic vasoconstriction, which leads to paradoxical vasodilation when sympathetic stimulation occurs. Tissue perfusion and blood flow control are compromised by this lack of natural vasoconstriction. Clinical Manifestations: Patients may experience changes in skin color, warmth, and increased vulnerability to ischemic damage. These anomalies can cause delays in wound healing and microvascular problems(Y. Yang et al., 2025).

2.7.3 Screening and Diagnosis of Diabetic Autonomic Neuropathy

The American Diabetes Association advocates for screening of DAN at diagnosis of T2DM. The screening process should incorporate both history and physical examination to elicit signs and symptoms of autonomic neuropathy. Patients who have positive signs and symptoms may need further tests to assess autonomic neuropathy. If the initial screening is unremarkable at the initial encounter, it should be repeated annually (Elsayed et al., 2023).

Several tests, some dating back to the early twentieth century, have been developed to identify, assess distribution, and degree of autonomic dysfunction. Over time collaborations involving the American Autonomic Society, the International Society for Autonomic Neuroscience, the European Federation of Autonomic Societies, and the American Academy of Neurology, among others have worked to standardize approaches to autonomic testing (Rukadikar et al., 2023).

Standardized diagnostic tools such as cardiovascular autonomic reflex tests (CARTs), heart rate variability (HRV) analysis, sudomotor function tests, gastric emptying studies, and urodynamic assessments remain the gold standard for evaluating the diverse components of autonomic dysfunction. These methods offer objective, quantifiable insights into cardiac, gastrointestinal, sudomotor, and genitourinary

autonomic regulation—information that is essential for identifying both early and advanced stages of diabetic autonomic neuropathy. Their ability to detect subtle abnormalities before symptoms appear makes them particularly valuable for guiding timely interventions and preventing long-term complications.

Despite their diagnostic utility, these specialized procedures demand considerable resources. They require advanced equipment, stable power supply, dedicated testing rooms, and personnel trained in autonomic physiology elements that are often limited or entirely lacking in low-resource healthcare settings. In many regions, including sub-Saharan Africa, health systems face chronic shortages of diagnostic technology and skilled staff. High patient volumes and limited consultation time further constrain the incorporation of objective autonomic testing into routine diabetes care. As a result, these gold standard tests remain underutilized, perpetuating reliance on alternatives.

Given these constraints, clinicians frequently depend on symptom-based questionnaires and clinical history to evaluate autonomic dysfunction. However, subjective tools alone are inherently limited in their ability to detect early-stage or asymptomatic DAN. Instruments such as the COMPASS-31 questionnaire, though validated and practical, rely entirely on patient self-reporting. Their accuracy is influenced by a patient's ability to understand, recall, and interpret symptoms—factors that vary widely with health literacy, cultural beliefs, emotional state, and comorbid psychological conditions. Symptoms such as dizziness, palpitations, sweating abnormalities, or gastrointestinal disturbances may also overlap with other diseases or medication side effects, further obscuring diagnostic clarity.

The diagnosis of DAN is further complicated by substantial variability in the tools and criteria used across studies and clinical settings. Differences in test combinations,

scoring systems, threshold values, and interpretation methods contribute to inconsistent definitions of DAN and wide disparities in reported prevalence. This heterogeneity makes it difficult to compare findings across populations or develop standardized screening guidelines. Collectively, these diagnostic gaps underscore the urgent need for integrated, context-appropriate diagnostic algorithms that combine both subjective and objective assessments, prioritize early detection, and are adaptable to resource-limited environments. Strengthening diagnostic capacity is essential for improving recognition and management of DAN and ultimately reducing diabetes-related morbidity and mortality.

Most of the recommended clinically available tests assess end-organ response to physiological stimuli because the autonomic nervous system is inaccessible to direct physiological testing. These autonomic function assessment tests can be done at the bedside using: a battery of cardiovascular reflex tests; the heart rate variability (HRV) with deep breathing; Valsalva ratio; 30-15th ratio; and

Cardiovascular Reflex Test: This test involves deep breathing and lying-to-standing assessments. The heart rate response to deep breathing (delta heart rate and expiration-to-inspiration ratio) and to standing (30: 15 ratio) reflect parasympathetic activity, while systolic blood pressure response to standing is also measured. During the procedures, an ECG in lead II and respiratory tracings are recorded to monitor heart rate and respiration, respectively. Automated blood pressure monitoring is also performed.

Deep Breathing Test (DBT): The patient sits quietly and is instructed to breathe smoothly, slowly, and deeply at a rate of 6 breaths per minute (5 seconds inhaling and 5 seconds exhaling). This pace produces maximum heart rate variation. Heart rate is

then measured from the ECG. The delta heart rate is typically the difference between the highest and lowest heart rates during inspiration and expiration, averaged over 6 cycles. The expiration-to-inspiration ratio is calculated as the ratio of the longest R- R interval during expiration to the shortest R- R interval during inspiration, averaged over 6 cycles.

Lying- to- Standing Test (LST): Heart rate and blood pressure responses to standing are recorded. The subject is instructed to stand within 3 seconds, and blood pressure and heart rate are measured at baseline and at 0.5, 1, 2, and 4 minutes after standing. The 30: 15 ratio is calculated as the ratio between the longest R- R interval at or around the 30th beat and the shortest R- R interval at or around the 15th beat. The difference between systolic blood pressure at rest and the lowest systolic blood pressure after standing is also measured.

Gastric emptying scintigraphy involves ingesting a radio- labeled standardized meal, with images taken while the patient is positioned in the supine position on a dual-head gamma camera. A series of images are captured at 0,30,60,120, and 180 minutes, with no other meals consumed during the study. According to new studies on the gut-brain axis, altering the gut microbiota with food, probiotics, and prebiotics may have an impact on autonomic function. Changes in the gut flora may provide biomarkers that are new indications of autonomic nerve health and treatment responsiveness.

Other tests are system-specific and include Isotope-based breath test, pupillometry for pupillary autonomic function testing and quantitative sudomotor axon reflex testing (QSART) which can be used for the detection of peripheral sympathetic denervation in patients with suspected peripheral sudomotor and vasomotor neuropathy;

urodynamic studies and assessment of post void volume for patients with genitourinary dysfunction.

Corneal confocal microscopy (CCM), an emerging imaging technique, is non-invasive with better sensitivity on identification of tiny fiber damage associated with autonomic neuropathy. As an early indicator of neuropathy, CCM may measure the density and shape of corneal nerve fibers. The scalability and consistency of diagnosis might be enhanced by more automation and standardization of this imaging analysis.

Conventional AFT setups involve large, stationary devices that are costly to acquire and maintain, making them mostly available in specialized centers or research settings. Tests often require attaching electrodes or chest belts, performing maneuvers like deep breathing, Valsalva, or tilt-table testing, and careful timing, all of which demand trained personnel and patient cooperation. The preparation, test execution, and manual data analysis prolong examination times, increasing costs and reducing patient throughput. Because of these factors, routine autonomic testing is rarely performed outside specialized clinics, despite recommendations for regular screening in diabetic populations.

Several advances are addressing these limitations. First, several studies have validated small, portable devices that measure heart rate variability (HRV) and autonomic responses with accuracy comparable to standard equipment. These devices enable point-of-care, bedside testing with minimal setup and shorter duration, facilitating broader screening for diabetic autonomic neuropathy (DAN). In addition, modern autonomic testing systems offer automated protocols, easy-to-interpret reports, and require less operator expertise, reducing barriers to implementation in primary care and outpatient settings. There are also Comprehensive systems that combine

cardiovagal, sudomotor, and adrenergic assessments with software-guided testing protocols, improving efficiency and standardization.

This has necessitated the development of symptom-based questionnaires as surrogate tools. In 1999, Prof. Phillip Low and colleagues at Mayo Clinic developed the 169-item autonomic symptom profile (ASP) questionnaire. Subsequently, 85 questions from ASP were carefully selected to produce the composite autonomic symptom score (COMPASS). To further increase utility, Singer and colleagues further refined COMPASS to a 31-item, questionnaire named (COMPASS 31) which is a simple, effective, and easy-to-use tool (Singh et al., 2019).

The Composite Autonomic Symptom Score 31 (COMPASS 31) is a validated questionnaire quantifying the severity and distribution of autonomic symptoms across six domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor function by scoring 31 clinically selected questions. The raw score for each domain is then calculated by aggregating the scores of the individual questions. The weighted score is then obtained by multiplying the raw values by a weighting factor unique to each domain. The overall score, which ranges from 0 to 100, is then calculated by adding the individual weighted scores; the greater the score, the more severe the symptoms. It was developed to detect and quantify the degree of autonomic failure, monitor disease progression and evaluate response to treatment (Greco et al., 2017).

COMPASS 31 has been successfully used in multiple clinical research settings to screen for and quantify autonomic symptom burden in diabetic populations, with reasonable diagnostic accuracy especially for established cardiovascular autonomic neuropathy and diabetic polyneuropathy. It is validated in diverse diabetes types and

correlates well with established autonomic function tests, offering a practical, time-efficient, and reliable patient-reported measure for DAN assessment.

Several studies have been conducted to assess the validity and reliability of the COMPASS 31 tool in different setups. In a cross-sectional study done in India that enrolled 60 T2DM patients, autonomic dysfunction was illustrated using COMPASS 31 as well as by the standard Ewing's Battery of tests. The study eluded that the COMPASS 31 tool qualifies as an acceptable screening tool for definite CAN (R. Singh et al., 2019).

COMPASS 31 scores were considerably higher in people with CAN and diabetic polyneuropathy (DPN) than in people without these conditions, according to a clinic-based Italian study including 73 diabetes patients. Neuropathy symptoms and signs and cardiovascular reflex test findings showed a moderate correlation with the overall score, indicating a fair diagnosis accuracy for DPN (AUC ~0.74) and CAN (AUC ~0.75). Reasonable sensitivity and specificity were offered by cut-off scores in the range of 16–17. COMPASS 31 Questionnaire was acknowledged as a user-friendly, quantitative measure for assessing autonomic symptoms in diabetes and shown strong internal consistency (Cronbach's $\alpha = 0.73$) (D'Amato et al., 2020).

Studies employing the Norwegian version found that individuals with longstanding diabetes had considerably higher COMPASS 31 scores than those with early diabetes or controls, particularly in the gastrointestinal domain. The COMPASS 31 tool has also been put in use for the assessment of the autonomic nervous system in individuals with multiple sclerosis, Parkinson's disease, fibromyalgia, and COVID-19 (Peng et al., 2021).

The COMPASS-31 questionnaire is a subjective, symptom-based tool that relies on patient self-report, which may be influenced by recall bias, health literacy, interpretation. Its non-specific symptoms and predetermined domain weights may overestimate autonomic dysfunction, while early or subclinical DAN can be missed. Additionally, COMPASS-31 does not provide direct physiological measurements, limiting objective quantification of autonomic impairment summarized

The survey of Autonomic Symptom (SAS) is another instrument that has been developed for assessment of the presence and severity of autonomic neuropathy. It has 11 items in women and 12 items in men and assesses for orthostatic, sudomotor, vasomotor, gastrointestinal, urinary and sexual dysfunction with each domain rated by an impact score ranging from 1(least severe) to 5(most severe). The SAS tool has been tested in several observational studies and compared to other validated autonomic scale, Autonomic Symptom Profile (ASP) and it has shown a high sensitivity and specificity (Zilliox et al., 2011).

2.7.4 Management of Diabetic Autonomic Neuropathy

Diabetic autonomic neuropathy in T2DM is irreversible and management is directed towards prevention, delaying progression of disease, alleviation of symptoms and improving quality of life (Vinik et al., 2013). Antihyperglycemics such as sulfonylureas, GLP1 agonist, and thiazolidinediones have been shown to be of benefit in patients with DAN. In contrast, metformin, a commonly used antihyperglycemic may worsen nerve damage because of its effect on vitamin B12 absorption(R. Yang et al., 2023).

Management of patients with CAN involves prevention of disease progression, treatment of associated morbidity and complications with the aim of improving

quality of life. Orthostatic hypotension can initially be managed by lifestyle and behavioral measures such as standing upright slowly, elevating head of bed and flexing hands and feet before standing (Kim et al., 2022). Commonly used medication for treatment of orthostatic hypotension includes alpha adrenoreceptor agonist like midodrine, norepinephrine prodrug (droxidopa) and somatostatin analogue (octreotide) (Palma et al., 2020).

Patients with silent myocardial infarcts require secondary prevention of underlying cardiovascular disease. These measures include lifestyle modification; heart healthy diet, regular exercise, weight loss in obese and overweight, smoking cessation, antiplatelet therapy with aspirin, lipid lowering therapy with statins and control of comorbidities like hypertension (Hritani et al., 2023) . Moreover, those with confirmed coronary heart disease should be treated with beta blockers in combination with calcium channel blockers or long-acting nitrates (Perings et al., 2016).

Diabetes patients with symptomatic gastropathy are initially advised on lifestyle modifications which include adequate fluid intake, high fiber low fat diet, small frequent feeding, avoiding carbonated drinks, cessation of alcohol and cigarette use. In addition, pharmacological therapy consisting of antiemetic and prokinetics can be prescribed. Several prokinetic agents have been recommended which comprise of itopride, metoclopramide, erythromycin and domperidone commonly used because of its central and peripheral effect. In patients with refractory symptoms gastrotomy tube for intermittent decompression by suction may be beneficial (Bharucha et al., 2019). Histamine 2 receptor antagonist(H2RA) and proton pump inhibitors (PPI) are the mainstay treatment options for GERD in diabetes. Management of diabetic diarrhea is mainly centered on stopping diarrhea using anti-diarrheal agents, and correction of electrolyte imbalance and nutrient deficiencies. Antibiotics use is only recommended

when there is concomitant infections or bacterial overgrowth(Adike & DiBaise, 2018).

First line treatment for ED are oral phosphodiesterase type 5 (PDE5) inhibitors which include sildenafil, tadalafil, and vardenafil. Studies have shown that sildenafil is safe and effective in patients with diabetes mellitus, spinal cord injury and men with ED associated with antidepressants therapy (Schultheiss et al., 2003). In addition, testosterone supplementation has also been proven to be beneficial in patients with ED associated with hypogonadism and helps improve sexual function and libido (Tsametis et al., 2018).

The second line therapeutic options for treatment of ED includes intra-cavernosal self-administration of alprostadil and Vacuum pump devices. In instances when first and second-line therapies have failed, surgical implantation of an inflatable penile prosthesis or penile revascularization can be considered (Lima et al., 2021).

Treatment of sudomotor and vasomotor autonomic neuropathy is supportive, patients are advised on lifestyle modification which can help improve symptoms. It is recommended that patients who are experiencing sweating issues such as excessive or absent perspiration, be advised to avoid situations that make their symptoms worse. They may also benefit from taking medicines or strong antiperspirants to treat excessive perspiration. In extreme situations, procedures can be done to surgically remove the sweat glands or remove their nerves may be considered (Akbar et al., 2023).

2.7.5 Diabetic Autonomic Neuropathy and Associated Risk Factors

2.7.5.1 Glycemic Control and Diabetic Autonomic Neuropathy

Glycemic control refers to the optimal glucose serum glucose concentration in patients with diabetes. This can be evaluated in T2DM patients using glycosylated hemoglobin (HbA1c), fasting blood glucose (FBS) and postprandial glucose (PPG) (Bin Rakhis et al., 2022). Glycosylated hemoglobin (HbA1c) reflects the average blood glucose levels over a period of two to three months. It is considered the gold standard test commonly used to determining glycemic control owing to its high predictive value, convenience, and its robustness against time of day or feeding state (Juarez et al., 2014).

There is enough evidence that acute fluctuation in blood sugar could play a role in the pathogenesis of diabetes related chronic complications. Hence diabetes management strategies should not be considering the HbA1c alone but should also take into account glycemic variability. Recently, several studies have recommended the use of PPG (either as an isolated value or as a component of glycemic variability) as a more precise test to determine the glycemic control in patients with T2DM (Flores-Fernandez et al., 2017).

Poor glycemic control increases the risk of diabetic autonomic neuropathy through several interrelated mechanisms, as supported by extensive literature: These mechanisms include

Metabolic and Molecular Pathways Activation: Chronic hyperglycemia triggers the formation of advanced glycation end-products (AGEs), activates the polyol pathway, and stimulates protein kinase C (PKC) signaling. These metabolic disturbances directly damage autonomic neurons and impair nerve

function. The “metabolic memory” phenomenon means that early periods of poor glycemic control cause lasting nerve damage, even if glucose levels improve later.

Oxidative Stress and Endothelial Dysfunction: Elevated glucose levels increase reactive oxygen species (ROS) production, causing oxidative stress that injures autonomic neurons and Schwann cells. This oxidative damage impairs endothelial function, reducing nitric oxide (NO) bioavailability and leading to microvascular dysfunction, which compromises blood flow to autonomic nerves and exacerbates ischemic injury.

Microcirculation Impairment: Hyperglycemia-induced endothelial dysfunction impairs the vasa nervorum microcirculation supplying autonomic fibers. Ischemia from reduced blood flow promotes neuronal apoptosis and axonal degeneration, key pathological features of CAN.

