ARSI UNIVERSITY

COLLEGE OF HEALTH SCIENCES

DEPARTMENT OF INTERNAL MEDICINE

PREVALENCE AND DETERMINANT FACTORS OF CARDIOVASCULAR AUTONOMIC NEUROPATHY AMONG ADULT PATIENTS WITH DIABETES MELLITUS AT ASELLA REFERRAL & TEACHING HOSPITAL, ETHIOPIA.

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A RESEARCH THESIS TO BE SUBMITTED TO ARSI UNIVERSITY COLLEGE OF HEALTH SCIENCES, SCHOOL OF MEDICINE, DEPARTMENT OF INTERNAL MEDICINE, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR SPECIALITY CERTIFICATE IN INTERNAL MEDICINE.

January 2026,

Asella Ethiopia

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ABSTRACT

Background: *Diabetic cardiovascular autonomic neuropathy (CAN) is a serious but often missed diabetes complication, damaging nerves that control heart and blood vessel functions. In Ethiopia, data on CAN is limited, screening protocols are lacking, and awareness is low, calling for research to improve diabetes care.*

Objective: *To assess the prevalence of cardiovascular autonomic neuropathy and identify determinant factors among adult patients with diabetes mellitus attending follow-up at the diabetic clinic of Asella Referral and Teaching Hospital, Asella, Ethiopia.*

Method: *An Institution-based cross-sectional study was conducted at Asella Referral & Teaching Hospital from July 1 to December 30, 2025. A systematic random sampling technique was employed to select 392 participants. Data were collected by trained data collectors using pretested, structured, interviewer-adminstred questioners and standardised tests (CARTs). The collected data was exported to SPSS version 27.0 for comprehensive statistical analysis. A bivariate and multivariable logistic regression was applied to asses associations between dependent and independent variables. The odds ratio with a 95% CI was used to declare the strength of associations between dependent and independent variables. p-values less than 0.05 were considered statistically significant. Results were summarized and presented through texts, tables, and figures.*

Result: *Among 392 diabetic patients, CAN was prevalent in 66.1% (n = 259), with 35.0% exhibiting early CAN, 25.3% definite CAN and 6.1 severe CAN according to Ewing's severity score. Multivariable logistic regression identified female sex (AOR = 1.773, 95%CI: 1.008-3.117, p-value = 0.047), unemployment (AOR = 2.237, 95%CI: 1.026-4.876, p-value = 0.043), longer diabetes duration (≥10 years; AOR = 6.562, 95% CI: 3.38–12.739, p-value < 0.001), poor glycaemic control (3 month average FBS >130; AOR = 4.452, 95% CI: 2.548–7.779, p-value < 0.001), and hypertension (AOR = 2.817, 95% CI: 1.332–5.957, p-value = 0.007) as independent risk factors for CAN.*

Conclusion and Recommendation: *These findings highlight the substantial burden of CAN in this population and the critical role of modifiable risk factors. Routine screening for CAN using standardized autonomic testing should be incorporated into diabetes care, particularly for patients with prolonged disease duration, suboptimal glycaemic control, or hypertension.*

Keywords*;CARTs, Ewing's battery tests, cardiovascular autonomic neuropathy*

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List of abbreviations and acronyms

ANS: Autonomic Nervous System

AAN: American Academy of Neurology

ADA: American Diabetes Association

CAN: Cardiovascular Autonomic Neuropathy

CART: Cardiac Autonomic Reflex Testing

DCAN: Diabetic Cardiovascular Autonomic Neuropathy

DM: Diabetes Mellitus

HRV: Heart Rate Variability

IDF: International Diabetes Federation

WHO: World Health Organization

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1. Introduction

1.1 Background

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized as an energy source and overproduced due to inappropriate gluconeogenesis and glycogenolysis, resulting in hyperglycemia. Diabetes can be diagnosed by demonstrating increased glucose concentrations in venous plasma or increased A1C in the blood(1).

Globally, diabetes affected 529 million individuals in 2021, representing a prevalence of 6.1%. The International Diabetes Federation (IDF) projects a 59.7% rise in diabetes prevalence by 2050, reaching 1.31 billion cases (9.8% prevalence), with an annualized growth rate of 3.31%. The African region, particularly Ethiopia, is witnessing a growing burden of diabetes. Ethiopia reported an increase in diabetes cases from 1.4 million in 2011 to 1.9 million in 2021, underscoring the urgent need for targeted interventions(2,3).

Diabetic neuropathies are common long-term complications of diabetes, affecting various parts of the nervous system and impacting multiple organ systems, including the circulatory, gastrointestinal, genitourinary, and skin systems. Among these, cardiac autonomic neuropathy (CAN) is the most frequent form. CAN occurs when autonomic nerve fibers that regulate the heart and blood vessels are damaged, causing abnormalities in heart rate and vascular dynamics. This condition significantly contributes to morbidity and mortality in diabetic patients. The autonomic nervous system (ANS) controls involuntary physiological processes, including heart rate regulation. It consists of three divisions: sympathetic, parasympathetic, and enteric. In diabetes, damage to these fibers, particularly the vagus nerve, impairs parasympathetic regulation, which results in an increased sympathetic tone. Early stages of CAN may not show symptoms but, as the condition progresses, it can lead to hypoglycemia unawareness, resting tachycardia, and orthostatic hypotension(4–8).

Its prevalence varies between 29%–54% in type 1 diabetes and 12%–73% in type 2 diabetes, depending on the study population. Research on CAN in Africa remains scarce. In South Africa, 32% of insulin-dependent diabetic patients exhibited abnormal autonomic function tests. In Ethiopia and much of sub-Saharan Africa, data on CAN prevalence is limited; however, a study by Migisha et al. in Uganda documented a prevalence of 52.2%. This underscores the need for more robust studies to better understand the burden and implications of CAN in the Ethiopian context(9–11).

The diagnosis of CAN typically involves tests such as Heart Rate Variability (HRV) analysis and Cardiac Autonomic Reflex Testing (CART). The diagnostic criteria include one abnormal cardiovagal test for possible or early CAN and at least two abnormal tests for definite or confirmed CAN, along with orthostatic hypotension and abnormal heart rate tests for severe or advanced CAN. Early detection is crucial, as managing glycemic control and cardiovascular risk factors can slow the progression and reduce the risk of complications(6,9).

Cardiac autonomic neuropathy (CAN) significantly elevates cardiovascular mortality risk, including a five-fold increase in cardiovascular death. O'Brien's study revealed a 27% five-year mortality rate for patients with asymptomatic CAN, compared to 8% for those with normal autonomic function. Diabetic individuals also exhibit higher mortality rates, with 50.6 vs. 43.5 deaths per 1000 person-years for all-cause mortality and 17.6 vs. 14.2 deaths per 1000 person-years for cardiovascular mortality, compared to non-diabetics(12,13).

Screening for CAN is recommended for asymptomatic type 2 diabetics at diagnosis and type 1 diabetics after five years, particularly those with poor glycemic control (HbA1c > 7%), cardiovascular risks, or angiopathic complications. It is also valuable for pre-operative assessment. Detecting CAN helps tailor diabetes therapy, exercise plans, perioperative care, and risk stratification for morbidity, mortality, and sudden death post-myocardial infarction, while addressing clinical inertia and improving patient adherence(14,15).

1.2 Statement of the problem

Diabetic cardiovascular autonomic neuropathy (CAN) is a significant yet underdiagnosed complication of diabetes mellitus, characterized by the impairment of autonomic control over cardiovascular functions. This condition is associated with increased morbidity and mortality, primarily due to its contribution to silent myocardial ischemia, arrhythmias, and sudden cardiac death.

Studies by Vinik et al. have highlighted the prevalence of CAN in both type 1 and type 2 diabetes, emphasizing its association with poor glycemic control and long-standing diabetes. Aron and Shuper have explored the pathophysiological mechanisms, including oxidative stress and inflammation, that contribute to autonomic dysfunction. Spallone's work has underscored the importance of early detection through cardiovascular reflex tests and heart rate variability analysis. Ziegler and Tesfaye have provided insights into the epidemiology and risk factors, noting a higher prevalence in populations with suboptimal diabetes management. Torsvik's research has further elucidated the

genetic and metabolic contributors to CAN, offering potential avenues for targeted interventions.

The growing prevalence of diabetes worldwide necessitates a concerted effort to address CAN through improved screening, early diagnosis, and comprehensive management strategies. This includes optimizing glycemic control, addressing cardiovascular risk factors, and exploring novel therapeutic approaches to mitigate the impact of this debilitating condition(5,10,13,16).

Despite its clinical importance, the true burden of CAN in low- and middle-income countries remains largely unknown, particularly in sub-Saharan Africa. In Ethiopia, CAN is rarely screened for in routine diabetic care, and local epidemiological data on its prevalence, severity, and associated factors are scarce, limiting evidence-based clinical decision-making. The absence of locally generated data, combined with variability in diagnostic approaches and limited use of standardized tests such as Ewing's criteria, hampers timely diagnosis and appropriate management in resource-limited settings.

To address this gap, the present study aims to determine the prevalence, severity, and associated factors of CAN among adults with diabetes using standardized cardiovascular autonomic reflex tests (CARTs) based on Ewing's criteria. By generating context-specific evidence, this study will inform clinical practice, support the integration of CAN screening into routine diabetic care, and contribute to improved prevention and management strategies in Ethiopia and similar settings.

1.3 Significance of the study

In a health resource-limited setting like Ethiopia, which is affected by numerous infectious diseases and emerging non-communicable diseases including DM, the presence of DCAN is another burden that presses the overwhelmed healthcare system in operation, increasing morbidity and mortality.

CAN progression is linked to increased cardiovascular morbidity and mortality, highlighting the importance of understanding its progression. The study aims to know the prevalence of DCAN and identify predictive factors for both CAN onset and progression, which could inform new follow-up and treatment strategies.

Findings of this study will establish the existing risk factors associated with DCAN, hence promoting the Clinical and Public Health departments to develop several interventions to prevent or reduce the burden of DCAN threats to the life of DM patients in the communities.

2. Literature review

2.1 Prevalence of CAN in diabetes

The prevalence of cardiovascular autonomic neuropathy (CAN) among individuals with diabetes shows wide variation, ranging from 1–90% in type 1 diabetes mellitus (T1DM) and 20–73% in type 2 diabetes mellitus (T2DM). This substantial heterogeneity is largely attributed to differences in diagnostic criteria, testing protocols, and study populations, as well as variability in key risk factors such as age, sex, duration of diabetes, and glycemic control. Inconsistent use of standardized diagnostic tools, particularly Ewing's battery, further contributes to these discrepancies(9).

Clinic-based studies tend to report higher prevalence estimates, likely due to referral bias and the inclusion of patients with longer disease duration or more advanced complications. For example, a prospective clinic-based study from the United States involving 1,211 patients with T1DM reported a CAN prevalence of 29% in intensively treated patients and 35% in conventionally treated patients. These findings underscore the high burden of CAN among patients receiving routine diabetes care in specialized clinical settings(17,18).

In contrast, population-based and community-based studies generally provide lower but more representative prevalence estimates and highlight the early onset of autonomic dysfunction. A clinic-based study from Bulgaria reported CAN prevalence of 12.3% in individuals with normal glucose tolerance, 19.8% in prediabetes, and 32.2% in newly diagnosed T2DM, demonstrating a stepwise increase in autonomic dysfunction with worsening glucose metabolism. Similarly, a population-based study conducted in Germany among adults aged 55–74 years found higher CAN prevalence among individuals with known diabetes (17.5%), combined impaired fasting glucose and impaired glucose tolerance (11.4%), and non-diabetic metabolic syndrome (11.7%), compared with 4.5% in those with normal glucose tolerance(19,20).

Community-based studies further support these findings. An Australian study among individuals with T2DM reported that 33.7% had possible CAN and 15.3% had definite CAN, while a large study from southern Taiwan observed increasing prevalence of orthostatic hypotension from 13.8% in normoglycemic individuals to 25.5% among those with diabetes. Together, these studies demonstrate a consistent gradient of autonomic dysfunction across the spectrum of glucose intolerance(21,22).

In sub-Saharan Africa, available evidence—predominantly from clinic-based studies—suggests a high burden of CAN among patients with diabetes. Studies from Tanzania and Uganda reported CAN prevalence rates of 49.1% and 52.2%, respectively, with associations including older age, longer diabetes duration, obesity, resting tachycardia, and diabetic retinopathy. In South Africa, a prevalence of 30.3% was reported for diabetic neuropathy, including autonomic involvement. However, the reliance on clinic-based samples limits generalizability and highlights the lack of population-based data in African settings, particularly in Ethiopia.

Overall, evidence from diverse settings indicates that CAN is a common and often under-recognized complication of diabetes, with prevalence estimates influenced by study design and diagnostic approach. The scarcity of standardized, population-based studies in low- and middle-income countries underscores a critical research gap that the present study seeks to address using Ewing's criteria within an Ethiopian clinical context(11)(23).

2.2 Predictors and associated factors

Well-Established Predictors

Duration of diabetes is one of the most consistently reported predictors of cardiovascular autonomic neuropathy (CAN) across both type 1 and type 2 diabetes mellitus. Numerous longitudinal and cross-sectional studies demonstrate a strong, independent association between longer diabetes duration and the presence and severity of CAN, reflecting cumulative exposure to chronic hyperglycemia and metabolic stress(5).