Neuronal Apoptosis and Axonal Degeneration: The combined effects of metabolic abnormalities, oxidative stress, and ischemia induce programmed cell death and degeneration of autonomic nerve fibers, leading to progressive loss of cardiovascular autonomic regulation.

Autonomic Imbalance and Functional Impairment: Poor glycemic control is associated with reduced heart rate variability (HRV), resting tachycardia, prolonged QTc intervals, and orthostatic hypotension. These reflect parasympathetic withdrawal and sympathetic overactivity, increasing arrhythmia and sudden cardiac death risk.

Glycemic Variability (GV): Beyond average glucose levels, fluctuations in blood glucose (GV) exacerbate oxidative stress and endothelial dysfunction,

further damaging autonomic nerves. GV correlates with the severity of CAN in both type 1 and type 2 diabetes, acting as an independent risk factor.

Cardiovascular Risk Factors: Hyperglycemia often coexists with hypertension, dyslipidemia, and obesity, which synergistically worsen autonomic nerve damage. Multifactorial interventions addressing glycemic control and these comorbidities are more effective in slowing CAN progression, especially in type 2 diabetes.

Glycemic control targets in the management of diabetes should be guided by the patient's age, underlying comorbidities, current complications, and risk of hypoglycemia (Williams et al., 2022). Several studies have suggested that both patient and healthcare provider factors are likely to influence the level of glycemic control in patients with diabetes. Age, duration of diabetes, level of education, monthly income, occupation, presence of comorbidities, frequency of clinic visits, diabetes-related complications, type of medications, insulin therapy, adherence, and self-monitoring practice influence glycemic control (Meseret et al., 2022).

In the United Kingdom Prospective Diabetes Study (UKPDS), a group of patients was followed up for 10 years, the results showed a decrease in HBA1c from 63mmol/l (7.9%) to 53mmol/l (7.0%) resulting in a 25% decrease in risk for microvascular complications (Matthews et al., 2004). The Diabetes Interventions and Complications (EDIC) study established an intensive glucose control leading to reduction in incidence and slowing of progression of autonomic neuropathy in T2DM

Metformin is still the recommended first line of treatment because of its effectiveness, safety, affordability, and shown ability to lower microvascular complications, metformin is still the recommended first line of treatment. Regardless of A1C level or

metformin usage, SGLT2 inhibitors and/or GLP-1 receptor agonists (GLP-1 RAs) with proven cardiovascular and renal advantages are advised for patients with established atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), or chronic kidney disease (CKD). These medications lower the risk of heart failure hospitalization, major adverse cardiovascular events (MACE), and renal disease progression. Beyond glycemic management, GLP-1 RAs may still have cardiovascular benefits in those with a decreased risk of ASCVD

2.7.5.2 Dyslipidemia and Diabetic Autonomic Neuropathy

Abnormalities in the metabolism of lipids are a significant contributor to development of diabetic autonomic neuropathy (Al-Ani et al., 2011). Increased triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C) are common symptoms of dyslipidemia in diabetes. Elevated TG and LDL levels have been correlated with worsening nerve conduction velocity and amplitude, indicating more severe nerve damage (Yun et al., 2022)

Dyslipidemia contributes to nerve damage in diabetes through multiple interrelated mechanisms, primarily involving metabolic, vascular, and inflammatory pathways:

Oxidative Stress and Mitochondrial Dysfunction: Elevated lipids, especially oxidized LDL (ox-LDL) and triglycerides, increase oxidative stress in peripheral nerves and dorsal root ganglia neurons by generating reactive oxygen species (ROS). Oxidative stress damages mitochondrial function, leading to energy deficits in neurons, impaired axonal transport, and eventual nerve degeneration.

Microvascular Ischemia and Endothelial Dysfunction: Dyslipidemia promotes endothelial dysfunction and reduces capillary blood flow to nerves,

causing ischemia and hypoxia. Lipid-induced microvascular damage compromises the blood-nerve barrier, exacerbating nerve fiber injury and impairing repair mechanisms.

Inflammation and Cytokine Secretion: Oxidized lipids stimulate inflammatory pathways, increasing cytokine release and endoplasmic reticulum (ER) stress in nerve-supporting cells such as Schwann cells and pericytes. This inflammation contributes to nerve fiber apoptosis and demyelination.

Impaired Lipid Supply for Nerve Repair: Cholesterol is essential for myelin sheath integrity and axonal regeneration. Lowered circulating lipoproteins (HDL, LDL) due to dyslipidemia or lipid-lowering therapy may reduce cholesterol availability to regenerating neurites and Schwann cells, impairing remyelination and nerve repair. This can paradoxically worsen neuropathy despite lipid lowering.

Advanced Glycation End Products (AGEs): Dyslipidemia, combined with hyperglycemia, enhances the formation of AGEs that cross-link proteins and lipids in nerves, disrupting normal function and promoting stiffness and damage.

Several studies report a significant association between dyslipidemia and diabetic neuropathy. For instance, Al-Azhar University research demonstrated that patients with diabetic neuropathy and concurrent dyslipidemia had more severe neurophysiological impairments in nerve conduction studies compared to those without dyslipidemia (Ali et al., 2021).

A cross-sectional study evaluating 548 T2DM patients for metabolic syndrome concluded that patients with dyslipidemia are twice as likely to have diabetic

neuropathy (Isomaa et al., 2001). Several studies have also confirmed that there is an established correlation between high TG and low HDL-C levels with diabetic neuropathy (Hua et al., 2019). However, variable findings correlate diabetic neuropathy and other serum lipid components such as total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) (Jende et al., 2019).

Another recent study from India that included 100 diabetic patients with diabetic neuropathy found that dyslipidemia was very common (88% hypertriglyceridemia, 90% elevated LDL). However, while trends were noted, there was no statistically significant correlations between lipid parameters and the type or severity of neuropathy. This implies that although dyslipidemia is prevalent in DAN, its precise effect on nerve conduction may differ or need further research to verify (Vikhe et al., 2025).

Other recent studies have also illustrated conflicting reports on the effect of dyslipidemia on diabetic neuropathy. A Taiwanese study involving over 2,400 patients with T2DM diabetes reported no significant association between hyperlipidemia or lipid-lowering therapy and diabetic neuropathy, suggesting that other factors may modulate this relationship in different populations (Chang et al., 2023).

Statin use in diabetic autonomic neuropathy (DAN) presents a complex picture with evidence supporting both potential beneficial and adverse effects on autonomic nerve function. Statins, particularly lipophilic types i.e simvastatin and atorvastatin, have been shown to improve autonomic circulatory regulation by reducing oxidative stress and inflammation in central nervous system regions controlling sympathetic and parasympathetic activity (Zhang et al., 2024). This leads to decreased sympathetic

outflow and potentially improved heart rate variability (HRV), which is often impaired in DAN. Statins exhibit anti-inflammatory, antioxidant, and endothelial function-enhancing properties. These effects may help curb the progression of cardiac autonomic neuropathy (CAN) by improving vascular health and reducing insulin resistance (Millar & Flo, 2014). Clinical studies also report reductions in muscle sympathetic nerve activity (MSNA) of 12–30% with statin therapy in patients with cardiovascular risk factors, which may translate to improved autonomic balance in diabetes (Deo et al., 2012).

Despite these proven benefits of statin use, there are case reports and observational studies linking statin use to the development of peripheral neuropathy, including sensory, motor, and autonomic fibers (Emad et al., 2018). Interestingly, symptoms often improve or resolve upon discontinuation of the statins. A study found that statin users had reduced epidermal and sweat gland nerve fiber densities at proximal sites, suggesting statin-associated small fiber sensory and autonomic ganglionopathy (Novak et al., 2015). However, symptom scales and autonomic testing outcomes were not significantly different from non-users, indicating subclinical nerve fiber degeneration. Additionally, statins may disrupt cholesterol synthesis, which is critical for maintaining cell membrane integrity in nerves, potentially affecting nerve function. Idiosyncratic immune-mediated mechanisms have also been proposed (Ward et al., 2019).

2.7.5.3 Age of Patient and Diabetic Autonomic Neuropathy

Patients' age is a critical factor in the management of diabetes as those with advanced age have a higher risk of early death, functional disability, hastened muscle loss, comorbidities, and other geriatric complications (Cesari et al., 2017). Existing guidelines highlight the importance of accurate and timely identification of diabetes associated complications in older adults and addressing them.

Age acts as an independent risk factor for diabetic autonomic neuropathy (DAN) due to several biological and physiological changes that increase vulnerability of autonomic nerves to damage, beyond the effects of diabetes duration or glycemic control. These include:

Metabolic and vascular damage: Aging is associated with progressive microvascular alterations, increased oxidative stress, and accumulation of advanced glycation end-products (AGEs), all of which impair nerve function and promote autonomic nerve injury over time. These processes are exacerbated by diabetes but also occur independently with aging.

Oxidative stress and impaired antioxidant: Older individuals have a reduced capacity to neutralize reactive oxygen and nitrogen species, leading to enhanced oxidative damage to autonomic neurons and supporting cells, accelerating neuropathy development.

Microvascular dysfunction: Age-related endothelial dysfunction diminishes blood flow and nutrient delivery to autonomic nerves, impairing nerve repair and survival, thus increasing susceptibility to neuropathy.

Regeneration and repair of nerves: Aging reduces the regenerative capacity of peripheral and autonomic nerves, making recovery from metabolic insults less effective and neuropathy more likely.

Autonomic nervous system structure and function: Normal aging leads to decreased parasympathetic activity and altered sympathetic responses, compounding diabetes-induced autonomic imbalance and increasing neuropathy risk.

Chronic low-grade inflammation: Aging is associated with a pro-inflammatory milieu that interacts with diabetes-related inflammation, further damaging autonomic nerves.

Diagnostic challenges: Age-related changes in nerve conduction and autonomic function tests require age-adjusted reference values, but overlapping effects of aging and diabetes complicate early detection and management.

Large cohort studies such as the DCCT/EDIC have identified older age as one of the strongest risk factors for both diabetic peripheral neuropathy and cardiovascular autonomic neuropathy (CAN), alongside poor glycemic control and longer diabetes duration. Importantly, autonomic nerve function declines with age even in non-diabetics, and young diabetics may exhibit autonomic impairment comparable to older non-diabetics, highlighting the additive effect of age and diabetes.

According to a study published by the IDF, approximately 23% of adults diagnosed with T2DM are aged sixty-five years and older (Yakaryılmaz & Öztürk, 2017). Older adults with diabetes often fail to adhere to prescribed treatment plans because of many factors: frailty, depression, cognitive impairment and polypharmacy. This may affect

diabetes self-management and increases their risk of developing complications including diabetic autonomic neuropathy (Cesari et al., 2022).

A study conducted in Europe assessed age as an independent risk factor for developing neuropathy on ambulatory T2DM patients. It revealed that the odds for developing diabetes neuropathy increased by 11.2% with every 1 years increase in patient's age. The same study revealed that diabetes neuropathy is more common among elderly patients (Popescu et al., 2016). However, multiple studies have shown that routine evaluation of DAN in older T2DM individuals is difficult due to other confounding factors associated with age related changes affecting the nervous system. Most standard tests on diabetic neuropathy are based on nerve conduction studies, perception of vibration threshold and assessment of autonomic neuropathy; hence reference values are likely to be influenced significantly by age and may need age adjusted reference interval on interpretation of findings (Belmin et al., 2012).

2.7.5.4 Duration of Disease and Diabetes Autonomic Neuropathy

The onset of neuropathy in diabetes correlates positively with the duration of diabetes, with a prevalence of approximately 8% at diagnosis and greater than 50% in longstanding disease (Deli et al., 2014). This is owing to increased exposure to glycosylation end products, metabolic dysfunction, and endothelial damage (Nishikawa et al., 2000). In a study by Oguejiofor et al., the prevalence of polyneuropathy was lower in those with diabetes for less than 5 years and higher in those with diabetes for more than 15 years. Another study in UK showed that neuropathy was evident in 36% of patients with diabetes for more than 10 years as compared to 20% when duration was only 6 years (M. J. Young et al., 1993). However, the risk of diabetes associated microvascular complication was reduced in

older T2DM individuals with longer duration of disease compared to younger persons with longer duration of disease (Zoungas et al., 2014)

2.7.5.5 Hypertension and Diabetes Autonomic Neuropathy

Hypertension is a leading modifiable independent risk factor for the development of diabetic neuropathy (Sethi et al., 2023). Hypertension mostly affects the myelinated fibers leading to decrease blood supply via a loss of myogenic tone and vascular hypertrophy (Shen et al., 2017). Some studies have also suggested that autonomic neuropathy may present as sustained arterial hypertension, tachycardia, and neuropathic pain in the extremities owing to a hyperactivity of the sympathetic nervous system and not necessarily an inactivation of the parasympathetic system (McDougall & McLeod, 1996).

The key mechanisms linking diabetic autonomic neuropathy (DAN) to hypertension include:

Autonomic imbalance and excessive sympathetic overactivity: Early in DAN, sympathetic predominance results from selective injury to parasympathetic fibers, particularly the vagus nerve. This sympathetic hyperactivity raises heart rate and peripheral vascular resistance, which leads to hypertension and persistently high blood pressure. Although early sympathetic dominance causes the development of hypertension, sympathetic denervation may occur as DAN worsens. Impaired autonomic regulation reduces the ability to buffer blood pressure fluctuations, causing labile or sustained hypertension.

Baroreflex Dysfunction: Damage to autonomic afferent pathways impairs baroreceptor sensitivity and reflex control of blood pressure. This results in

aberrant blood pressure control, orthostatic hypotension, and nocturnal hypertension with loss of normal circadian dipping. The compromised baroreflex function contributes to blood pressure fluctuations and increased cardiovascular risk.

Vascular stiffness and endothelial dysfunction: hyperglycemia-induced oxidative stress and inflammation in diabetes cause endothelial dysfunction, reducing nitric oxide bioavailability and impairing vasodilation. DAN is linked to elevated arterial rigidity and vascular stiffness, which leads to elevation of pulse and systolic blood pressure. Vascular stiffness and endothelial dysfunction exacerbate hypertension and decrease vascular compliance. Studies show that endothelial dysfunction markers (e.g., von Willebrand factor, soluble E-selectin) are elevated in patients with impaired glucose tolerance and type 2 diabetes, correlating with early autonomic dysfunction such as reduced heart rate variability (HRV)

Renin-Angiotensin-Aldosterone System (RAAS) activation: Autonomic dysfunction may intensify RAAS activation, promoting vasoconstriction, sodium retention, and volume expansion, which increase blood pressure. Additionally, RAAS activation also exacerbates hypertension by promoting vascular remodeling and fibrosis.

Metabolic and Inflammatory Contributions: Chronic hyperglycemia leads to formation of advanced glycation end products (AGEs) and increased reactive oxygen/nitrogen species (RONS), which damage nerves and blood vessels. Inflammatory cytokines (e.g., IL-6, TNF- α) are elevated, further

impairing vascular and autonomic function. These metabolic disturbances contribute to both nerve damage and hypertension.

Several studies have shown an association between hypertension and CAN in T2DM (Ayad et al., 2010). The presence of CAN is associated with silent myocardial infarct, cardiac arrhythmias and cardiorespiratory instability (Ponirakis et al., 2019). Other studies have also illustrated that angiotensin II inhibitor use in hypertensive T2DM patients is associated with improvement in nerve conduction, neuropathic symptoms and thermal threshold. However, there is conflicting data from a study illustrated that there is no effect on neuropathic symptoms, vibration perception or autonomic neuropathy in diabetes patients treated with angiotensin converting enzyme (Ponirakis et al., 2019).

The coexistence of diabetic autonomic neuropathy and hypertension creates a vicious cycle of autonomic imbalance, impaired blood pressure regulation, and end-organ damage. This combination significantly increases cardiovascular morbidity, mortality, and complicates clinical management, underscoring the need for early diagnosis using ambulatory blood pressure monitoring and aggressive multifactorial risk reduction.

Effective blood pressure management, alongside glycemic control and lifestyle modification, is critical to slowing the progression of autonomic dysfunction and reducing adverse outcomes. In a study by Vinik et al., 2014 their findings demonstrated that multifactorial intervention including blood pressure control, slows the progression of CAN in type 2 diabetes. Similarly, Hermida et al. (2011) demonstrated that antihypertensive drugs administered at bedtime decreased blood pressure and cardiovascular events at night in hypertensive type 2 diabetes,

emphasizing the significance of blood pressure control in individuals with autonomic dysfunction.

2.7.5.6 Nephropathy and Diabetes Autonomic Neuropathy

Diabetic autonomic neuropathy (DAN) and diabetic nephropathy (DN) are both microangiopathic complications owing to their common pathophysiology. The mechanisms linking autonomic nerve damage to microvascular complications such as nephropathy in diabetes include:

Microvascular Damage: Both the renal glomeruli and the autonomic nerve microvasculature are affected by chronic hyperglycemia. This causes endothelial dysfunction, thickening of the basement membrane, and capillary rarefaction which results in ischemia and tissue damage.

Autonomic dysfunction and hemodynamic changes: Autonomic neuropathy impair blood pressure regulation, leading to elevated systolic blood pressure and loss of nocturnal dipping. These effects further worsen glomerular hypertension and albuminuria.

Oxidative Stress and Inflammation: Both neuropathy and nephropathy are accelerated by hyperglycemia-induced oxidative stress and inflammatory cytokines, which promote progression of neuropathy and nephropathy

Neurovascular Interactions: Neurovascular Interactions: Damage to autonomic nerves innervating renal vasculature may alter renal blood flow and sodium handling, further worsening nephropathy

Several studies have demonstrated a significant association between autonomic neuropathy and nephropathy, suggesting these complications reflect a generalized microangiopathic process in diabetes. A study on insulin-dependent diabetes mellitus (IDDM) patients showed that cardiovascular autonomic neuropathy was associated with reduced nocturnal blood pressure fall and increased urinary albumin excretion rate (UAE), linking autonomic dysfunction to early nephropathy. In Assam, North India, another study looking at the frequency and risk factors of CAN found it to be linked with higher prevalence of microvascular complications; nephropathy, retinopathy and peripheral neuropathy (Bhuyan et al., 2019). The study also demonstrated a negative correlation between estimated glomerular filtration rate and levels of CAN (Bhuyan et al., 2019). A similar study showed that diabetes mellitus and autonomic neuropathy was associated with increased albuminuria and higher rates of eGFR reduction (Orlov et al., 2015).

In diabetic patients with or without nephropathy, autonomic neuropathy in particular, cardiac autonomic neuropathy, or CAN, is a strong and independent predictor of increased cardiovascular morbidity and death. This cardiovascular risk is further increased when nephropathy is present together with CAN. Although most studies have linked CAN to increased uACR and its development, a recent study done by Cho et al., 2024 demonstrated that definite CAN was linked to increased uACR but not to decreased eGFR (OR=3.43, 95% CI 0.62-18.90). This suggests a primary link to early renal damage (albuminuria) rather than a direct acceleration of GFR decline in this specific cohort.

The coexistence of diabetic autonomic neuropathy and nephropathy identifies a high-risk subgroup of patients prone to cardiovascular events and mortality. Several studies have demonstrated that early screening for autonomic dysfunction and nephropathy is

crucial, to enable timely implement timely interventions. The main goals of management strategies should focus on optimal glycemic control, blood pressure regulation, and reduction of inflammation and oxidative stress. There is also need of an Integrated multi-disciplinary approach to care involving endocrinologists, nephrologists, and cardiologists are critical for improving outcomes.

2.7.5.7 Obesity and Diabetes Autonomic Neuropathy

Adipose tissue is one of the largest endocrine tissue whose main roles are to store energy and regulate energy/metabolic homeostasis. Obesity disrupts autonomic function by increasing sympathetic nervous system activity and decreasing parasympathetic tone, leading to impaired cardiovascular regulation and metabolic disturbances. Over the past decades the prevalence of obesity has increased significantly, becoming a global health problem. Obesity increases the risk of developing major health complications among them T2DM, cardiovascular disorders, non-alcoholic fatty liver disease, renal disease (Bentham et al., 2017)

The mechanisms linking obesity to autonomic nerve damage include:

Insulin resistance and hyperinsulinemia: Prolonged sympathetic stimulation by elevated insulin levels results in parasympathetic withdrawal, downregulation of the baroreflex, and a hemodynamic condition with high output and low resistance. These alterations encourage cardiovascular stress and hypertension.

Low ghrelin levels: Obesity may be associated with elevated sympathetic tone due to decreased levels of ghrelin, a hormone produced in the gut that typically regulates autonomic function.

Chronic low-grade inflammation and oxidative stress are brought on by obesity, and these conditions impair autonomic nerve function and encourage neurovascular disease.

Hormonal and metabolic dysregulation: By influencing energy balance and stress reactions, changes in gut hormones, adipokines, and the hypothalamic-pituitary-adrenal (HPA) axis leads to autonomic dysfunction.

Neurovascular dysregulation: Microvascular malfunction brought on by obesity reduces blood supply to autonomic nerves, aggravating nerve damage and dysfunction.

Studies in obese individuals without cardiovascular risk factors demonstrate that central adiposity correlates with reduced heart rate recovery and other markers of autonomic dysfunction, indicating that obesity alone can impair autonomic control. It has also been demonstrated that losing weight reverses metabolic anomalies as well as autonomic dysfunction, highlighting the causative involvement of obesity in autonomic impairment. Additionally, there is growing evidence that medications like GLP-1 receptor agonists, SGLT2 inhibitors, and metformin, which target metabolic abnormalities linked to obesity and prediabetes, have the potential to improve autonomic function. lastly, bariatric surgery also improves HRV and may prevent CAN in severe obesity through sustained weight loss.

2.7.5.8 Gender and Diabetes Autonomic Neuropathy

Sex steroids play a significant and complex role in the development and progression of diabetic autonomic neuropathy (DAN), influencing both the prevalence and severity of autonomic nerve damage in a sex-specific manner. In women with diabetes there is an increased testosterone/estradiol ratio is associated with a higher

prevalence and severity of cardiovascular autonomic neuropathy (CAN), particularly after menopause when estrogen levels decline sharply. This hormonal imbalance contributes to increased autonomic dysfunction in peri- and postmenopausal women. On the other hand, men with diabetes have a lower testosterone concentrations correlate with greater autonomic nerve damage, whereas androgens tend to have a protective effect on heart rate variability and autonomic function .

Studied have also shown that diabetes induces changes in neuroactive steroid levels in both central and peripheral nervous systems, with distinct patterns in males and females. For example, diabetic male animals show increased certain neuroactive steroids that may be neuroprotective, while females exhibit different changes that may exacerbate nerve damage. These differences suggest that sex steroids modulate nerve vulnerability and repair mechanisms, influencing the incidence and progression of diabetic neuropathy

Sex steroids influence nerve vulnerability differently through multiple complex mechanisms involving genomic and non-genomic signaling pathways, modulation of neuroinflammation, neural plasticity, vascular function, and neurotransmission. These mechanisms vary by sex due to differences in hormone levels, receptor distribution, and downstream molecular effects.

Key Mechanisms Explaining Sex Steroid Influence on Nerve Vulnerability

Regulation of Neural Activity and Synaptic Plasticity: Sex steroids (estrogens, testosterone, progesterone) modulate neural activity by altering synaptic plasticity, spine density, and neuron sensitivity. For example, estradiol promotes dendritic spine formation via activation of MAPK/ERK signaling pathways in hippocampal neurons, enhancing neural connectivity

and repair capacity. Testosterone and its metabolites regulate spine formation through androgen receptors localized in dendritic spines, influencing cytoskeletal dynamics essential for neural plasticity.

Neuroinflammation and Immune Responses: Estrogens exert anti-inflammatory effects by reducing activation of microglia, astrocytes, and leukocyte infiltration into neural tissue. They inhibit pro-inflammatory transcription factors such as NF- κ B and cytokines like IL-1 β , thereby protecting nerves from inflammation-induced damage. Progesterone and androgens also modulate inflammatory responses, but with different effects depending on sex and tissue context.

Vascular Effects and Blood–Nerve Barrier Integrity: Estrogens promote vasodilation by enhancing endothelial nitric oxide synthase (eNOS) expression and activity, improving blood flow and nutrient delivery to nerves. They stimulate angiogenesis and endothelial cell survival through upregulation of growth factors like VEGF and FGF2, supporting vascular health essential for nerve maintenance. Estrogen help maintain blood–brain and blood–nerve barrier integrity by regulating tight junction proteins and reducing leukocyte transmigration, thus preventing neurovascular inflammation.

Neurotransmitter Systems and Sympathetic Neuroeffector : Sex steroids modulate synthesis, release, and reuptake of neurotransmitters such as norepinephrine at sympathetic nerve terminals, affecting autonomic nerve function. Estrogens and its metabolites increase norepinephrine uptake and decrease its degradation, influencing sympathetic tone and vascular responses.

Genomic and Non-Genomic Signaling: Sex steroids act via nuclear receptors to regulate gene transcription (genomic effects) and via membrane-associated receptors to rapidly modulate signaling cascades (non-genomic effects), such as MAPK/ERK and PI3K/AKT pathways, affecting neuronal survival, apoptosis, and plasticity. The dual modes of action allow sex steroids to finely tune neural responses to injury and metabolic stress.

Sex-Specific Expression of Receptors and Enzymes: Differences in expression levels of estrogen receptors (ER α , ER β), androgen receptors, and enzymes involved in steroid metabolism contribute to sex-specific neural effects. Females often have higher ER expression in certain brain regions, making them more sensitive to estrogen's neuroprotective or neuroinflammatory modulation.

One study showed men developed neuropathic complications approximately 4 years earlier than women (63 vs. 67 years). This suggests gender influences the timing of neuropathy onset, possibly due to differences in metabolic risk factors or hormonal milieu and is linked to hormonal changes, especially the loss of estrogen's protective effects and altered androgen/estrogen balance in women.

A large study from the ACCORD trial (7,866 participants) found significant sex differences in the association between CAN and mortality in type 2 diabetes. CAN was strongly associated with increased all-cause and cardiovascular mortality in women, but not in men. A 2023 cross-sectional study found that the overall prevalence of asymptomatic cardiovascular autonomic neuropathy (CAN) was similar between men and women with T1DM. However, women over 50 years old (peri- and postmenopausal) had a twofold higher prevalence of CAN compared to younger women, and more severe autonomic dysfunction than men of similar age. Another

study also demonstrated that cardiovascular autonomic neuropathy is associated with a significantly increased mortality risk in women with T2DM, but not in men, according to data from the ACCORD trial. This indicates that although men may develop neuropathy earlier, women may experience worse outcomes once autonomic dysfunction is present.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study Design

This study employed a descriptive cross-sectional design.

3.2 Study Site

The study was conducted at Moi Teaching and Referral Hospital (MTRH) Diabetes Outpatient Clinics (DOPC). MTRH is in Eldoret town, Uasin Gishu County, which is approximately 300 kilometers northwest of Nairobi. MTRH is the second largest referral hospital in Kenya after Kenyatta National Hospital and serves the greater Western Kenya region representing about 40% (approximately 16.2 million people) of the country's population. It also serves Eastern Uganda and parts of Southern Sudan. It is the teaching hospital for Moi University, School of Medicine and other middle level health colleges. It has a bed capacity of about 1000 patients and admits patients requiring specialized treatment including cancer treatment, renal replacement therapy, neurosurgical treatment among others. There are several specialist clinics including Diabetes clinic(DOPC) which runs on Monday, Thursday, and Friday. On average, there are about 285 patients attending the DOPC on a monthly basis.

3.3 Target Population

Patients with T2DM attending the diabetes outpatient clinic at MTRH.

3.3.1 Eligibility Criteria

3.3.1.1 Inclusion Criteria

The study included adult patients with type 2 diabetes mellitus; patients aged >30 years at time of diagnosis and managed on oral glucose-lowering agents (OGLAs) or

insulin and OGLAs; any patient regardless of age managed on OGLAs without insulin.

3.3.1.2: Exclusion Criteria

The study excluded patients with documented or reported history of the following conditions as they have been shown to cause non-diabetic neuropathy:

- Connective tissue diseases: myasthenia gravis, rheumatoid arthritis, Sjogren's syndrome, Gullian Barr syndrome, multiple sclerosis, fibromyalgia
- Infections: human immunodeficiency virus, herpes simplex virus, flavivirus, enterovirus and lyssavirus; diphtheria; leprosy; COVID 19; Lyme disease and tetanus
- Endocrine and metabolic disorders: hypothyroidism, amyloidosis
- Toxin and drugs: chemotherapy and heavy metal
- Other conditions: Parkinson's disease, liver failure

The study also excluded pregnant or lactation, due to hormonal influences on autonomic function.

3.4 Sample Size Determination

Sample size was calculated for objective 1 and 2.

Objective 1 Sample Size Determination: Prevalence of Diabetic Autonomic Neuropathy

Sample size calculation was done using a formula for calculation based on a single proportion by Fisher's 1998.

$$n = [Z_{(1-\alpha/2)} / d]^2 \cdot P(1-P)$$

Where,

n= minimum sample size required,

$Z_{(1-\alpha/2)}^2$ = Critical value for standard normal distribution at α -level of significance ($\alpha=0.05$, $Z_{(1-\alpha/2)} = 1.96$),

p = prevalence of autonomic neuropathy among patients with T2DM of 34% from a study done by Pop-Busui et al., (2017).

d = Margin of error ($d=0.05$),

$n = [1.96/0.05]^2 \times 0.34(1-0.34) = 344$.

Substituting the above values, the minimum sample size required is 344 patients with T2DM.

Objective 2 Sample Size Determination: Sociodemographic and clinical factors associated with Diabetic Autonomic Neuropathy

A formula for logistic regression was used. The minimum sample size (N) based on logistic regression model was obtained using the formula suggested by Peduzzi et al, $N = 10k/p$, where k is the number of independent variables and p is the number or events or prevalence of the condition of interest as determined from previous studies (Peduzzi et al., 1996). The number of independent variables in this study were 9; age, gender, duration of T2DM, treatment modality, HTN, BMI, HbA1c, dyslipidemia and creatinine levels. p was derived from a study by Pop-Busui et al., (2017) where prevalence of autonomic neuropathy among patients with T2DM was 34%. The calculated sample size was. $N = 10 \times 9 / 0.34 = 265$ patients

3.5 Sampling Method

Systematic random sampling was done. Diabetes clinic runs three days a week and on average, sees 50 patients per day yielding approximately 150 patients attended to at the DOPC on a weekly basis. The study period was 10 weeks, giving a total of approximately 1500 patients on follow up for diabetes during the study period. This number divided by the sample size of 344 gave a value of approximately 4. Every

fourth patient was thus approached for enrollment into the study over the 10-week study period.

3.6: Data Collection

3.6.1 Data Collection Tools

Data collection instruments included:

- i. The Composite Autonomic Symptom Score tool (COMPASS-31) was used to screen for diabetic autonomic neuropathy.
- ii. Researcher administered questionnaire for age, gender, duration of disease and treatment modality.
- iii. An automated Cobas Integra 400 Plus chemistry analyzer for analysis of glycated hemoglobin.
- iv. Digital blood pressure machine (Omron Healthcare, Inc., 1200 Lakeside Drive, Bannockburn, Illinois 60015).
- v. Lipid profile analyzer.

3.6.2 Study Procedure

On DOPC clinic days, every Monday, Thursday and Friday, the investigator identified adult patients with type 2 diabetes. They were assessed based on the inclusion and exclusion criteria. Those who meet the inclusion criteria had the rationale of the study explained to them, after which an informed consent was obtained to participate in the study.

The investigator then administered a structured questionnaire as well as the Composite Autonomic Symptom Score tool (COMPASS-31). Subsequently, aseptic

technique was used to draw 2mls of venous blood to enable laboratory analysis of creatinine levels, HbA1c and lipid profile.

The study procedure is summarized in Figure 2 below.