Glycemic control, commonly assessed using glycated hemoglobin (HbA1c), is another well-established determinant of CAN. Poor long-term glycemic control has been repeatedly associated with reduced heart rate variability and progression of autonomic dysfunction. In both T1DM and T2DM, higher HbA1c levels independently predict CAN development and progression, emphasizing the role of sustained hyperglycemia in autonomic nerve damage(9).

Hypertension has also been identified as a major contributor to CAN. Several studies report that both the presence and duration of hypertension increase the risk of autonomic dysfunction, particularly when abnormal circadian blood pressure patterns such as non-dipping or reverse dipping are present. Hypertension may exacerbate microvascular ischemia, accelerating autonomic nerve injury(24).

Microvascular complications, including diabetic retinopathy, nephropathy, and peripheral neuropathy, are strongly linked to CAN. The coexistence of these complications suggests shared pathogenic mechanisms involving microvascular damage, oxidative stress, and chronic inflammation. Studies consistently demonstrate higher CAN prevalence among patients with established microvascular disease, particularly in those with peripheral neuropathy, where severe CAN is frequently observed (5,14).

Emerging or Inconsistent Evidence

Beyond the established predictors, evidence regarding additional risk factors remains mixed. In type 2 diabetes, some longitudinal studies suggest that body mass index (BMI) and triglyceride levels independently predict CAN, though findings are not uniform across populations. Similarly, biomarkers such as von Willebrand factor, urinary albumin excretion rate, and markers of endothelial dysfunction have been associated with autonomic impairment, but their predictive value varies between studies(25).

Oxidative stress and inflammatory markers are increasingly recognized in the pathogenesis of CAN. Elevated superoxide anion levels have been associated with reduced heart rate variability, sensory nerve dysfunction, and increased long-term mortality. Lower levels of brain-derived neurotrophic factor (BDNF) have also been implicated in CAN progression, suggesting a role in neuronal repair and survival. However, these markers are not routinely assessed in clinical practice, limiting their applicability(26,27).

Other factors such as QT interval prolongation, smoking, and nutritional deficiencies (including low vitamin B12 and fluctuating vitamin D levels) have shown associations with CAN in selected studies, but findings remain inconsistent. In type 1 diabetes, lower BMI—possibly reflecting poor metabolic control—and selective serotonin reuptake inhibitor (SSRI) use have been linked to CAN progression, though no clear predictors for CAN onset have been consistently identified. Notably, some studies report no significant association between CAN progression and diabetic nephropathy, highlighting variability in reported risk profiles(5,14).

2.3 Geographical variations in CAN prevalence

In general, CAN is influenced by factors such as diabetes duration, glycemic control, and associated complications. In high-income countries, such as the United States, studies suggest significant rates of CAN among individuals with diabetes, often highlighting differences between intensive and

conventional treatment groups or between type 1 and type 2 diabetes. European research also notes distinct prevalence rates based on glucose tolerance status, with higher rates among those with impaired fasting glucose or newly diagnosed diabetes. Asia-based studies focus on specific manifestations like orthostatic hypotension in different glucose tolerance categories, while African studies, though limited, have reported significant prevalence rates in local populations(2,28–30).

Geographical variations in CAN prevalence are likely due to differences in diagnostic criteria, healthcare accessibility, socioeconomic factors, and the unique characteristics of study populations, such as age and gender distributions. Countries with well-established diabetes management programs often report higher detection rates due to systematic screening, while regions with limited healthcare resources may have fewer documented cases. Furthermore, genetic, lifestyle, and environmental factors may contribute to differences in susceptibility and clinical presentation of CAN across diverse populations(6,31–33).

2.4 Conceptual framework

These are the potential risk or contributing factors that may influence the development of Cardiovascular autonomic neuropathy (CAN) in adult patients with type 1 & 2 diabetes mellitus:

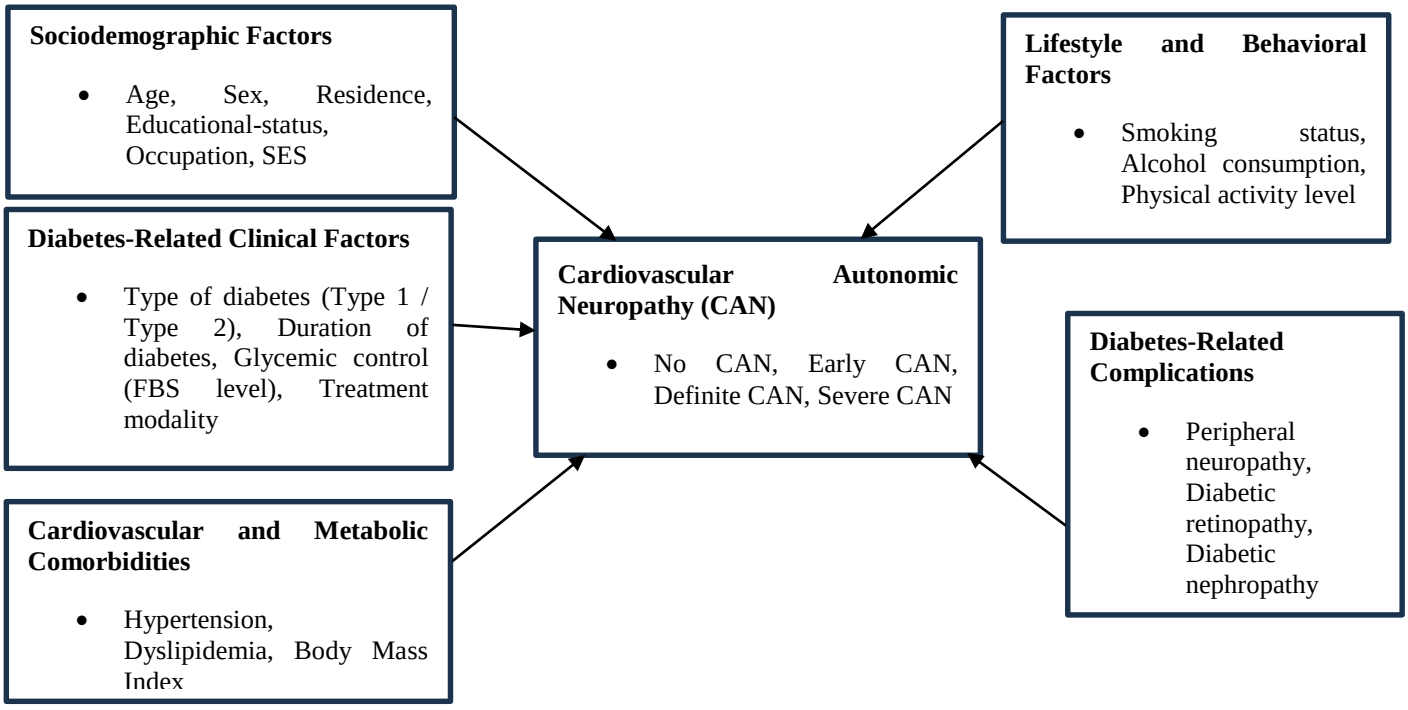

Figure 1. Conceptual framework of Cardiovascular autonomic neuropathy in adult patients with DM (1,5,9,14,26,43).