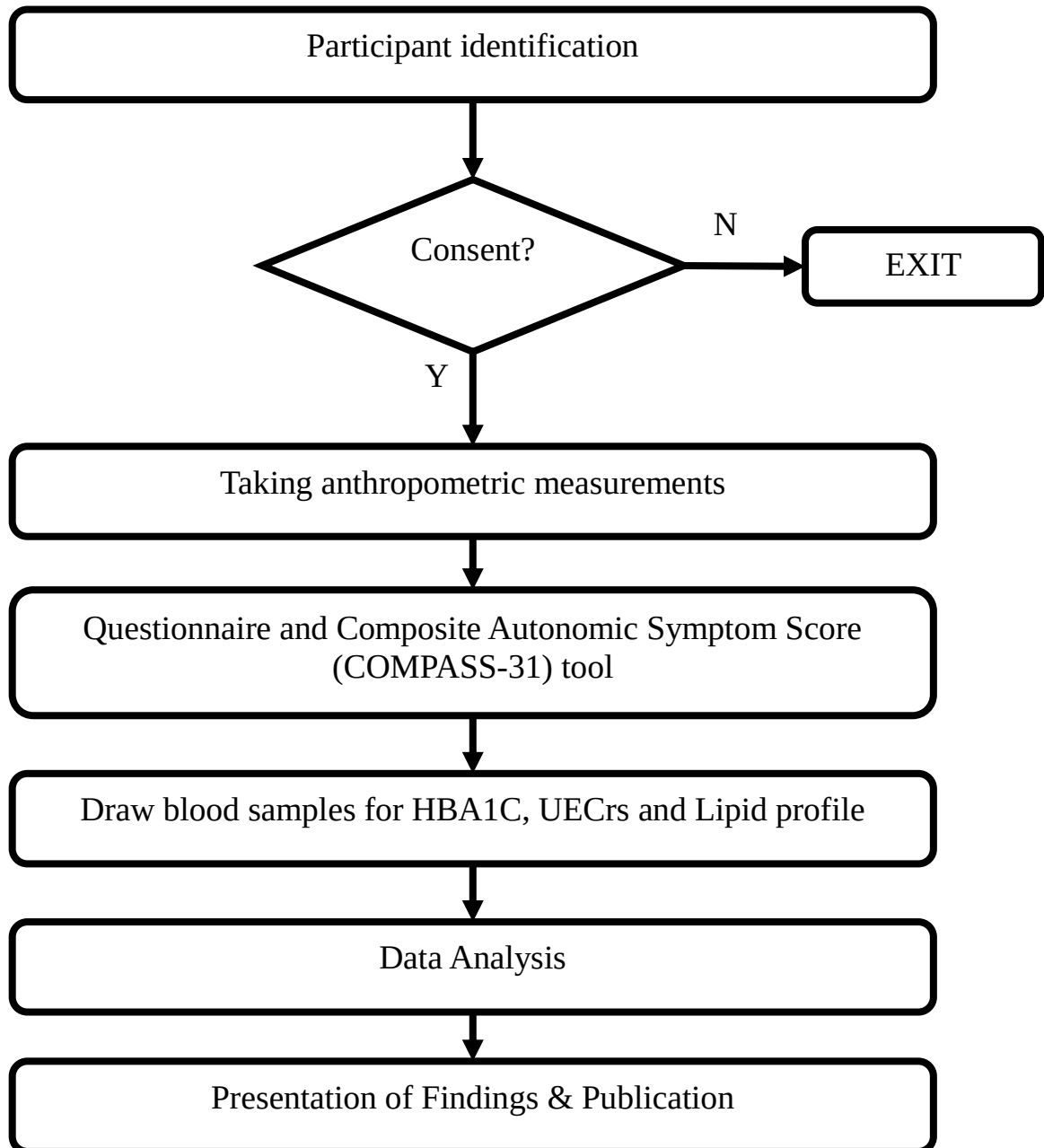


Figure 2: Study Procedure

3.7 Study Variables

Independent Variables:

- i. Age – this refers to the current age of the patient.
- ii. Duration of diabetes – this refers to the time period between the time of diagnosis and time of data collection.
- iii. HbA1c – this refers to the measurement done at the time of data collection.
- iv. Lipid profile - this refers to the measurement done at the time of data collection.
- v. Treatment modality – this refers to the use of either antihyperglycemic agents, insulin or a combination of insulin and antihyperglycemic agents.
- vi. BMI-this refers to the measurement done at the time of data collection
- vii. Hypertension-this refers to a confirmed diagnosis of HTN on routine treatment

Dependent Variable – Diabetic autonomic neuropathy.

3.8 Data Analysis

Parametric data were expressed as mean $\pm$ standard deviation while non-parametric data was expressed as median and interquartile range. Categorical data were summarized as frequency and proportions.

Bivariate and multivariate logistic regression analyses were applied to test for associations between independent factors and diabetic autonomic neuropathy. Variables with significant association in bivariate analysis were entered into a multivariable model. Statistical significance was set at 0.05.

3.9 Ethical Considerations.

Ethical clearance was obtained from the Institutional Research and Ethics Committee (IREC) of Moi Teaching and Referral Hospital (MTRH) and Moi University School of Medicine, then a license was obtained from the National Commission for Science, Technology and Innovation NACOSTI.

A written informed consent was obtained from all the participants and strict confidentiality was maintained when recruiting and handling data.

All data received was entered into a password-protected computer. The hard-copy data was placed under lock and key. All clinical data relevant to the management of the participants was relayed to the primary clinician for prompt medical action.

CHAPTER FOUR

4.0 RESULTS

4.1 Recruitment

A total of 373 participants were enumerated for this study. Eighteen participants did not meet the inclusion criteria and were excluded. Among those excluded, 9 participants had another form of neuropathy, 6 were under the age of 35 years at diagnosis of diabetes and 3 had hemoglobin levels less than 10g/dL. Eleven participants declined to participate in the study. The final analysis included results of 344 participants (Figure 3).

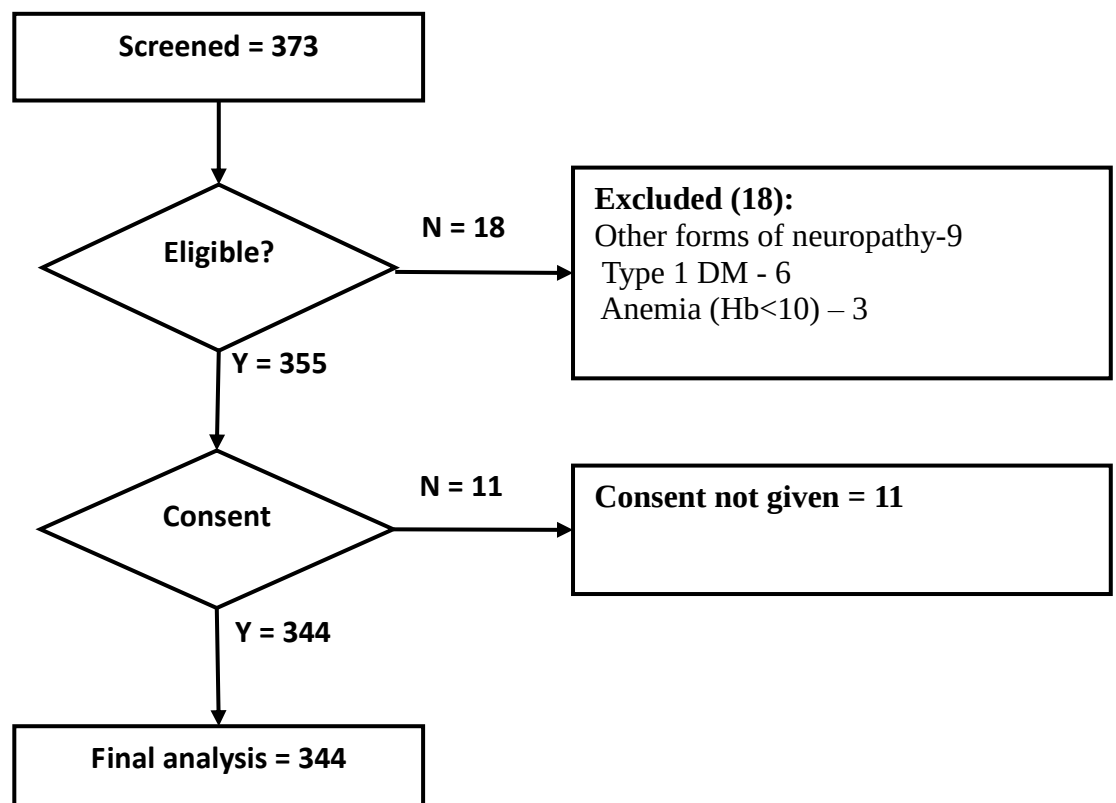


Figure 3: Recruitment Schema

4.2 Socio Demographic Characteristics

A total of 344 participants were enrolled in the study. The mean age of participants was 61.0 years (SD 9.1) with the youngest being 37.0 and the oldest 84.0 years. These findings are illustrated in the histogram below (Figure 4)

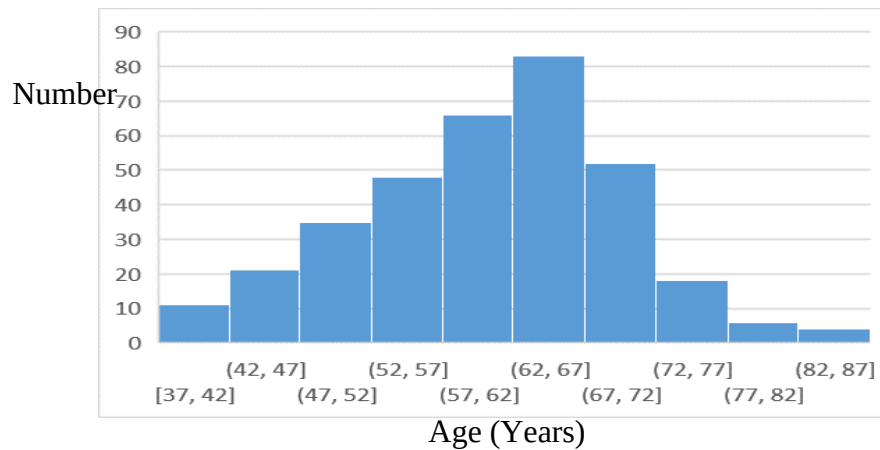


Figure 4: Age Distribution

In terms of gender distribution there were more female participants 225 (65.4%) than male participants 119 (34.6%) as shown in the pie chart below (Figure 5)

Majority of study participants had their highest level of education being primary, 198 (57.56%) followed by secondary, 75 (21.80%) and tertiary education 71 (20.64%) respectively (Figure 6).

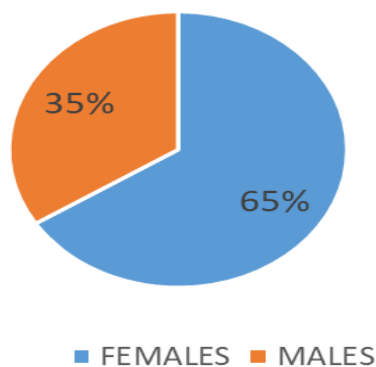


Figure 5: Gender Distribution

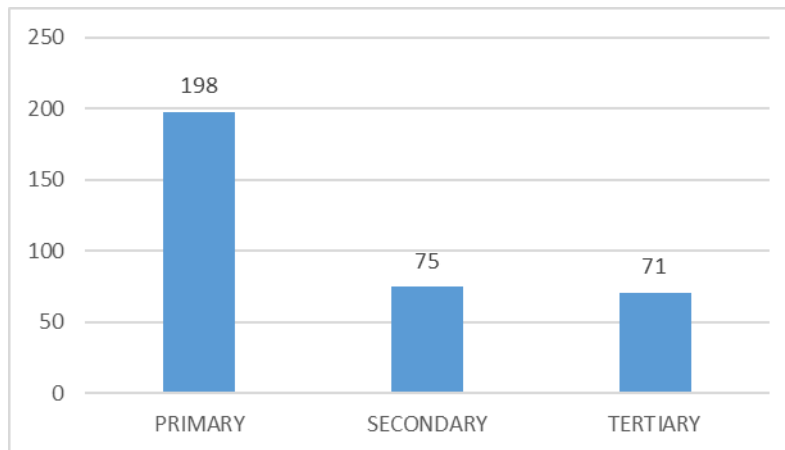


Figure 6: Level of Education

A majority of the study participants reported being married (90.7%) (Figure 7)

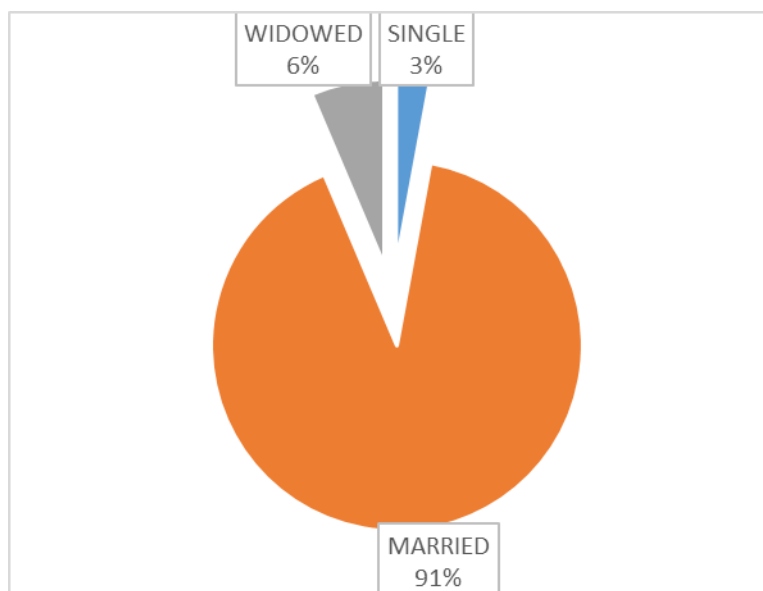


Figure 7: Marital Status

4.3 Prevalence of Diabetic Autonomic Neuropathy

Out of the 344 participants studied, 183 participants had diabetic autonomic neuropathy, corresponding to a prevalence of 53.2% (Figure 8)

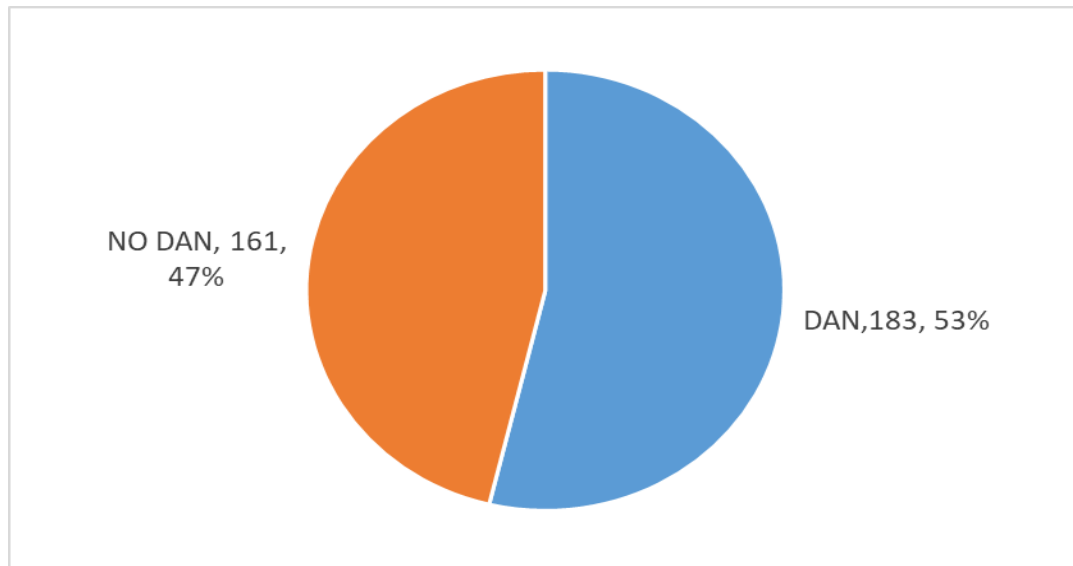


Figure 8: Prevalence of Diabetic Autonomic Neuropathy

The median COMPASS 31 score was 23.9 (IQR 7.80 – 41.71) (Figure 9)

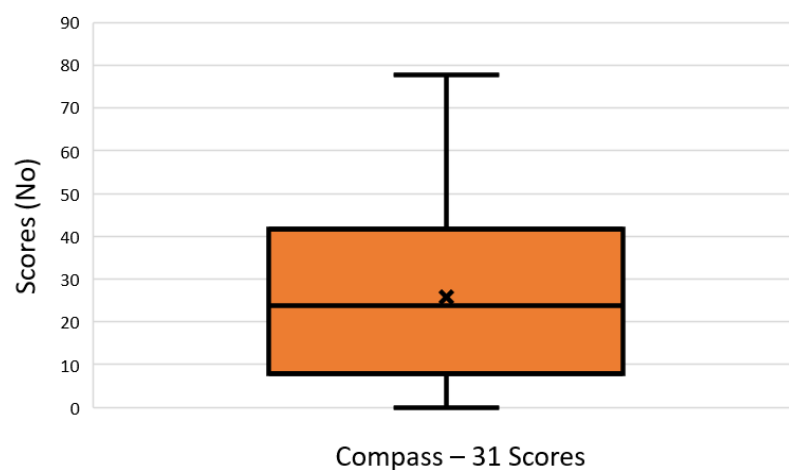


Figure 9: Compass-31 Scores

The median scores of the six domains were orthostatic 0.00 (IQR 0.00 – 24.00); vasomotor 0.00 (IQR 0.00 – 2.50); secretomotor 2.14 (IQR 0.00 – 8.57); gastrointestinal 4.46 (IQR 0.00 – 8.93); bladder 0.00 (IQR 0.00 – 2.22) and pupillomotor 1.83 (IQR 0.00 – 4.33) (Figure 10).

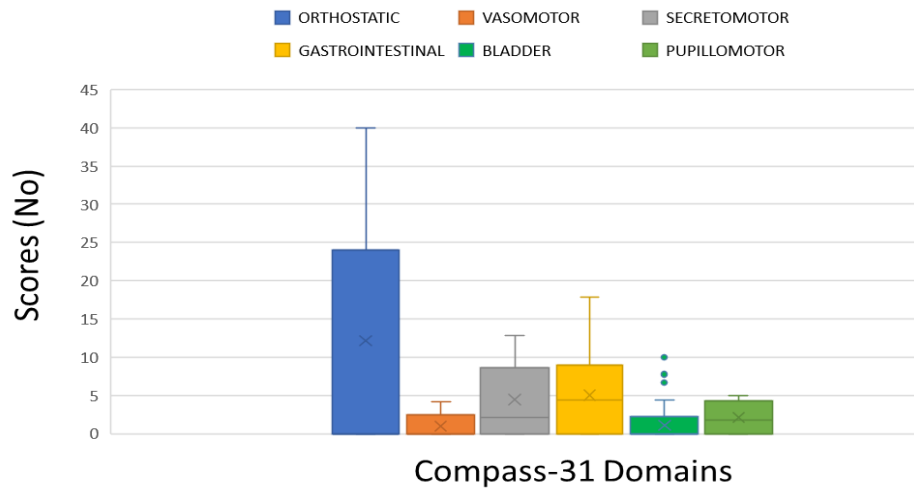


Figure 10: Domain Specific Compass-31 Scores

4.4 Clinical Characteristics

4.4.1 Duration of Diabetes

The median duration since diagnosis of diabetes in this study was 8.62 (IQR 4-12) years with a range of 1 and 34 years (Figure 11).

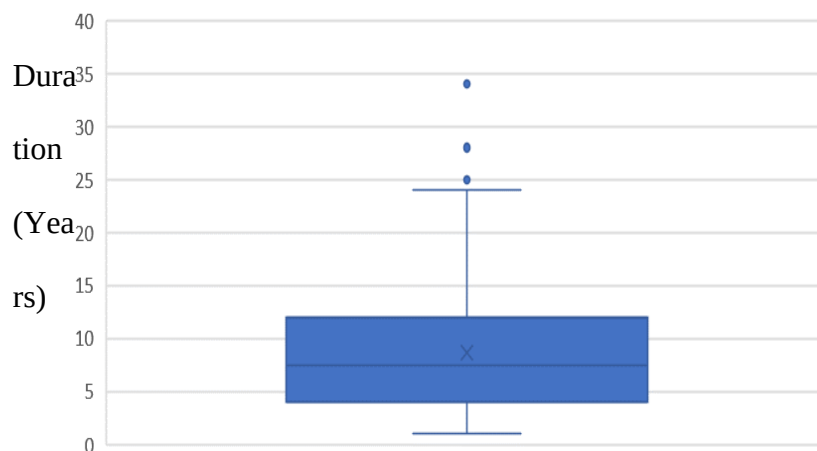


Figure 11: Duration of since Diagnosis

4.4.2 Treatment Modality

The findings on treatment modality for glycemic control demonstrated that 141 (41%) were on oral glucose lowering agents, 58(16.87%) were on insulin alone and 145 (42%) were on combined therapy of both oral glucose lowering agents and insulin (Figure 12).

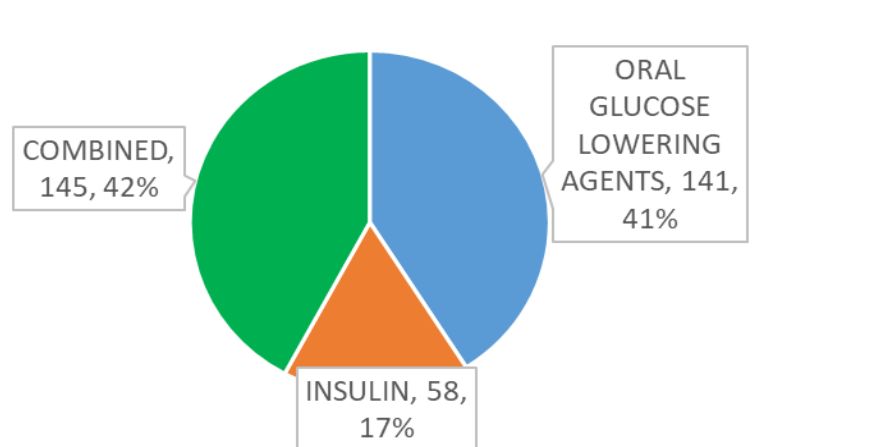


Figure 12: Treatment Modality

4.4.3 Hypertension Co-morbidity

Two hundred and fifty-two (73.26%) study participants reported hypertension co-morbidity (Figure 13).

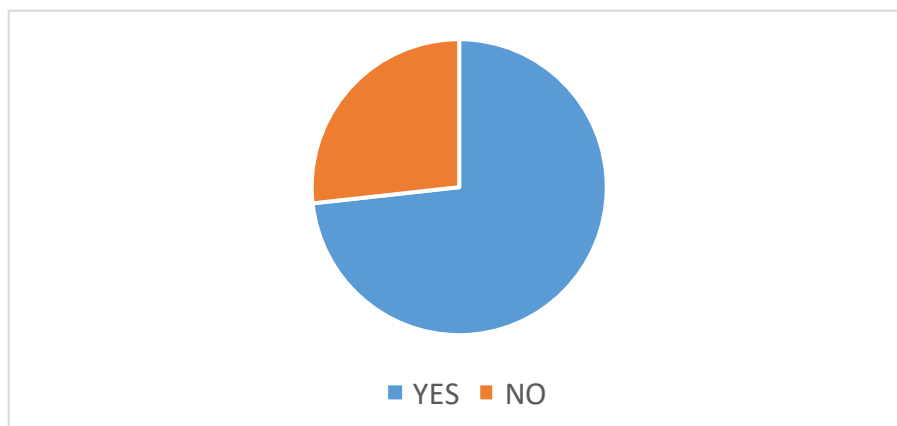


Figure 13: Hypertension comorbidity

4.4.4 Use of Lipid Lowering Agents

In this study, a majority of participants; 233 (67.73%) were found to be taking lipid lowering agents (Figure 14)

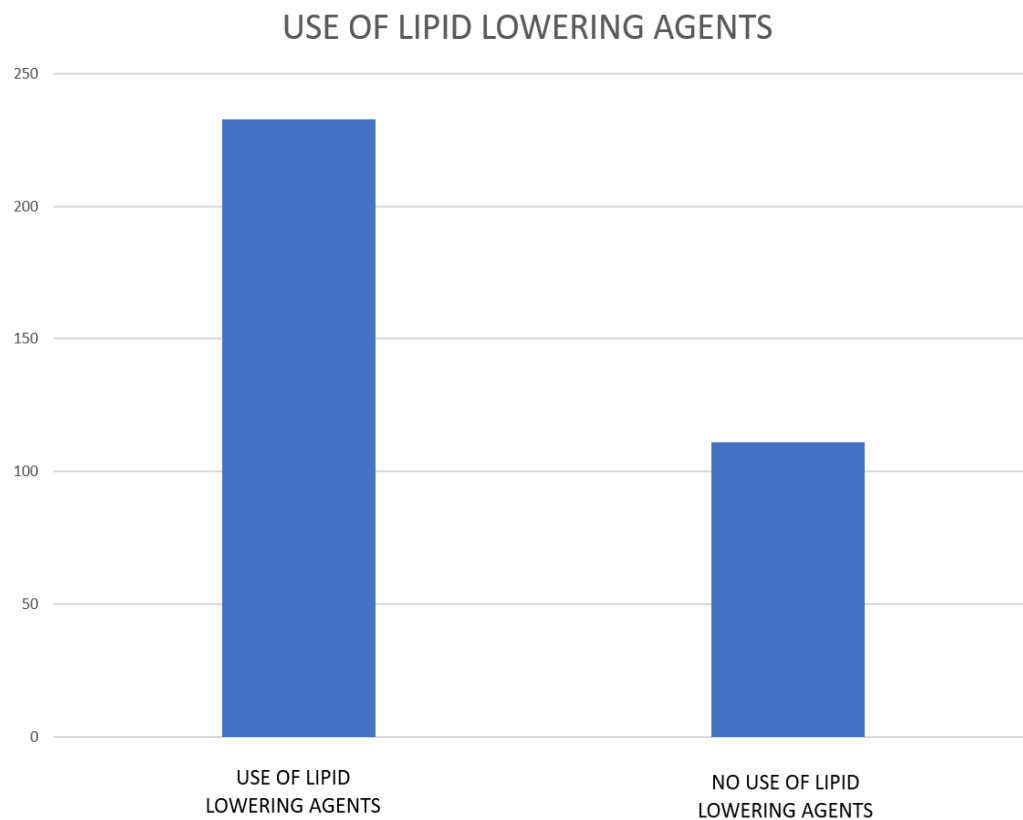
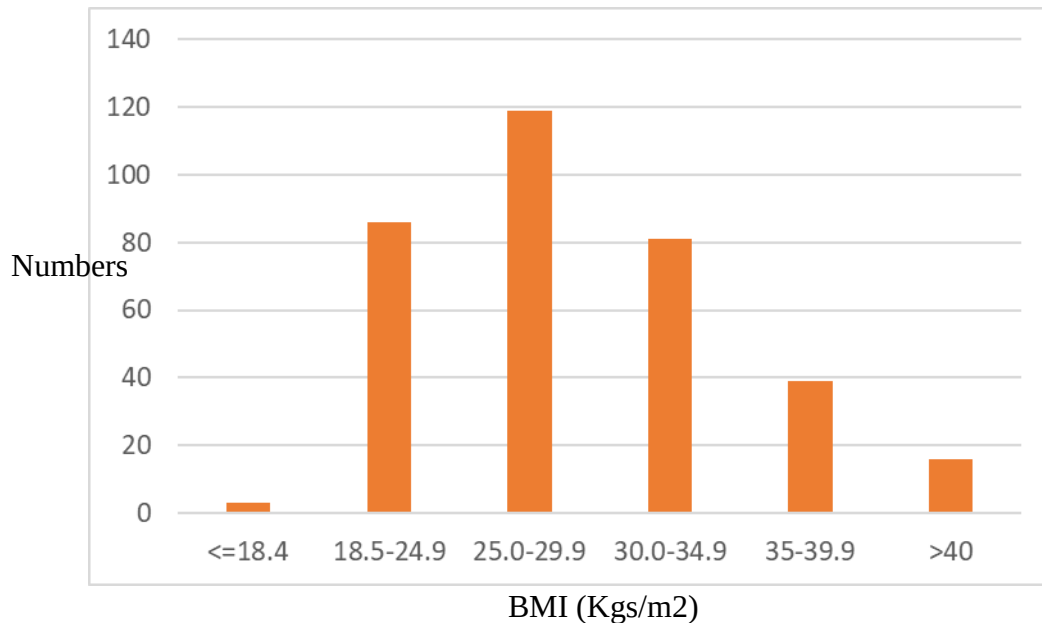


Figure 14: Use of Lipid Lowering Agents

4.4.5 Body Mass Index (BMI)

The mean BMI was 29.2 (SD 9.1) Kgs/m². Only 86 (25%) of the participants had a normal BMI. A total of 119 (34.59%) participants were overweight, while 136 (39.54%) were obese (Figure 15).

Figure 15: Body Mass Index



4.4.6 Blood Pressure

A total of 252 (73.3%) participants reported prior diagnosis of hypertension. The mean measured systolic blood pressure was 136 (SD 20.3) mmHg. The mean diastolic blood pressure was 80 (11.9) mmHg. There were 139 participants out of the total of 344 with elevated blood pressure (defined as SBP $\geq$ 140 and/or DBP $\geq$ 90 mmHg). This corresponds with a prevalence of 40.40% of uncontrolled blood pressure (Figure 16).

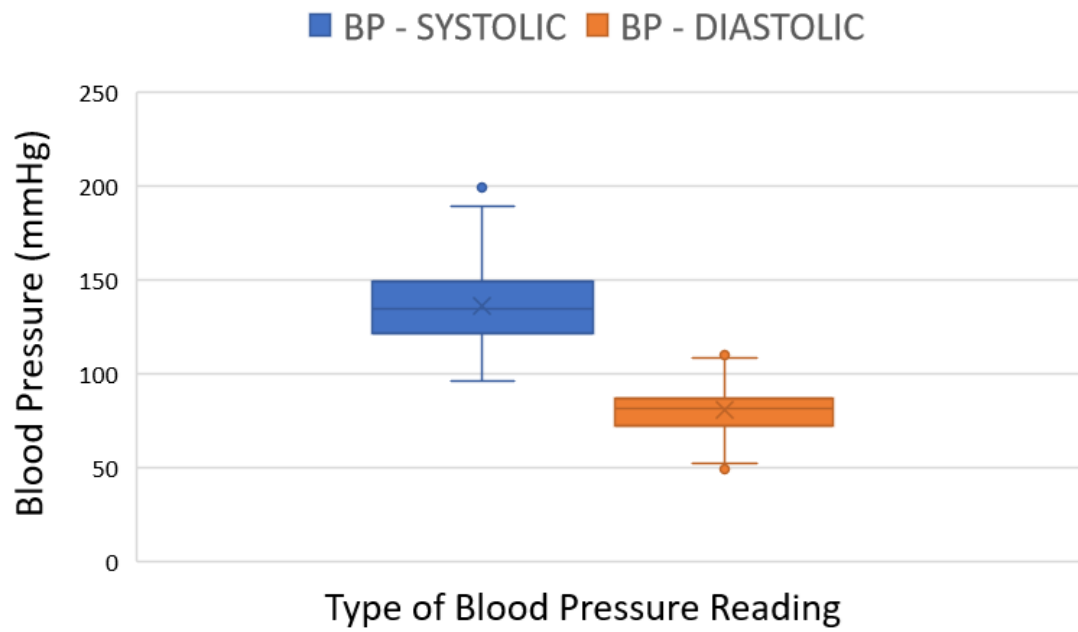


Figure 16: Blood Pressure

4.5 Laboratory Findings

4.5.1 HBA1C

The median HBA1 C was 9.60% (SD 4.5). Only a total of 60 (17.44%) of the participants achieved the desired HBA1C level of 7% and below (Figure 17)

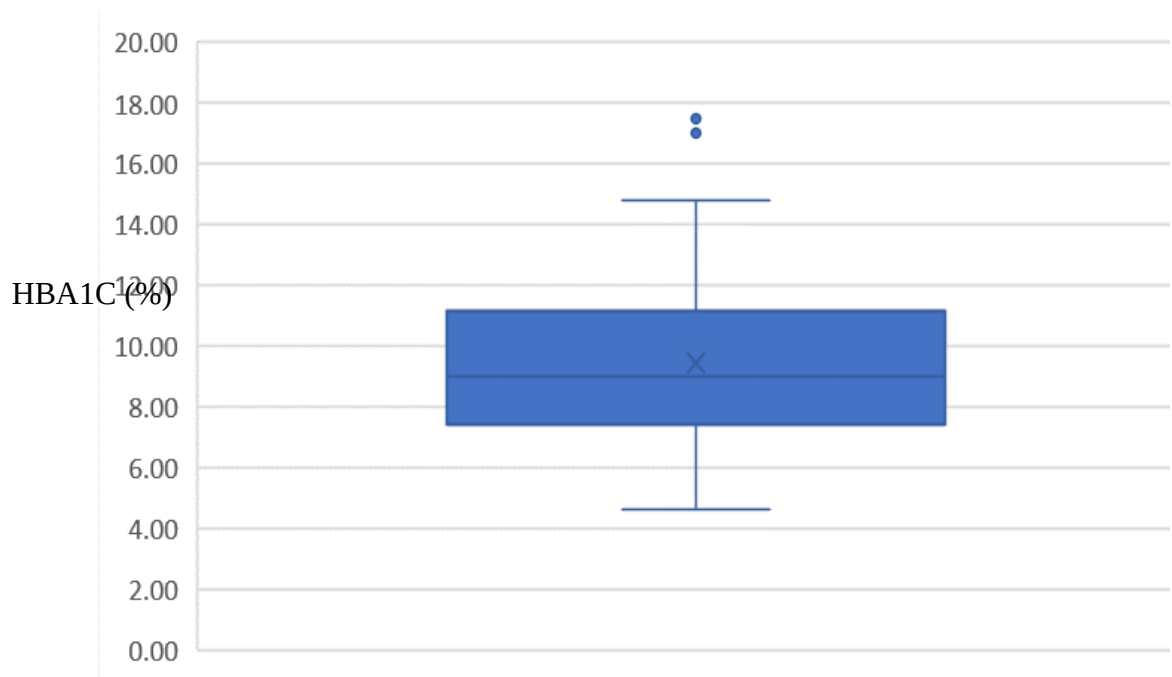


Figure 17: HBA1c Levels

4.5.2 Lipid Profile

The mean LDL level was determined to be 2.6 mmol/L (SD 0.9). A total of 156 (45.3%) participants had LDL- cholesterol greater than the reference upper limit of 2.6 mmol/L. The mean HDL level was determined to be at 1.3 mmol/L (SD 0.4). A total of 151 (43.9%) participants had HDL-cholesterol levels lower than the reference level (female <1.3mmol/L and Male <1 mmol/L). The mean total cholesterol was 4.2 mmol/L (SD 1.1). A total of 62 (18.02%) participants had total cholesterol greater than the reference upper limit of 5.17 mmol/L. The mean triglyceride level was 1.62 mmol/L (SD 5.0). A total of 156 (45.35%) had triglycerides levels greater than the reference upper limit of 1.7 mmol/L (Figure 18)

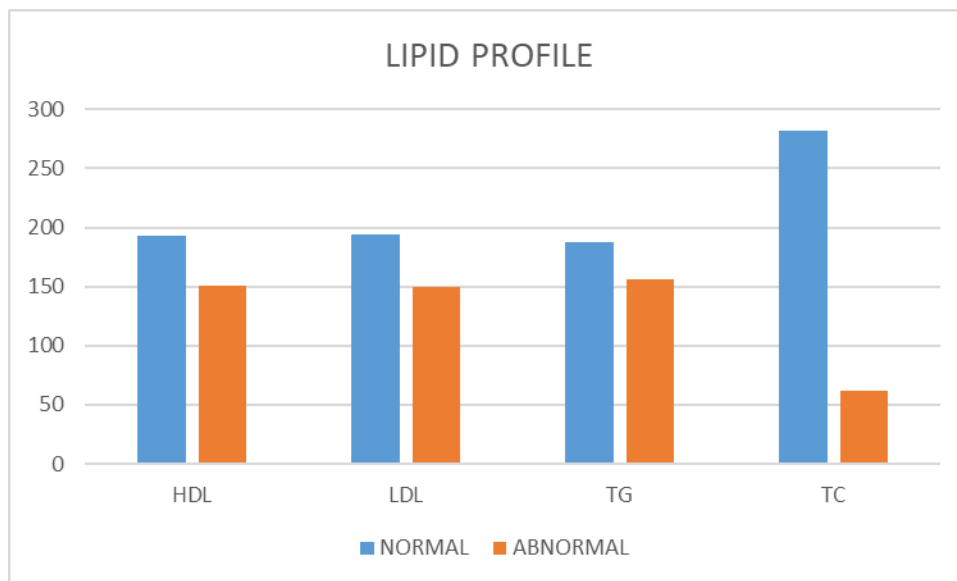


Figure 18: Lipid Profile

4.5.3 Estimated Glomerular Filtration Rate

The mean estimated glomerular filtration rate (eGFR) was 76.3 mL/min/1.73m² (SD 49.7). A total of 92 (26.74%) participants had eGFR of greater or equal to 90 mL/min/1.73m² corresponding to normal (Grade I). A total of 147 (42.73%) participants had eGFR between 60 and 90 mL/min/1.73m² corresponding to mildly decreased kidney function (Grade II). A total of 69 (20.06%) participants had eGFR between 45 and 59 mL/min/1.73m² corresponding to mild to moderate decreased kidney function (Grade IIIa). A total of 27 (7.85%) participants had eGFR between 30 and 44 mL/min/1.73m² corresponding to moderate to severe decreased kidney function (Grade IIIb). Nine (2.61%) participants had eGFR between 15 and 29 mL/min/1.73m² corresponding to severely decreased kidney function (Grade IV) (Figure 19).