3. Objectives

3.1 General objectives

- To determine the prevalence, severity, and associated factors of cardiovascular autonomic neuropathy among adult patients with diabetes mellitus attending follow-up care at Asella Referral and Teaching Hospital, Asella, Ethiopia.

3.2 Specific objectives

1. To determine the prevalence of cardiovascular autonomic neuropathy among adult patients with diabetes mellitus attending follow-up at Asella Referral and Teaching Hospital.
2. To assess the severity of cardiovascular autonomic neuropathy using standardized cardiac autonomic reflex tests among adult patients with diabetes mellitus at Asella Referral and Teaching Hospital.
3. To identify sociodemographic, clinical, and behavioral factors associated with cardiovascular autonomic neuropathy among adult patients with diabetes mellitus attending follow-up at Asella Referral and Teaching Hospital.

4. Methods and materials

4.1 Study area and period

This study was conducted at Asella Referral and Teaching Hospital (ARTH) from July 1 to December 30, 2025.

ARTH is a major referral and teaching hospital located in Asella town, Arsi Zone, Oromia Regional State, Ethiopia, approximately 167 km southeast of Addis Ababa. Established in 1964, the hospital serves as a key healthcare facility for the Arsi Zone and surrounding areas, providing both specialized and general medical services to a large catchment population.

The hospital has a capacity of approximately 265 beds and delivers a wide range of services, including outpatient and inpatient care, emergency services, diagnostic laboratory and radiology services, pharmacy services, and chronic disease follow-up care. The Internal Medicine Department hosts specialized clinics, including a diabetes mellitus follow-up clinic, where adult patients with diabetes receive regular care and monitoring. This clinic serves a substantial number of patients from both urban and rural settings, making it an appropriate site for studying diabetes-related complications.

The Internal Medicine Department includes outpatient clinics, male and female medical wards, an emergency unit, a high dependency unit (HDU), and an intensive care unit (ICU). Care is provided by a multidisciplinary team comprising specialist physicians, resident doctors, general practitioners, and nurses.

4.2 Study design

An institution-based cross-sectional study design was employed to determine the prevalence of cardiovascular autonomic neuropathy and identify associated factors among adult patients with diabetes mellitus attending follow-up care at Asella Referral and Teaching Hospital.

4.3 Population

4.3.1 Source population

The source population comprised all adult (≥18 years) patients with diabetes mellitus attending the diabetes mellitus follow-up clinic at Asella Referral and Teaching Hospital, Asella, Ethiopia.

4.3.2 Study population

The study population comprised adult patients (aged ≥18 years) with diabetes mellitus who gave consent, met inclusion criteria and were attending follow-up care at the diabetes mellitus clinic of Asella Referral and Teaching Hospital during the study period.

4.4 Inclusion and exclusion criteria

4.4.1 Inclusion criteria

Participants were eligible for inclusion if they met all of the following criteria:

Diagnosed with diabetes mellitus (Type 1 or Type 2)

- Aged 18 years or older
- Attending diabetes mellitus follow-up care at Asella Referral and Teaching Hospital during the study period and had at least two prior visits
- Willing to participate and able to provide written informed consent

4.4.2 Exclusion criteria

Participants were excluded if they met any of the following criteria:

Permanent Exclusion Criteria

- Type 1 diabetes mellitus with a duration of less than five years since diagnosis
- Known severe cardiovascular or cardiorespiratory diseases that could affect autonomic function testing, including:
  - Coronary artery disease (CAD)
  - Rheumatic heart disease (RHD)
  - Cardiac arrhythmias
  - Congestive heart failure (CHF)
  - Pregnancy

Temporary / Testing-Related Exclusion Criteria

- Presence of acute illness within 48 hours prior to assessment
- Smoking or consumption of caffeine- or alcohol-containing beverages within two hours before autonomic function testing
- Patients lacking previous two FBG measurements

4.5 Sample size determination and sampling technique

4.5.1 Sample size determination

Sample size calculation for a study on cardiovascular autonomic neuropathy (CAN) in adult diabetes mellitus patients was done, using the single population proportion formula with Cochran's correction and a 10% non-response rate:

Given Parameters:

1. Total population (N) = 4,133
2. Estimated proportion (p) = 49.1% (0.491) (Due to the absence of local data, the proportion was estimated based on previous study done in Tanzania)
3. Margin of error (d) = 5% (0.05)
4. Z-score (Z) = 1.96 (for 95% confidence level)
5. Non-response rate = 10%

Step 1: Calculate Initial Sample Size (n_0)

Use the single population proportion formula:

$$n0=Z2 \cdot p \cdot (1-p)/d2$$

Calculation:

$$n0=(1.96)2 \cdot 0.491 \cdot (1-0.491)/(0.05)2$$

$$= 3.8416 \cdot 0.491 \cdot 0.5090/0025 = 0.9600/0025 = 384$$

Step 2: Apply Cochran's Correction (Finite Population Adjustment)

Since total population (N = 4,133) is known and <10,000, I will use Cochran's formula to adjust the sample size:

$$n=n0/1+n0-1/N$$

Calculation:

n=384/1+384−1/4,133 = 384/1+0.0926 = 384/1.0926 = 351.5≈352

Step 3: Add 10% Non-Response Rate

Adjust for potential non-responses:

Final sample size = n1−Nonresponse rate=352/1−0.10 = 352/0.90 =391.1 ≈ 392

Using the OpenEpi, Version 3 open-source calculator, the sample size for the second goal is determined to be 298, 272, and 322 for variables that are significantly associated with DCAN in a previous study conducted in Tanzania (Age > 60, DM duration, and BMI >30 with OR of 2.91, 3.43, and 3.15, respectively). The ultimate sample size will be 392 because all sample sizes are smaller than the size determined for prevalence.

4.5.2 Sampling technique

Systematic random sampling was applied to a registry of 4,133 DM patients. With a calculated interval of 10 and a random start at patient #7, every 10th patient was selected until 392 participants are enrolled. Non-responses were replaced by the next consecutive patient to preserve sample size.

4.6 Study variables

4.6.1 Dependent variable

Cardiovascular Autonomic Neuropathy (CAN)

Categorized as:

- No CAN
- Early (possible) CAN
- Definite CAN
- Severe CAN (Assessed using standardized cardiac autonomic reflex tests based on Ewing's criteria)

4.6.2 Independent variables

A. Sociodemographic Factors

- Age (years)
- Sex (male/female)
- Educational status

- Socioeconomic status
- Residence
- Occupation

B. Diabetes-Related Clinical Factors

- Duration of diabetes mellitus (years)
- Glycemic control (HbA1c, %)
- Type of diabetes (Type 1 / Type 2)
- Treatment modality (insulin, oral hypoglycemic agents, combination)

C. Cardiovascular and Metabolic Factors

- Hypertension (yes/no)
- Dyslipidemia:
    - Low-density lipoprotein (LDL)
    - High-density lipoprotein (HDL)
    - Total cholesterol
- Body mass index (BMI, kg/m^2)

D. Diabetes-Related Complications

- Peripheral neuropathy
- Diabetic retinopathy
- Diabetic nephropathy

E. Lifestyle and Behavioral Factors

- Alcohol consumption
- Khat chewing
- Cigarette smoking

4.7 Operational definitions

CAN is defined as the impairment of autonomic control of the cardiovascular system in the setting of diabetes after exclusion of other causes(15).

No CAN: all Ewing's test performed are normal or borderline(15).

Early or possible CAN: - one abnormal result in any of Ewing's test(15).

Definite CAN: – abnormal results in two heart rate-based Ewing's test (heart rate response to deep breathing/E:I ratio and immediate heart rate response to standing/30:15 ratio)(15).

Severe CAN: - abnormal results in two heart rate-based Ewing's test (heart rate response to deep breathing/E:I ratio and immediate heart rate response to standing/30:15 ratio) plus any of abnormal result in blood pressure response to standing/orthostatic hypotension test or isometric handgrip test(15).

Good glycemic control: - FBS 80 - 130 mg/dl on three-month average, HbA1C <7%(26).

Poor glycemic control: FBS > 130 mg/dl on three-month average(26).

Hypertension- A person with a systolic blood pressure of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher, or on antihypertensive medication(34).

Diabetic nephropathy: documented physician diagnosis of diabetic kidney disease(1).

Diabetic retinopathy: documented diagnosis by an ophthalmologist, attributable to diabetes(1,35).

Diabetic neuropathy was defined as the presence of symptoms and/or signs of peripheral nerve dysfunction (e.g., numbness, tingling, burning pain, loss of vibration or pressure sensation) consistent with diabetic neuropathy, after exclusion of other causes, or a clinician-documented diagnosis of diabetic neuropathy(14).

Elevated Low-Density Lipoprotein (LDL) Cholesterol: Elevated LDL cholesterol was defined as a fasting LDL-C level ≥130 mg/dL (≥3.4 mmol/L), in accordance with standard cardiovascular risk classification, or current use of lipid-lowering therapy for elevated LDL(36).

Elevated Total Cholesterol: Elevated total cholesterol was defined as a fasting total cholesterol level ≥200 mg/dL (≥5.2 mmol/L), based on standard adult dyslipidemia thresholds, or current treatment for hypercholesterolemia(36).

Body mass index: Weight in kg to the square of height in m2 will be used to classify as;

- Underweight- A person having a BMI of < 18.5 kg/m2
- Normal – A person having a BMI of 18.5- 24.9 kg/m2
- Overweight- A person having a BMI of 25- 29.9 kg/m2

- Obese- A person having a BMI of ≥ 30 kg/m2(37).

4.8 Data collection tools & procedure

Data were collected by three trained clinical nurses, with the principal investigator also participating as a supervisor. Initially, the inclusion criteria were verified, and the exclusion criteria were assessed through objective evaluations of the participants.

Questionnaires

Information regarding socio-demographic, economic, lifestyle & behavioral characteristics, as well as symptoms of diabetic neuropathy, were gathered using semi-structured, interviewer-administered questionnaires.

Record Review

Clinical data, including the duration of diabetes, prior glycemic control (measured by fasting blood glucose & HbA1C), lipid profiles, treatment types, comorbidities, and diabetes-related complications, were extracted from the patients' medical records.

Physical Measurements

Physical measurements included weight, height, BMI, heart rate, and blood pressure, taken using standardized methods. Weight was recorded with participants in light clothing and no shoes, while height was measured with a stadiometer in an erect posture.

Laboratory Measurements

To determine glycemic control levels, the average of three consecutive fasting blood glucose (FBG) readings (two from the patient's records and one taken on the data collection day).

CARTs procedures, scoring, and precautions

Procedural steps:

Heart rate response to deep breathing test (DBT): After 5 minutes of rest in the supine position, the participant performs deep breathing at 6 breaths/min (5 s inhale, 5 s exhale) for 1 minute while pulse rate is monitored. The E/I ratio is calculated.

30:15 Ratio (Standing Test): From a supine position, the participant stands up quickly. PR intervals around the 15th and 30th beats after standing are recorded, and the 30:15 ratio is calculated.

Orthostatic Hypotension Test: Blood pressure is measured after 5 minutes supine and again within 3 minutes of standing. Changes in systolic BP is recorded.

Isometric Handgrip Test: The participant squeezes a tightly rolled cloth at maximal voluntary contraction for up to 3 minutes; the rise in diastolic BP is measured(31).

Scoring system for CARTs (Ewing score):

Each test result is scored as 0 = normal, 0.5 = borderline, or 1 = abnormal using age-adjusted reference values(31).

Scores from all performed tests are summed to generate the Ewing score.

CAN classification (Ewing's criteria):

- No CAN: All tests normal
- Early (possible) CAN: One abnormal heart rate-based test
- Definite CAN: ≥2 abnormal heart rate–based tests
- Severe CAN: ≥2 abnormal heart rate–based tests plus ≥ abnormal orthostatic hypotension test/Isometric handgrip test

Essential precautions:

Participants fast for 2–4 hours and avoid caffeine, alcohol, and smoking before testing.

Testing is avoided in patients with unstable cardiac conditions, recent myocardial infarction, severe arrhythmias, or uncontrolled hypertension.

Continuous monitoring is used; testing is stopped immediately if dizziness, syncope, or significant discomfort occurs.

4.9 Data analysis procedure

Data were checked for completeness, consistency, and accuracy prior to analysis. After data cleaning, the dataset was exported from KoboToolbox to SPSS version 27.0 for statistical analysis.

Descriptive statistics were used to summarize the study variables. Frequencies and percentages were computed for categorical variables, while means and standard deviations were calculated for continuous variables.

Cardiovascular autonomic neuropathy (DCAN) was treated as a binary outcome variable and categorized as CAN (early, definite and severe CAN) and no CAN.

Binary logistic regression analysis was first performed to examine the crude association between each independent variable and DCAN. Variables with a p-value less than 0.25 in the binary analysis were selected as candidates for the multivariable logistic regression model, in accordance with standard model-building recommendations to avoid excluding potential confounders.