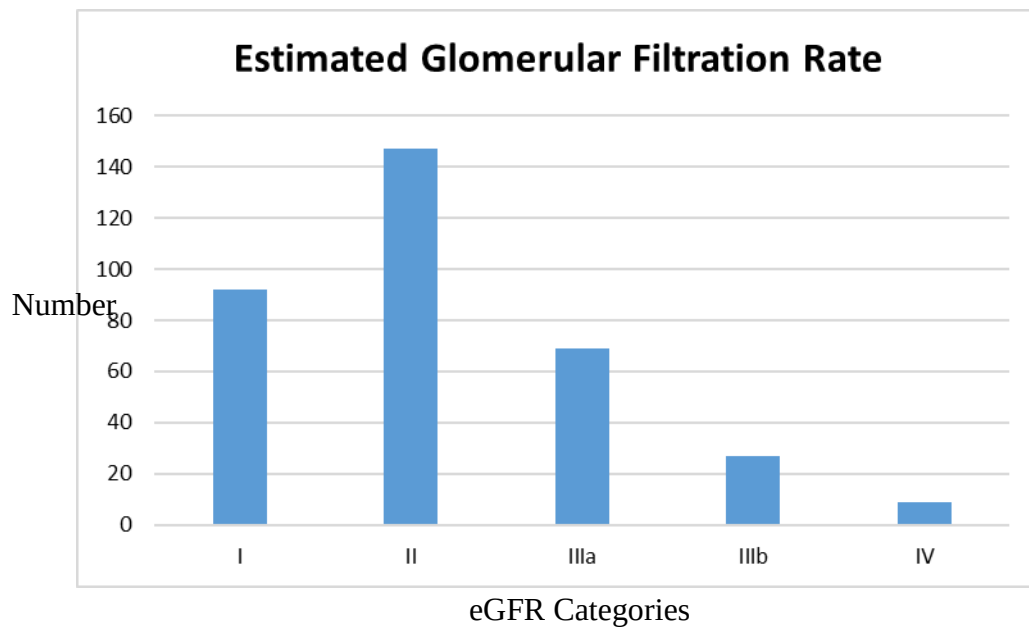


Figure 19: Estimated Glomerular Filtration

4.6 Correlation between Diabetic Autonomic Neuropathy and Independent Factors

Binary and multivariate logistic regression analyses were applied to test for associations between independent factors and diabetic autonomic neuropathy. Variables with significant association in bivariate analysis were entered into a multivariable model. Statistical significance was set at 0.05.

On bivariate analysis, the factors that were associated with diabetic autonomic neuropathy were gender, lipid-lowering agents, HbA1c, and eGFR. The proportion of females with DAN was significantly higher (58.7%) compared to males (42.9%) ($p=0.005$). Likewise, the proportion of participants on lipid-lowering agents with DAN was significantly lower (47.2%) relative to those not using lipid-lowering agents (65.8%) ($p=0.001$). There was a significantly higher proportion of patients with abnormal HbA1C who had diabetic autonomic neuropathy (56%) compared to those

who had normal HbA1C (40%) ($p = 0.024$). The results on the bivariate analysis are summarized in table 1 below.

Table 1: Association between Diabetic Autonomic Neuropathy and patient's factors on Bivariate Analysis

	Diabetic Autonomic Neuropathy		
Variables	Absent	Present	p-value
Age			0.521 ^t
Mean (SD)	60.6 (9.7)	61.3 (8.6)	
Range	37 – 84	41 – 82	
Gender			0.005^c
Male	68 (57.1%)	51 (42.9%)	
Female	93 (41.3%)	132 (58.7%)	
Education level			0.100 ^c
Primary	85 (42.9%)	113 (57.1%)	
Secondary	35 (46.7%)	40 (53.3%)	
Tertiary	41 (57.7%)	30 (42.3%)	
Use of statin			0.001^c
No	38 (34.2%)	73 (65.8%)	
Yes	123 (52.8%)	110 (47.2%)	
BMI			0.482 ^f
Underweight	1 (33.3%)	2 (66.7%)	
Normal	44 (51.2%)	42 (48.8%)	
Overweight	59 (49.6%)	60 (50.4%)	
Obese	57 (41.9%)	79 (58.1%)	

Duration of DM			0.475 ^m
Median (IQR)	7.0 (3.0-12.0)	8.0 (4.0-12.0)	
Range	1 – 25	1 – 34	
Treatment modality			0.893 ^c
Insulin	26 (44.8%)	32 (55.2%)	
Oral	68 (48.2%)	73 (51.8%)	
Combined	67 (46.2%)	78 (53.8%)	
HbA1C			0.024^c
Normal	36 (60.0%)	24 (40.0%)	
Abnormal	125 (44.0%)	159 (56.0%)	
eGFR			0.025^f
Grade I	48 (52.2%)	44 (47.8%)	
Grade II	71 (48.3%)	76 (51.7%)	
Grade IIIa	21 (30.4%)	48 (69.6%)	
Grade IIIb	15 (55.6%)	12 (44.4%)	
Grade IV	6 (66.7%)	3 (33.3%)	
LDL			0.360 ^c
Normal	95 (49.0%)	99 (51.0%)	
Abnormal	66 (44.0%)	84 (56.0%)	
HDL			0.309 ^c
Normal	95 (49.2%)	98 (50.8%)	
Abnormal	66 (43.7%)	85 (56.3%)	
Total cholesterol			0.571 ^c
Normal	134 (47.5%)	148 (52.5%)	

Abnormal	27 (43.5%)	35 (56.5%)	
Triglyceride			0.830 ^c
Normal	87 (46.3%)	101 (53.7%)	
Abnormal	74 (47.4%)	82 (52.6%)	
HTN			0.818 ^c
No	44 (47.8%)	48 (52.2%)	
Yes	117 (46.4%)	135 (53.6%)	

^c Chi Square test

^f Fishers exact test

^t ttest

^m Mann Whitney U test

The multivariable logistic regression showed that gender and the use of lipid lowering agents were independently associated with diabetic autonomic neuropathy. Holding HbA1c, the use of lipid-lowering agents, and eGFR constant, females were found to be 1.9 times (95% CI 1.196 – 3.141) more likely to have diabetic autonomic neuropathy compared to males. The use of lipid-lowering agents was protective against developing diabetic autonomic neuropathy, where the users were 60.3% less likely to have diabetic autonomic neuropathy compared to non-users.

Although not achieving statistical significance ($p=0.060$), those who had abnormal HbA1c were 1.783 times more likely to have diabetic autonomic neuropathy than those with normal HbA1c.

Table 2: Factors associated with diabetic autonomic neuropathy**Table 2: Factors associated with diabetic autonomic neuropathy on multivariate analysis**

Variables	AOR	p-value	95% CI
Gender			
Male	Ref		
Female	1.938	0.007	1.196-3.141
Use of statin			
No	Ref		
Yes	0.397	<0.001	0.241-0.654
HBa1C			
Normal	Ref		
Abnormal	1.783	0.060	0.976-3.258
Egfr			
Grade I	Ref		
Grade II	1.320	0.320	0.763-2.282
Grade IIIa	2.738	0.004	1.371-5.470
Grade IIIb	0.931	0.877	0.378-2.296
Grade IV	0.452	0.303	0.100-2.044

CHAPTER FIVE

5.0 DISCUSSION

5.1 Introduction

The Prevalence of diabetic autonomic neuropathy (DAN) among individuals with type 2 diabetes(T2DM) in western Kenya remains largely unknown despite it being a devastating complication with a great negative impact on patients' quality of life. This cross-sectional study was conducted to evaluate the prevalence, sociodemographic, and clinical factors associated with autonomic neuropathy among T2DM patients in western Kenya.

5.2 Prevalence of Diabetic Autonomic Neuropathy

This study established a prevalence of DAN of 53.2.% among 344 individuals with T2DM in DOPC at MTRH Eldoret, Kenya. This prevalence is comparable to that of a similar cross-sectional study conducted in Italy among one hundred and two participants with diabetes by D'Amato et al (2019) which reported a prevalence of 48%. Similarly, Bitsch et al (2024) in a Danish population-based survey reported a prevalence of approximately 44.2% in patients with T2DM. These similarities in prevalence could be attributed to the similarity in the methodologies employed in the diagnosis and classification of DAN. All these studies used the COMPASS 31 questionnaire, a validated screening tool for autonomic dysfunction that has been used extensively in research.

The findings of the current study also agree with studies conducted in Africa. Notably, Migisha et al (2020), looking at cardiovascular autonomic neuropathy, a component of diabetes autonomic neuropathy, documented a prevalence of 52% among patients with diabetes in Uganda. In addition, Eze et al (2013) in Nigeria found

a similar prevalence of 48%. This consistently high prevalence of autonomic dysfunction among individuals with diabetes in low and middle-income countries may be attributed to late diagnosis and suboptimal glycemic control of diabetes in these study populations.

The findings of the current study contrast with some studies looking at DAN. Hossain et al (2022) in Rajshahi, Bangladesh, found a significantly lower prevalence of 19.33%. The variance in results may stem from differences in study population, methodology, and data collection tools used to assess autonomic abnormalities. First, the Bangladesh study might have recorded a lower prevalence because of the younger mean age of their participants of 55 years, compared to our study which had a mean age of 61 years. In addition, the variance seen between the current study and the study by Hossain et al (2022) could be attributed to the use of different diagnostic tools. Their study screened for DAN using investigator self-generated questions identifying the presence or absence of DAN which included: nocturnal diarrhea, sexual dysfunction, urinary incontinence, abnormal sweating, and postural hypotension, whereas our study employed the use of standardized and validated COMPASS 31.

The prevalence of 53% demonstrated in our study is much lower compared to a study conducted by Meyer et al., (2004) among 45 T2DM patients, which reported autonomic neuropathy at 73% of its participants. The study by Meyer had a significantly smaller sample size and primarily utilized a cardiovascular reflex test to assess DAN. In contrast, the current study used scores generated from the COMPASS 31 questionnaire. In addition, the difference in prevalence might be attributed to differences in the characteristics of the study populations: age, diabetes duration, and glycemic control.

Analysis of autonomic dysfunction according to the domains affected revealed that the most common domain affected is the gastrointestinal at 65.41%. This is followed by secretomotor at 62.41%, pupillomotor at 53.78%, orthostatic domain at 48.26%, vasomotor domain at 31.40% and the bladder domain at 29.36%. These trends are consistent with those reported by Meling et al (2024) who identified that the most reported autonomic dysfunction was Gastrointestinal and secretomotor symptoms.

Notably, the females' COMPASS 31 non-weighted total scores were higher than the male gender in this study. Similar trends were also demonstrated in all 6 domains of the COMPASS 31. These results could be attributed to underreporting of symptoms among men, which has been proposed for other conditions, including self-reporting in depression (Shi et al., 2021). In addition, female sex hormones have been shown to affect GI motility causing females to have a slower gastric emptying rate compared to males (Khalil et al., 2024). Our findings agree with those of Choung et al., 2012, who observed that females with T2DM tend to report more frequent and severe GI symptoms than males. Other studies with similar findings include a study by Ko et al (2000) which reported that up to 70% of outpatients with Diabetes had GI symptoms and Huang et al 2020 reported a prevalence of 62 % in a cohort of T2DM evaluated at a hospital in South Korea.

The findings of our study highlight the need for better recognition of DAN as a common complication of T2DM with multiorgan implications. Furthermore, several studies showed that autonomic dysfunction in individuals with T2DM has a devastating impact on physical function and quality of life. There is thus a major role for early screening and timely institution of patient-centered individualized management of this complication to avert its effect on morbidity and mortality.

5.3 Sociodemographic Factors

5.3.1 Age

The mean age of our participants was 61, with a range of 31 to 84. Our findings also revealed that the majority of the patients were above the age of 60, which is comparable with figures in the International Diabetes Federation (IDF) 2018 fact sheet report. The report documented highest prevalence of diabetes in Africa being among adults aged 55-64 years. The higher prevalence of diabetes among older populations is expected owing to the gradual decline in β -cell function as well as increased obesity with aging, resulting in higher insulin resistance.

Contrasting with the findings of Schramm et al., 2024; and Thekkur et al., 2019, who demonstrated increased diabetic autonomic neuropathy with increasing age, the current study demonstrated no statistically significant association. This difference could be because majority of our participants were aged above 60 years, a population that has been shown to have multiple other age-related factors affecting the nervous system.

5.3.2 Gender

5.3.2.1 Gender Distribution among Study Participants

The current study randomly enrolled more females (65.4%) than males, indicating a higher clinic attendance among females. Similar trends were reported by Thekkur P et al (2019) and Meling S et al (2023) who both showed a higher female proportion among their study population. These findings could be explained by a higher prevalence of T2DM females, as previously documented by Alrashed et al., (2024). Secondly, this distribution might be explained by the fact that females have been shown to have better health-seeking behavior (Boerma et al., 2016).

5.3.2.2 Gender and Diabetic Autonomic Neuropathy

In the current study, females were found to have higher COMPASS-31 scores than males indicating worse DAN among females. This finding agrees with that of Thekkur et al., (2019) who also showed higher DAN among females. Several factors could explain these gender differences in the association of DAN. First, hormonal factors may influence diabetic autonomic neuropathy and lead to different clinical outcomes and risks between men and women. Further, the influence of estrogen on neuroinflammation and autonomic function may exacerbate autonomic dysfunction in women with T2DM (Fouda et al., 2020). Moreover, other studies have established that females with T2DM have higher glycemic variability due to hormonal variability, which reduces autonomic modulation and increases DAN risk (Fleischer et al., 2015). In contrast to our study, Tesface et. al., (2020) found no association, demonstrating that factors such as age, diabetes duration, and glycemic control might have overshadowed the effect of gender on autonomic dysfunction.

5.2.3 Education Level

The current study demonstrated that a majority of study participants had their highest level of education being primary, 198 (57.56%) followed by secondary, 75 (21.80%) and tertiary education 71 (20.64%) respectively. There was no statistically significant association between DAN as measured by COMPASS-31 and the level of education in this study. This finding contrasts with those from prior studies that have shown that individuals with lower educational attainment have less awareness of diabetes complications and adhere less to lifestyle modification recommendations. Higher educational attainment is linked to earlier diabetes detection, which may potentially lower the risk of complications during the initial stages of diagnosis (Liao et al.,

2023). The differences between our study and these other prior studies could be explained by differences in geographic distribution and socio-economic status.