Multivariable logistic regression analysis was then conducted to identify independent factors associated with DCAN while controlling for potential confounding variables. A backward likelihood ratio (LR) method was employed to retain statistically significant predictors in the final model. Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were used to measure the strength of associations.

Model fitness was assessed using the Hosmer–Lemeshow goodness-of-fit test, and multicollinearity among independent variables was evaluated using variance inflation factors (VIF). A p-value of less than 0.05 was considered statistically significant.

4.10 Data quality management

A pre-test was conducted on 5% (n=207) of the total sample size at Asella Referral and Teaching Hospital prior to the actual data collection. Based on the findings of the pre-test, necessary modifications were made to the data collection tools to improve clarity and consistency.

Before data collection, two days of training were provided to the data collectors on the objectives of the study, interview techniques, measurement procedures, and ethical considerations. Data were collected by three trained clinical nurses, under close supervision of the principal investigator.

The questionnaire was initially prepared in English and then translated into Afan Oromo and Amharic. To ensure consistency and accuracy, the translated versions were back-translated into English by an independent translator.

During the data collection period, the completed questionnaires were reviewed daily by the supervisor and the principal investigator for completeness, accuracy, and consistency. Any identified errors or omissions were addressed promptly through immediate correction and feedback to the data collectors.

4.11 Ethical consideration

Ethical clearance was obtained from Arsi University's Institute of Health review board, and a letter of collaboration was requested and obtained from the AURTH medical director's office. To begin data collection, study participants has given their informed consent. All incidental findings identified during screening was reported to the responsible physicians for additional care.

4.12 Dissemination plan of results

After completing the study, the findings will be defended at Arsi University, College of Health Sciences, School of Medicine, Department of Internal Medicine and submitted to AURTH and other relevant bodies. Workshops, seminars, and a publication in an internationally reputable journal will also be used to disseminate the findings.

5. Results

5.1 Socio-demographic characteristics of study participants

A total of 392 participants were included in the study. Most were aged 40–59 years (43.1%) and male (65.6%). The mean age of participants was 46.77 years (SD = 16.29), with no missing age data (n = 392). This wide age dispersion supports age-stratified analysis, consistent with Ewing's criteria, which require age-adjusted interpretation of cardiovascular autonomic reflex tests in CAN assessment(38).

The majority were married (77.3%) and resided in urban areas (64.3%). Government employees constituted the largest occupational group (37.2%). More than half of the participants were Christian (56.6%) and of Oromo ethnicity (70.2%). Half of the study population had attained college or university education (50.8%).

Nearly half of the participants were in the middle-income category (46.2%), followed by those with low income (41.8%), while a smaller proportion belonged to the high-income group (12.0%). This distribution indicates that the study population was predominantly from low- to middle-income households.

Table 1. ***Socio-demographic characteristics of study participants***

Variable	Category	Frequency (n)	Percentage (%)
Age	18–39 years	124	31.6
	40–59 years	169	43.1
	≥60 years	99	25.3
Sex	Male	257	65.6
	Female	135	34.4
Marital status	Single	76	19.4
	Married	303	77.3
	Widowed	11	2.8
Residence	Urban	252	64.3
	Rural	140	35.7
Occupation	Government employee	146	37.2
	Unemployed	85	21.7

	Farmer	108	27.6
	Student	52	13.3
Religion	Christian	222	56.6
	Muslim	164	41.8
	Other	5	1.3
Ethnicity	Oromo	275	70.2
	Amhara	84	21.4
	Tigre	9	2.3
	Others	23	5.9
Level of education	No formal education	59	15.1
	Primary school	76	19.4
	Secondary school	55	14.0
	College/University	199	50.8
Socioeconomic status	Low income	164	41.8
	Middle income	181	46.2
	High income	47	12.0

5.2 Behavioural & Lifestyle factors

Regarding physical activity, the majority of participants, 260 individuals (66.3%), reported a moderate (600 -2999 WHO MET mins/week) level of physical activity. A substantial proportion, 125 participants (31.9%), engaged in low (<600 WHO MET mins/week) physical activity, while only 7 respondents (1.8%) reported a high (>3000 WHO MET mins/week) level of physical activity.

357 participants (91.1%), reported no alcohol consumption, whereas 35 individuals (8.9%) indicated occasional alcohol use (only on special occasions like holidays).

With respect to smoking, the study population exhibited 99.5%, had never smoked, while 2 individuals (0.5%) reported being smokers.

Table 2. ***Behavioral and lifestyle characteristics of the study participants***

Variable	Category	Frequency (n)	Percentage (%)
Physical activity level	Low	125	31.9
	Moderate	260	66.3
	High	7	1.8
Alcohol consumption	No	357	91.1
	Yes/Occasional	35	8.9
Smoking status	No	390	99.5
	Yes	2	0.5

5.3 Diabetes-related clinical characteristics of study participants

The clinical profile of the 392 participants with diabetes revealed the following key features.

Most participants had type 2 diabetes (67.1%), were treated with oral agents only (44.4%) or insulin alone (41.8%), and had a diabetes duration of ≤9 years (63.5%). Poor glycaemic control was common, as indicated by fasting blood sugar (FBS), with 64.8% classified as poorly controlled. Diabetic complications were relatively infrequent, particularly eye (7.4%) and kidney problems (3.8%), while nerve problems were reported by 28.8% of participants.

HbA1c was categorized as good (</=7%) or poor (>7%) control based on standard clinical cutoffs commonly used in diabetes care to reflect long-term glycaemic control. However, HbA1c measurements were missing for a substantial proportion of participants (61.5%), which may introduce information bias and reduce the precision of analyses involving long-term glycaemic control. Consequently, greater emphasis was placed on FBS in the main analyses.

Table 3. ***Diabetes-related clinical characteristics of study participants***

Variable	Category	Frequency	Percentage (%)
Type of Diabetes	Type 1 diabetes	129	32.9
	Type 2 diabetes	263	67.1

Current Treatment for Diabetes	Oral agents only	174	44.4
	Insulin only	164	41.8
	Combination (insulin + oral)	54	13.8
Duration of Diabetes	</=9 years	249	63.5
	≥ 10 years	143	36.5
HbA1c Status	Not measured	241	61.5
	Good control (</=7%)	14	3.6
	Poor control (>7%)	137	34.9
Fasting Blood Sugar (FBS)	Good control (80-130 mg/dl)	137	34.9
	Poor control (>130 mg/dl)	254	64.8
Diabetic retinopathy	No	363	92.6
	Yes	29	7.4
Diabetic peripheral neuropathy	No	279	71.2
	Yes	113	28.8
Diabetic nephropathy	No	377	96.2
	Yes	15	3.8

5.4 Cardiovascular & metabolic factors

About one-quarter of participants had hypertension (24.7%), while most were normotensive (75.0%). Measurement of total cholesterol and LDL cholesterol was unavailable for the majority of participants (79.8% and 80.5%, respectively). Due to this substantial missing data their associations with the outcome should be interpreted with caution. 73.5% of participants had a normal BMI, whereas 16.8% were overweight or obese and 5.6% were underweight.

Table 4. ***Cardiovascular & metabolic factors characteristics of study participants***

Variable	Category	Frequency	Percentage (%)
Hypertension (HTN)	No	294	75.0
	Yes	97	24.7

Total Cholesterol	Not measured	313	79.8
	Normal (<200)	47	12.0
	Elevated ((>200)	32	8.2
LDL Cholesterol	Not measured	310	80.5
	Normal (<150)	48	12.5
	Elevated (>150)	27	7.0
Body Mass Index (BMI)	16–18.49 (Underweight)	22	5.6
	18.5–24.9 (Normal)	288	73.5
	≥25 (Overweight/Obese)	66	16.8

5.5 Prevalence and Severity of Cardiac Autonomic Neuropathy

Cardiovascular autonomic neuropathy (CAN) was assessed in all 392 study participants using standardized diagnostic criteria and Ewing's battery of tests.

According to the binary CAN classification, 259 participants (66.1%) were diagnosed with cardiovascular autonomic neuropathy, while 133 participants (33.9%) showed no evidence of CAN. This indicates a high overall prevalence of CAN within the study population.

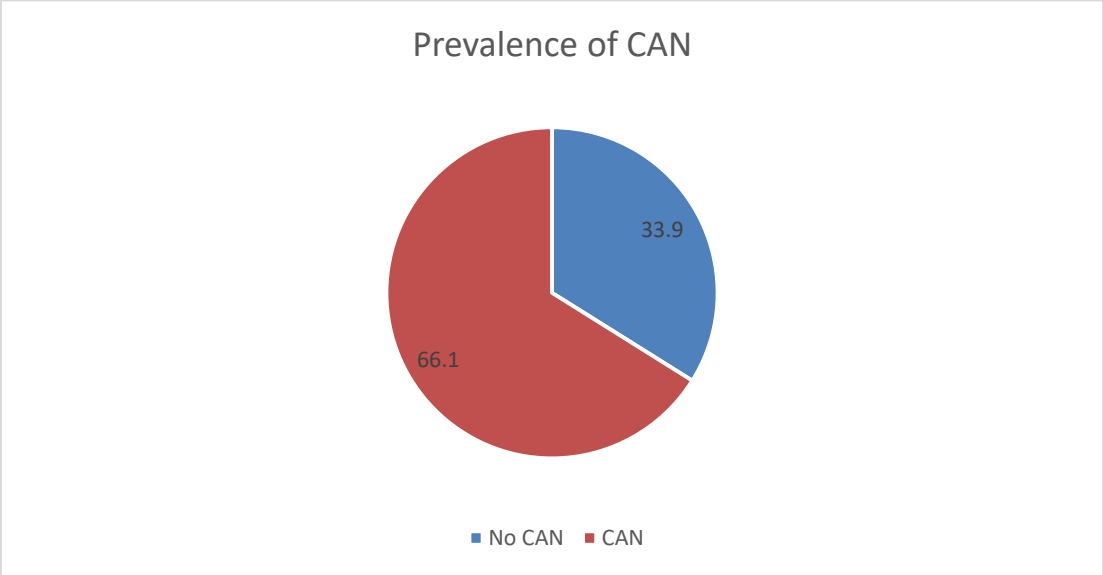

Figure 2. Prevalence of CAN

When classified according to the severity grading based on Ewing's score, the distribution was as follows:

- 133 participants (33.9%) had no CAN,
- 136 participants (35.0%) exhibited early CAN,
- 99 participants (25.3%) demonstrated definite CAN,
- 24 participants (6.1%) demonstrated severe CAN.

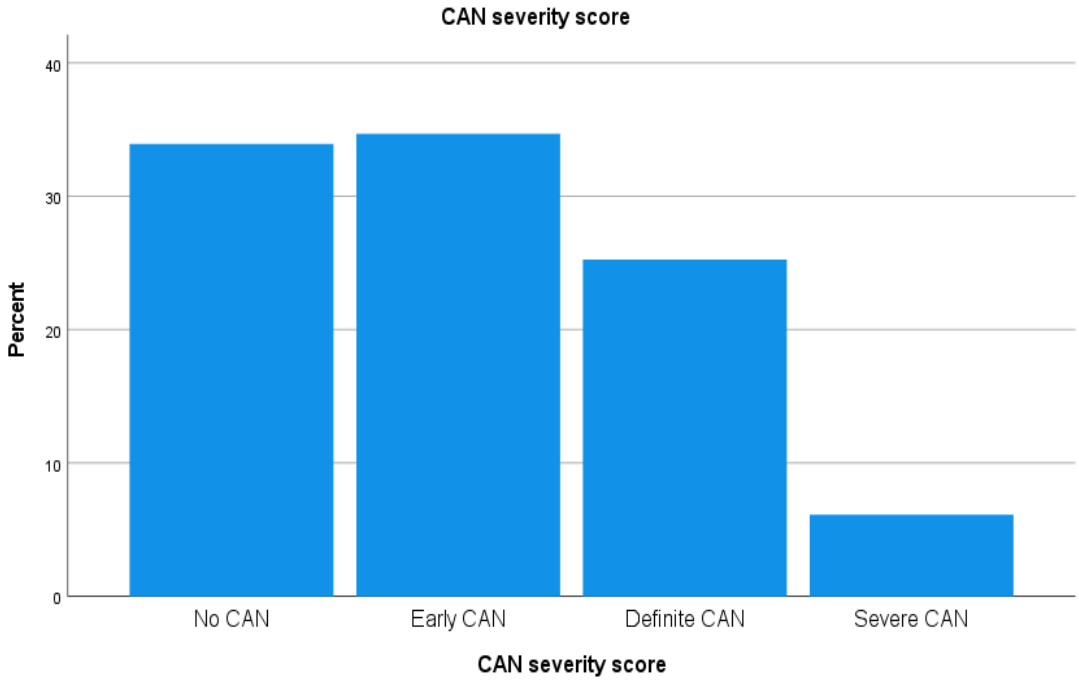

Figure 3. CAN severity outcome

The slight discrepancy in the number of participants classified as having no CAN and early CAN (133 vs. 136) may reflect minor differences in diagnostic thresholds or categorization criteria applied.

In summary, the study revealed a substantial burden of cardiovascular autonomic neuropathy, with approximately two-thirds of participants affected. The severity distribution was relatively balanced, with early and definite CAN each affecting roughly one-third of the total sample. These findings underscore the high frequency and clinical relevance of CAN in this diabetic population.