5.4 Clinical Factors

5.4.1 Glycemic Control and Diabetic Autonomic Neuropathy

Glycemic control was determined by measuring levels of HbA1c, with findings demonstrating largely poorly controlled diabetes. Notably, only 17.44% of the participants had achieved the desired HbA1C level of $\leq 7\%$ as recommended by the American Diabetes Association (Rodríguez-Gutiérrez & Montori, 2016b). Several recent studies have also established poor glycemic control to be prevalent among individuals with T2DM, with some reporting rates as high as 73% (Gabriel et al., 2024). This suboptimal control could be due to suboptimal knowledge on diabetes, poor compliance, financial constraints, the presence of co-morbid states like obesity, and poor health-seeking habits (Ogurtsova et al., 2022)

The exploration of correlation between HbA1c and DAN demonstrated that there was no statistically significant association. These findings are in agreement those of a study by Schramm et al., (2024), which found no association between DAN and HbA1c. A possible explanation for their findings is that HbA1c levels are only a reflection of short-term glycemic control (past 2-3 months) whereas DAN development occurs over years to decades. Moreover, there could be the effect of reverse causality, where patients become proactive in controlling their blood sugar once they develop complications attributed to diabetes.

These findings contrast those of a study by Hossian et al., (2022), which demonstrated a significant correlation between HbA1c above 9.0% and the prevalence of DAN. These observations could be attributed to the central role of persistent hyperglycemia

in the pathophysiology of DAN, where damage to autonomic nerve fibers, is driven by impaired neuronal blood flow, accumulation of advanced glycosylation end products and oxidative stress.(Hossain et al., 2022).

5.4.2 Renal Function and Diabetic Autonomic Neuropathy

Kidney function was assessed by measuring the serum creatinine levels and calculating the estimated glomerular filtration rate (eGFR). This study established that two-thirds of the study participants had abnormal kidney function, with approximately 30% having CKD stages 3–5(eGFR<60 mL/min/1.73m²). This distribution agrees with findings of Rodriguez-Poncelas et. al., (2013) and Kittiskulnam et al., (2018). Similar trends were also documented in studies by Jitraknatee et. al., (2020) and Silva-Tinoco et. al., (2024), which reported CKD stages 3–5 (eGFR<60 mL/min/1.73m²) at 24.4% vs. 35.4%, respectively.

The current study demonstrated that there was a positive association between DAN and kidney dysfunction as measured by estimated glomerular filtration rate (eGFR). This finding agrees with findings by Cho et. al., (2024) and Tang et. al., (2024). In addition, Lai et. al., (2021) and Tang et. al., (2024) demonstrated that autonomic dysfunction is a significant predictor of rapid decline in kidney function and influences the severity of kidney disease in individuals with T2DM. These findings are attributed to the central role of chronic hyperglycemia in the pathophysiological mechanisms of DAN and other microvascular complications. These microvascular complications result from increased oxidative stress, accumulation of advanced glycosylated end products, concentration of sorbitol, as well as disturbance in the hexosamine and protein C kinase pathways(González et al., 2023).

5.4.3 Lipid Profile and Diabetic Autonomic Neuropathy

The current study demonstrated that almost 50% of participants had dyslipidemia. The mean LDL level was determined to be 2.6 mmol/L (SD 0.9). A total of 156 (45.3%) participants had LDL-cholesterol greater than the reference upper limit of 2.6 mmol/L. The mean HDL level was determined to be at 1.3 mmol/L (SD 0.4). A total of 151 (43.9%) participants had HDL-cholesterol levels lower than the reference level (female <1.3mmol/L and Male <1 mmol/L). The mean total cholesterol was 4.2 mmol/L (SD 1.1). A total of 62 (18.02%) participants had total cholesterol greater than the reference upper limit of 5.17 mmol/L. The mean triglyceride level was 1.62 mmol/L (SD 5.0). A total of 156 (45.35%) had triglycerides levels greater than the reference upper limit of 1.7 mmol/L

The findings of the current study on the prevalence of dyslipidemia among patients with diabetes agree with those Ekpor et al., (2024) that showed rates of 24% to 64% for the various components of the lipid profile. These lipid abnormalities have been implicated in the pathogenesis of DAN as they play a role in endothelial dysfunction and vascular inflammation (Serhiyenko & Serhiyenko, 2018). Despite these deranged lipid profile levels, two-thirds of the study participants were on lipid-lowering agents.

Our study did not find any significant association between DAN and dyslipidemia. This is in agreement with findings of a study in Iraq conducted in 2011 that demonstrated no significant association between DAN and lipid profile (Al-Ani et al., 2011). Our findings contrast with those of Wang et al., (2022) that demonstrated a positive correlation between average blood glucose levels and TG levels, LDL and LDL-C/HDL-C ratio. This difference could be explained by differences in diets,

different levels of metabolic syndrome as well as differences in the population genetic makeup.

The findings of this study also demonstrate DAN was inversely correlated with the use of lipid-lowering agents, where users were 60.3% less likely to have diabetic autonomic neuropathy compared to non-users. These findings are aligned with those of a Danish cohort study, which demonstrated a 35% risk reduction in the development of diabetic neuropathy among 15,679 T2DM statin users (Kristensen et al., 2020). Similarly, a Taiwanese study investigating the effect of statins on diabetic neuropathy among T2DM individuals found a 15% reduction in risk of new neuropathy among statin users relative to non-statin users (Chang et al., 2023).

5.5 Study Strengths and Limitation

The strength of this study on the prevalence and factors associated with DAN in T2DM patients lies in the diagnostic tool used to assess for autonomic neuropathy, the COMPASS 31 questionnaire. It evaluates the severity and distribution of autonomic dysfunction in multiple domains enabling a comprehensive and objective assessment of autonomic symptoms. This study also includes evaluation of laboratory tests for recognized risk factors for DAN, allowing extensive exploration of associated factors.

Although our study provides valuable insights into the prevalence and factors associated with DAN in T2DM patients, it is important to acknowledge certain limitations. First, the COMPASS-31 is a subjective, symptom-based tool that may overestimate autonomic dysfunction due to non-specific symptoms, recall bias, and fixed domain weights, and it cannot detect subclinical DAN or provide direct physiological measurements. This was mitigated by providing a Kiswahili translated

version of the questionnaire and collaborating responses with clinician observation and caregiver response. In addition, referral bias may have influenced this study's findings because participants were recruited from a tertiary hospital, where patients often have more severe or complicated diabetes and multiple comorbidities. Consequently, the observed prevalence of diabetic autonomic neuropathy may be higher than in the general population, and some associated risk factors may appear stronger. This limits the generalizability of the results, and future studies should include participants from community or primary care settings to obtain more representative estimates. This effect was limited by using a randomized systematic sampling technique to recruit participants for the study. Moreover, this was a cross-sectional study, limiting the ability to assign the time directionality of the association between factors associated with DAN and DAN itself.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The current study demonstrated the prevalence of diabetic autonomic neuropathy among patients with T2DM attending the diabetes outpatient clinic at MTRH to be 53%. There was an inverse correlation between DAN and the use of lipid-lowering agents. There was a positive association between DAN and kidney dysfunction.

6.2 Recommendation

Autonomic dysfunction assessment should be considered in all persons with diabetes during follow-up clinics given the high prevalence of diabetic autonomic neuropathy (DAN) and the rising global burden of diabetes.

The management of diabetes should include targeting the modifiable factors associated with DAN. This would include early initiation of lipid lowering agents, optimal glycemic control and management of diabetic nephropathy.

The Current guidelines may be reviewed to accord DAN more emphasis as it is a prevalent complication and it impacts the quality of life, morbidity, and mortality.

Lastly, there is a need for future longitudinal studies exploring the clinical significance and long-term outcomes associated with DAN among individuals with diabetes.

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APPENDICES

Appendix 1: The Composite Autonomic Symptom Score tool (COMPASS-31)

1. In the past year, have you ever felt faint, dizzy, “goofy”, or had difficulty thinking soon after standing up from a sitting or lying position?
 - 1 Yes
 - 2 No (if you marked No, please skip to question 5)
2. When standing up, how frequently do you get these feelings or symptoms?
 - 1 Rarely
 - 2 Occasionally
 - 3 Frequently
 - 4 Almost Always
3. How would you rate the severity of these feelings or symptoms?
 - 1 Mild
 - 2 Moderate
 - 3 Severe
4. In the past year, have these feelings or symptoms that you have experienced:
 - 1 Gotten much worse
 - 2 Gotten somewhat worse
 - 3 Stayed about the same
 - 4 Gotten somewhat better
 - 5 Gotten much better
 - 6 Completely gone
5. In the past year, have you ever noticed color changes in your skin, such as red, white, or purple?
 - 1 Yes
 - 2 No (if you marked No, please skip to question 8)
6. What parts of your body are affected by these color changes? (Check all that apply)
 - 1 Hands
 - 2 Feet
7. Are these changes in your skin color:
 - 1 Getting much worse
 - 2 Getting somewhat worse
 - 3 Staying about the same
 - 4 Getting somewhat better
 - 5 Getting much better

6 Completely gone

8. In the past 5 years, what changes, if any, have occurred in your general body sweating?

- 1 I sweat much more than I used to
- 2 I sweat somewhat more than I used to
- 3 I haven't noticed any changes in my sweating
- 4 I sweat somewhat less than I used to
- 5 I sweat much less than I used to

9. Do your eyes feel excessively dry?

- 1 Yes
- 2 No

10. Does your mouth feel excessively dry?

- 1 Yes
- 2 No

11. For the symptom of dry eyes or dry mouth that you have had for the longest period of time, is this symptom:

- 1 I have not had any of these symptoms
- 2 Getting much worse
- 3 Getting somewhat worse
- 4 Staying about the same
- 5 Getting somewhat better
- 6 Getting much better
- 7 Completely gone

12. In the past year, have you noticed any changes in how quickly you get full when eating a meal?

- 1 I get full a lot more quickly now than I used to
- 2 I get full more quickly now than I used to
- 3 I haven't noticed any change
- 4 I get full less quickly now than I used to
- 5 I get full a lot less quickly now than I used to

13. In the past year, have you felt excessively full or persistently full (bloated feeling) after a meal?

- 1 Never
- 2 Sometimes
- 3 A lot of the time

14. In the past year, have you vomited after a meal?

- 1 Never
- 2 Sometimes
- 3 A lot of the time

15. In the past year, have you had a cramping or colicky abdominal pain?

- 2 No (if you marked No, please skip to question 20)
17. How frequently does this occur?
- 1 Rarely
 - 2 Occasionally
 - 3 Frequently _____ times per month
 - 4 Constantly
18. How severe are these bouts of diarrhea?
- 1 Mild
 - 2 Moderate
 - 3 Severe
19. Are your bouts of diarrhea getting:
- 1 Much worse
 - 2 Somewhat worse
 - 3 Staying the same
 - 4 Somewhat better
 - 5 Much better
 - 6 Completely gone
20. In the past year, have you been constipated?
- 1 Yes
 - 2 No (if you marked No, please skip to question 24)
21. How frequently are you constipated?
- 1 Rarely
 - 2 Occasionally
 - 3 Frequently _____ times per month
 - 4 Constantly
22. How severe are these episodes of constipation?
- 1 Mild
 - 2 Moderate
 - 3 Severe
23. Is your constipation getting:
- 1 Much worse
 - 2 Somewhat worse
 - 3 Staying the same
 - 4 Somewhat better
 - 5 Much better
 - 6 Completely gone
24. In the past year, have you ever lost control of your bladder function?
- 1 Never
 - 2 Occasionally
 - 3 Frequently _____ times per month

- 4 Constantly
25. In the past year, have you had difficulty passing urine?
- 1 Never
 - 2 Occasionally
 - 3 Frequently _____ times per month
 - 4 Constantly
26. In the past year, have you had trouble completely emptying your bladder?
- 1 Never
 - 2 Occasionally
 - 3 Frequently _____ times per month
 - 4 Constantly
27. In the past year, without sunglasses or tinted glasses, has bright light bothered your eyes?
- 1 Never (if you marked Never, please skip to question 29)
 - 2 Occasionally
 - 3 Frequently
 - 4 Constantly
28. How severe is this sensitivity to bright light?
- 1 Mild
 - 2 Moderate
 - 3 Severe
29. In the past year, have you had trouble focusing your eyes?
- 1 Never (if you marked Never, please skip to question 31)
 - 2 Occasionally
 - 3 Frequently
 - 4 Constantly
30. How severe is this focusing problem?
- 1 Mild
 - 2 Moderate
 - 3 Severe
31. Is the most troublesome symptom with your eyes (i.e. sensitivity to bright light or trouble focusing) getting:
- 1 I have not had any of these symptoms
 - 2 Much worse
 - 3 Somewhat worse
 - 4 Staying about the same
 - 5 Somewhat better
 - 6 Much better
 - 7 Completely gone

4 Staying about the same

5 Somewhat better

6 Much better

7 Completely gone

1) COMPASS-31 Scoring Algorithm

Domain	Item	Answer	Points
Orthostatic Intolerance	1	1	1
		2	0
	2	1	0
		2	1
		3	2
		4	3
	3	1	1
		2	2
		3	3
	4	1	3
		2	2
		3	1
		4-6	0
Vasomotor	5	1	1
		2	0
	6	1	1
		2	1
	7	1	3
		2	2
		3	1
		4-6	0
Secretomotor	8	1	1
		2	0
		3	0
		4	1
		5	2
		6	0
	9	1	1
		2	0
	10	1	1
		2	0
	11	1	0
		2	3
		3	2
		4	1

		5-7	0
Gastrointestinal	12	1	2
		2	1
		3-5	0
	13	1	0
		2	1
		3	2
	14	1	0
		2	1
		3	2
	15	1	0
		2	1
		3	2
	16	1	1
		2	0
	17	1	0
		2	1
		3	2
		4	3
	18	1	1
		2	2
		3	3
	19	1	3
		2	2
		3	1
		4-6	0
	20	1	1
		2	0
	21	1	0
		2	1
		3	2
		4	3
	22	1	1
		2	2
		3	3
	23	1	3
		2	2
		3	1
		4-6	0
Bladder	24	1	0
		2	1
		3	2
		4	3
	25	1	0
		2	1
		3	2
		4	3
	26	1	0
		2	1
		3	2
		4	3

Pupillomotor	27	1	0
		2	1
		3	2
		4	3
	28	1	1
		2	2
		3	3
	29	1	0
		2	1
		3	2
		4	3
	30	1	1
		2	2
		3	3
	31	1	0
		2	3
		3	2
		4	1
		5-7	0

Calculation of COMPASS-31-score

1. Orthostatic Intolerance-score: Sum of items 1-4 multiplied by 4
2. Vasomotor-score: Sum of items 5-7 multiplied by 0.8333
3. Secretomotor-score: Sum of items 8-11 multiplied by 2.1428571
4. Gastrointestinal-score: Sum of items 12-23 multiplied by 0.8928571
5. Bladder-score: Sum of items 24-26 multiplied by 1.111
6. Pupillomotor-score: Sum of items 27-31 multiplied by 0.333
7. COMPASS-31-score: Sum of all 6 domain scores

Appendix 2: Questionnaire.**Autonomic Neuropathy among Diabetes Patient's at Moi Teaching And Referral Hospital, Eldoret, Kenya.**

Study Number: _____ Date: _____

PART A: HISTORY

1. Age (years): _____

2. Sex: _____

3. Marrital Status:

Single ☐ Married ☐ Separated/Divorced ☐ ☐

Widowed

4. Level of Education

Single ☐ Married ☐ Separated/Divorced ☐ ☐

Widowed

5. Duration of Diabetes (years): _____

6. Treatment Modality:

Oral antihyperglycemic agents ☐Insulin ☐Insulin + Oral antihyperglycemic agents ☐

7. Reported Compliance

Number of days medication missed in the last 1 month: _____

8. Cormobidities

Hypertension: Yes ☐ No ☐**PART B: PHYSICAL EXAM**

9. Weight (Kgs): _____

10. Height (Meters): _____

11. BMI (Kgs/m²): _____

12. Blood Pressure (mmHg): _____ / _____

13. Heart Rate (Beats/Min): _____

14. Respiratory Rate (Breathes/ Min): _____

15. Monofilament Test:

Positive ☐Negative ☐

PART C: THE COMPOSITE AUTONOMIC SYMPTOM SCORE TOOL**(COMPASS-31)**

1. In the past year, have you ever felt faint, dizzy, “goofy”, or had difficulty thinking soon after standing up from a sitting or lying position?
 - 1 Yes
 - 2 No (if you marked No, please skip to question 5)
2. When standing up, how frequently do you get these feelings or symptoms?
 - 1 Rarely
 - 2 Occasionally
 - 3 Frequently
 - 4 Almost Always
3. How would you rate the severity of these feelings or symptoms?
 - 1 Mild
 - 2 Moderate
 - 3 Severe
4. In the past year, have these feelings or symptoms that you have experienced:
 - 1 Gotten much worse
 - 2 Gotten somewhat worse
 - 3 Stayed about the same
 - 4 Gotten somewhat better
 - 5 Gotten much better
 - 6 Completely gone
5. In the past year, have you ever noticed color changes in your skin, such as red, white, or purple?
 - 1 Yes
 - 2 No (if you marked No, please skip to question 8)
6. What parts of your body are affected by these color changes? (Check all that apply)
 - 1 Hands
 - 2 Feet
7. Are these changes in your skin color:
 - 1 Getting much worse
 - 2 Getting somewhat worse
 - 3 Staying about the same
 - 4 Getting somewhat better
 - 5 Getting much better
 - 6 Completely gone
8. In the past 5 years, what changes, if any, have occurred in your general body sweating?
 - 1 I sweat much more than I used to
 - 2 I sweat somewhat more than I used to

- 3 I haven't noticed any changes in my sweating
- 4 I sweat somewhat less than I used to
- 5 I sweat much less than I used to

9. Do your eyes feel excessively dry?

- 1 Yes
- 2 No

10. Does your mouth feel excessively dry?

- 1 Yes
- 2 No

11. For the symptom of dry eyes or dry mouth that you have had for the longest period of time, is this symptom:

- 1 I have not had any of these symptoms
- 2 Getting much worse
- 3 Getting somewhat worse
- 4 Staying about the same
- 5 Getting somewhat better
- 6 Getting much better
- 7 Completely gone

12. In the past year, have you noticed any changes in how quickly you get full when eating a meal?

- 1 I get full a lot more quickly now than I used to
- 2 I get full more quickly now than I used to
- 3 I haven't noticed any change
- 4 I get full less quickly now than I used to
- 5 I get full a lot less quickly now than I used to

13. In the past year, have you felt excessively full or persistently full (bloated feeling) after a meal?

- 1 Never
- 2 Sometimes
- 3 A lot of the time

14. In the past year, have you vomited after a meal?

- 1 Never
- 2 Sometimes
- 3 A lot of the time

15. In the past year, have you had a cramping or colicky abdominal pain?

- 1 Never
- 2 Sometimes
- 3 A lot of the time

16. In the past year, have you had any bouts of diarrhea?

- 1 Yes

- 2 No (if you marked No, please skip to question 20)
17. How frequently does this occur?
- 1 Rarely
 - 2 Occasionally
 - 3 Frequently _____ times per month
 - 4 Constantly
18. How severe are these bouts of diarrhea?
- 1 Mild
 - 2 Moderate
 - 3 Severe
19. Are your bouts of diarrhea getting:
- 1 Much worse
 - 2 Somewhat worse
 - 3 Staying the same
 - 4 Somewhat better
 - 5 Much better
 - 6 Completely gone
20. In the past year, have you been constipated?
- 1 Yes
 - 2 No (if you marked No, please skip to question 24)
21. How frequently are you constipated?
- 1 Rarely
 - 2 Occasionally
 - 3 Frequently _____ times per month
 - 4 Constantly
22. How severe are these episodes of constipation?
- 1 Mild
 - 2 Moderate
 - 3 Severe
23. Is your constipation getting:
- 1 Much worse
 - 2 Somewhat worse
 - 3 Staying the same
 - 4 Somewhat better
 - 5 Much better
 - 6 Completely gone
24. In the past year, have you ever lost control of your bladder function?
- 1 Never
 - 2 Occasionally
 - 3 Frequently _____ times per month

- 4 Constantly
25. In the past year, have you had difficulty passing urine?
- 1 Never
- 2 Occasionally
- 3 Frequently _____ times per month
- 4 Constantly
26. In the past year, have you had trouble completely emptying your bladder?
- 1 Never
- 2 Occasionally
- 3 Frequently _____ times per month
- 4 Constantly
27. In the past year, without sunglasses or tinted glasses, has bright light bothered your eyes?
- 1 Never (if you marked Never, please skip to question 29)
- 2 Occasionally
- 3 Frequently
- 4 Constantly
28. How severe is this sensitivity to bright light?
- 1 Mild
- 2 Moderate
- 3 Severe
29. In the past year, have you had trouble focusing your eyes?
- 1 Never (if you marked Never, please skip to question 31)
- 2 Occasionally
- 3 Frequently
- 4 Constantly
30. How severe is this focusing problem?
- 1 Mild
- 2 Moderate
- 3 Severe
31. Is the most troublesome symptom with your eyes (i.e. sensitivity to bright light or trouble focusing) getting:
- 1 I have not had any of these symptoms
- 2 Much worse
- 3 Somewhat worse
- 4 Staying about the same
- 5 Somewhat better
- 6 Much better
- 7 Completely gone

PART D: LABORATORY INVESTIGATION

No:	Test	Date	Result
1	HbA1c		
2	Lipid	Low	Density
	Profile	Lipoprotein	
		High	Density
		Lipoprotein	
		Total	
		Cholesterol	
		Triglyceride	
3	U/E/Crs		

*Interviewer Signature*_____

Appendix 3A: Informed Consent (English)**Title: Prevalence And Factors Associated with Autonomic Neuropathy Among Diabetes Patients at Moi Teaching and Referral Hospital, Kenya.**

My name is Dr Lorna Kimetto. I am a medical doctor currently pursuing a Master's degree in Internal Medicine at Moi University. I would like to recruit you today into my research which is looking at autonomic neuropathy in T2DM patients that are receiving care at MTRH DOPC.

Purpose of the study:

The purpose of this study is to establish the burden of autonomic neuropathy among patients with T2DM in MTRH in order to institute appropriate measures to manage the condition and improve quality of life.

What does the study involve?

In this study, you will be asked to provide your sociodemographic information which includes age, sex, marital status, occupation, level of education among others. A tool called COMPASS-31 shall also be used to assess for diabetes autonomic neuropathy. Blood will also be drawn from you and taken to the laboratory for biochemical assessment of the levels of HBA1c and LDL Cholesterol

There are minimal risks involved in this study. These include but not limited to pain at the injection site and swelling at the site of the injection. Blood samples will be safely discarded after the study. In addition, your involvement in the study shall consume approximately 30 minutes of your time.

The result of the study will be stored in a database that is password protected and only accessible by those conducting the study. No one will be able to identify you or your results should data be published; no

individual information will be disclosed. Your participation in this study is voluntary. If you decide to participate you can change your mind later and quit the study before the end. If you decide not to participate or if you quit the study it will not affect the health care services you receive at the clinic. By signing this document, you are voluntarily agreeing to participate. You are free to decline to answer any question you don't wish to answer for any reason.

Consent form

I....., having been explained to and well understood the nature and purpose of this study by....., do hereby voluntarily agree to participate in the study. I agree to willingly answer the questions honestly and undergo the laboratory investigations that have been explained to me.

Signature of Participant

Date/Time

I have explained to the above Participant the nature and purpose, the potential benefits, and possible risks associated with participation in this research study. I have answered all questions that have been raised.

Name of Person Obtaining
Consent

Signature of Person Obtaining
Consent

Date/Time

If you need further clarifications, feel free to contact IREC using the address below.

The Administrator IREC

Moi Teaching and Referral Hospital,

PO Box 3,

Eldoret.

Tel: 33471/2/3

You can also contact me (Dr. Lorna Kimetto) on 0711479294

Appendix 3B: Informed Consent (Kiswahili)

Jina langu ni Daktari Lorna Kimetto. Nimehitimu udaktari na nimesajiliwa na bodi ya madaktari ya Kenya (Kenya Medical Practitioners and Dentists Board). Mimi ni msomi wa shahada ya juu (Masters) ya udaktari (Internal medicine) katika chuo kikuu cha Moi. Nimekuona leo kwa sababu ninafanya utafiti wa kuangalia matatizo ya mishipa kati ya watu walio na ugonjwa wa sukari.

Lengo kuu la utafiti huu ni kutambua jinsi shida hii ilivyo kidhiri kati ya wale wanao ugua ugonjwa wa sukari na wanaopata matibabu yao katika hospitali kuu ya MTRH. Hii itatuwezesha kuweka mikakati bora ya matibabu kabla ugonjwa huu haujaenea na kuleta madhara mwilini.

Katika utafiti huu, utahitajika kutueleza maswala kadha wa kadha kukuhusu. Kwa mfano, miaka, jinsia, kiwango ulichokifikia cha masomo na kadhalika. Kifaa chenye maswali kiitwacho COMPASS-31 kitatumika kuangazia uwepo wa shida ya mishipa. Utahitajika pia kutolewa damu itakayo pelekwa mahabara nakuangalia kiwango cha mafuta mwilini na kipimo cha sukari mwilini.

Utafiti huu hauna madhara kuu kwako mbali na uchungu utakaosikia unapotolewa damu ama uvimbe mdogo mahala utakapotolewa damu. Hata hivyo, uvimbe huu hautakawia kwa muda mrefu. Kuhusika kwako kwa utafiti huu utakugarimu takriban dakita thelathini.

Una huru wa kukubali ama kukataa kuwa katika utafiti huu. Unaweza pia kujiiondoa wakati wowote unapohisi. Kukataa kwako ama kujiiondoa katika utafiti huu hauta dhuru jinsi utakavyo hudumiwa katika hospitali hii sasa wala siku za usoni.

Unajulishwa kwamba kushiriki kwako katika utafiti huu ni kwa hiari yako na sio kwa kulazimishwa naunaweza jiondoa katika utafiti huu wakati wowote. Habari zote tutakazopata kuhusiana nawe na afya yako italindwa na uaminifu wote.

Mimi.....baada ya kufafanuliwa nakuelezwa na..... kiini cha utafiti huu na jinsi utakavyotekelezwa nimekubali kushiriki katika utafiti huu bila kushurutishwa. Nakubali kuyajibu maswali yote kwa uaminifu na pia kutolewa damu itakayopelekwa kwenye mahabara kwa uchunguzi.

Sahihi

Tarehe/ Saa

Nimemweleza mhusika nia, uzuri na hatari ya kujihusisha kwa utafiti huuna nimejibu maswali zote zilizoulizwa.

Jina ya Mtafiti

Sahihi

Tarehe/Saa

Iwapo utahitaji maelezo zaidi, usikose kuwasilianana IREC ukitumia anwani ifuatayo

Administrator IREC

Moi Teaching and Referral Hospital,

Sanduku la Posta 3,

Eldoret.

Simu: 33471/2/3

Unaweza pia wasilianana mi (Dr.Lorna Kimetto) ukitumia nambari ya simu ifuatayo:

0711479294

Appendix 4: Time Schedule

Activity	Commencement Date	Completion Date
Proposal Development and Writing	January 2023	August 2023
IREC Approval	August 2023	October 2023
Data Collection	March 2024	June 2024
Data Cleaning and Analysis	June 2024	July 2024
Thesis Writing	July 2024	December 2024

Appendix 5: Estimated Project Budget

The projected budget estimate for this study is as below. The funds required for this study was obtained from the researcher's personal resources.

Item	Cost
Laboratory Costs	450,000/-
Research Assistants	25,000/-
Statistical Consultation	25,000/-
Stationery	18,000/-
Printing Costs	30,000/-
Miscellaneous	20,000/-
Total	568,000/-

Appendix 6: IREC Approval Letter

 MTRH/MU-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC) MOI TEACHING AND REFERRAL HOSPITAL P.O. BOX 3 ELDORET Tel: 33471/2/3	 MOI UNIVERSITY COLLEGE OF HEALTH SCIENCES P.O. BOX 4606 ELDORET Tel: 33471/2/3 25th January, 2024																						
Reference: IREC/658/2023 Approval Number: 0004623																							
Dr. Lorna Chepng'etich Kimetto, Moi University, School of Medicine, P.O. Box 4606-30100, <u>ELDORET-KENYA.</u>																							
Dear Dr. Kimetto,																							
<u>PREVALENCE AND FACTORS ASSOCIATED WITH AUTONOMIC NEUROPATHY AMONG DIABETES PATIENTS AT MOI TEACHING AND REFERRAL HOSPITAL, KENYA</u>																							
This is to inform you that MTRH/MU-IREC has reviewed and approved the above referenced research proposal. Your application approval number is FAN: 0004623. The approval period is 25th January, 2024 – 24th January, 2025. This approval is subject to compliance with the following requirements;																							
i. Only approved documents including (informed consents, study instruments, Material Transfer Agreements (MTA) will be used. ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by MTRH/MU-IREC. iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to MTRH/MU-IREC within 72 hours of notification. iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to MTRH/MU-IREC within 72 hours. v. Clearance for export of biological specimens must be obtained from MOH at the recommendation of NACOSTI for each batch of shipment. vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal. vii. Submission of an executive summary report within 90 days upon completion of the study to MTRH/ MU-IREC.																							
Prior to commencing your study; you will be required to obtain a research license from the National Commission for Science, Technology and Innovation (NACOSTI) https://oris.nacosti.go.ke and other relevant clearances from study sites including a written approval from the CEO-MTRH which is mandatory for studies to be undertaken within the jurisdiction of Moi Teaching & Referral Hospital (MTRH) and its satellites sites.																							
Sincerely,  PROF. E. WERE CHAIRMAN INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE  25 JAN 2024 APPROVED																							
<table border="0" style="width: 100%;"> <tr> <td>cc</td> <td>CEO</td> <td>-</td> <td>MTRH</td> <td>-</td> <td>Dean</td> <td>-</td> <td>SOP</td> <td>Dean</td> <td>-</td> <td>SOM</td> </tr> <tr> <td></td> <td>Principal</td> <td>-</td> <td>CHS</td> <td>-</td> <td>Dean</td> <td>-</td> <td>SON</td> <td>Dean</td> <td>-</td> <td>SOD</td> </tr> </table>		cc	CEO	-	MTRH	-	Dean	-	SOP	Dean	-	SOM		Principal	-	CHS	-	Dean	-	SON	Dean	-	SOD
cc	CEO	-	MTRH	-	Dean	-	SOP	Dean	-	SOM													
	Principal	-	CHS	-	Dean	-	SON	Dean	-	SOD													

Appendix 7: MTRH Approval Letter



MOI TEACHING AND REFERRAL HOSPITAL

Telephone: (+254)-0532033471/2/3/4
 Fax: 0532061749
 Email: ceo@mtrh.go.ke/ceosoffice@mtrh.go.ke

NANDI ROAD
 P.O. BOX 3-30100
ELDOR ET, KENYA

Ref: ELD/MTRH/R&F/10/2/V.2/2010 29th January, 2024

Dr. Lorna Chepng'etich Kimetto,
 Moi University,
 School of Medicine,
 P.O. Box 4606-30100,
ELDOR ET-KENYA.

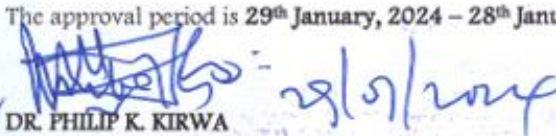
PREVALENCE AND FACTORS ASSOCIATED WITH AUTONOMIC NEUROPATHY AMONG DIABETES PATIENTS AT MOI TEACHING AND REFERRAL HOSPITAL, KENYA

You have been authorised to conduct research within the jurisdiction of Moi Teaching and Referral Hospital (MTRH) and its satellites sites. You are required to strictly adhere to the regulations stated below in order to safeguard the safety and well-being of staff, patients and study participants seen at MTRH.

- 1 The study shall be under Moi Teaching and Referral Hospital regulation.
- 2 A copy of MTRH/MU-IREC approval shall be a prerequisite to conducting the study.
- 3 Studies intending to export human bio-specimens must provide a permit from MOH at the recommendation of NACOSTI for each shipment.
- 4 No data collection will be allowed without an approved consent form(s) to participants unless waiver of written consent has been granted by MTRH/MU-IREC.
- 5 Take note that **data** collected must be treated with due confidentiality and anonymity.

The continued permission to conduct research shall only be sustained subject to fulfilling all the requirements stated above.

The approval period is **29th January, 2024 – 28th January, 2025.**



DR. PHILIP K. KIRWA
Ag. CHIEF EXECUTIVE OFFICER



c.c. - Ag. Senior Director, Clinical Services
 - Director, Nursing Services
 - HOD, HRISM

All correspondences should be addressed to the Chief Executive Officer
 Visit our Website: www.mtrh.go.ke
TO BE A GLOBAL LEADER IN THE PROVISION OF EXCEPTIONAL MULTI-SPECIALTY HEALTH CARE, TRAINING AND RESEARCH

Appendix 8: NACOSTI Research Approval

 REPUBLIC OF KENYA Ref No: 532328	 NATIONAL COMMISSION FOR SCIENCE, TECHNOLOGY & INNOVATION Date of Issue: 02/September/2024
RESEARCH LICENSE	
	
This is to Certify that Dr. Jorna chepngetich chepngetich of Moi University , has been licensed to conduct research as per the provision of the Science, Technology and Innovation Act, 2013 (Rev.2014) in Uasin-Gishu on the topic: Prevalence And Factors Associated with Autonomic Neuropathy Among Diabetes Patients at Moi Teaching and Referral Hospital, Kenya for the period ending : 02/September/2025 .	
License No: NACOSTI/P/24/38490 Applicant Identification Number	 Director General NATIONAL COMMISSION FOR SCIENCE, TECHNOLOGY & INNOVATION
Verification QR Code 	
NOTE: This is a computer generated License. To verify the authenticity of this document, Scan the QR Code using QR scanner application.	
See overleaf for conditions	