5.6 Factors Associated with Cardiovascular Autonomic Neuropathy

Bivariate and multivariable logistic regression analyses were performed to identify factors associated with cardiovascular autonomic neuropathy (CAN) among adult patients with diabetes mellitus. Variables with a p-value < 0.25 in the bivariate analysis were entered into the multivariable logistic regression model. The results are summarized in Table 5.

In the bivariate analysis, age (40–59 years & ≥ 60years), female sex, unemployment, urban residence, low-moderate physical activity, longer duration of diabetes (≥10 years), poor glycaemic control (FBS > 130), overweight/obesity (BMI ≥25 kg/m²), presence of hypertension, diabetic retinopathy, and type of diabetes were significantly associated with CAN (p < 0.25).

After adjusting for potential confounders in the multivariable logistic regression model, five variables remained independently associated with CAN.

Sex was independently associated with CAN. female participants had nearly **twofold higher odds of CAN** compared with females (AOR = 1.77 95%CI: 1.01–3.12, p = 0.047).

Occupation showed a significant independent association with CAN. Compared with government employees, unemployed individuals had almost **twofold increased odds** of CAN (AOR = 2.24; 95% CI: 1.03–4.48; *p* = 0.043).

Participants with a **diabetes duration** of 10 years or longer had more than seven times higher odds of CAN compared with those with a shorter duration (AOR = 6.56, 95% CI: 3.38–12.74, p<0.001).

Hypertension remained a strong independent predictor of CAN. Individuals with a prior diagnosis of hypertension had nearly **threefold increased odds** of CAN compared with those without hypertension (AOR = 2.82; 95% CI 1.33–5.96, p = 0.007).

Glycaemic control, as measured by fasting blood sugar (FBS), was independently associated with CAN. Individuals with poor FBS control had more than **fourfold increased odds** of CAN compared with those with good glycemic control (AOR = 4.45; 95% CI 2.55–7.78, p = <0.001).

Age demonstrated a strong and graded association with CAN. Compared with individuals aged 18–39 years, those aged 40–59 years had significantly higher odds of CAN (COR = 1.61; 95% CI: 1.01–2.58; p = 0.046), while participants aged ≥60 years had markedly increased odds (COR = 24.53; 95% CI:

8.49–70.84; p < 0.001). Age was excluded due to its strong correlation with diabetes duration and other age-related clinical factors.

Current treatment for diabetes showed a statistically significant overall association with CAN (p = 0.007). Insulin-based and combination therapies were associated with altered odds of CAN compared with oral agents, likely reflecting more advanced disease or longer duration. Treatment modality was excluded because of strong overlap with diabetes duration and glycemic control.

HbA1c above 7% demonstrated a borderline association (COR = 1.53; 95% CI: 0.97–2.41; p = 0.070). HbA1c was excluded from multivariate analysis due to substantial missing data and collinearity with fasting blood glucose (FBS), which was retained as the primary glycemic indicator.

Total cholesterol was not significantly associated with CAN (p = 0.205), and LDL cholesterol also showed no significant association (p = 0.185), were excluded from the multivariable model because of large missing data.

Regarding diabetes-related complications, diabetic kidney problems were not associated with CAN (COR = 1.03; 95% CI: 0.34–3.07; p = 0.960), and diabetic nerve problems also showed no significant association (COR = 1.08; 95% CI: 0.68–1.71; p = 0.752).

Table 5. ***Factors Associated with the Outcome: Bivariable and Multivariable Logistic Regression Analysis***

Variable	Category	No CAN (n)	CAN (n)	COR (95% CI)	AOR (95% CI)	p-value
Occupation	Government employee	59	87	1	1	
	Unemployed	48	145	2.049	2.24 (1.03–4.88)	**0.043**
	Student	25	27	0.73	1.05 (0.40–2.78)	0.917
Sex	Male	93	164	1	1	
	Female	40	95	1.35 (0.86–2.11)	1.77 (1.01–3.12)	**0.047**
Residence	Rural	38	102	1		
	Urban	95	157	1.62 (1.03–2.55)	1.16 (0.57–2.36)	0.683
Diabetic retinopathy	No	129	233	1		
	Yes	5	25	3.45 (1.17–10.12)	1.39 (0.32–5.94)	0.659
Hypertension	No	116	178	1		

	Yes	17	80	3.07 (1.73–5.44)	2.82 (1.33–5.96)	**0.007**
FBS	Good control	75	62	1		
	Poor control	57	197	4.18 (2.67–6.54)	4.45 (2.55–7.78)	**<0.001**
Duration of diabetes	<10 years	118	131	1		
	≥10 years	15	128	7.69 (4.26–13.87)	6.56 (3.38–12.74)	**<0.001**
Type of diabetes	Type 1	57	72	1		
	Type 2	76	187	1.95 (1.26–3.02)	1.75 (0.86–3.58)	0.125
BMI	Normal	86	201	1		
	Underweight	8	14	1.458	2.27 (0.77–6.69)	0.138
	Overweight/obese	30	36	1.948	1.03 (0.30–3.48)	0.968

Key. 1: Reference category

6. Discussion

The present study investigated the prevalence, severity, and associated factors of cardiovascular autonomic neuropathy (CAN) among 392 diabetic patients in a clinical setting, revealing a high burden of this complication. The findings are interpreted below in the context of existing literature, with comparisons drawn from worldwide, African, and local (Ethiopian) studies where available. This discussion highlights the clinical implications, potential explanations for observed associations, and study limitations.

6.1 Prevalence and Severity of Cardiovascular Autonomic Neuropathy

The overall prevalence of CAN in this study was 66.1%, with approximately two-thirds of participants affected. When stratified by severity using Ewing's score, 35.0% exhibited early CAN and 25.3% & 6.1 had definite and severe CAN respectively, indicating a substantial proportion with advanced autonomic dysfunction. This high prevalence underscores CAN as a significant yet often underdiagnosed complication in diabetic populations.

Worldwide, the prevalence of CAN among diabetic patients varies considerably, ranging from 1% to 90%, influenced by diagnostic criteria, disease duration, and population characteristics. For instance, a large population-based study of 3,010 individuals with type 1 diabetes reported a 36% prevalence of possible CAN, while estimates in type 2 diabetes cohorts have ranged from 27.5% in cross-sectional surveys to as high as 84.1% in specific populations. Lower rates, such as 1.8% for confirmed CAN in a cohort study, have also been documented, particularly in early-stage diabetes. The heterogeneity in global estimates is attributed to differences in testing methodologies, with Ewing's battery—employed in this study—often yielding higher detection rates due to its comprehensive assessment of autonomic function(15).

In Africa, data on CAN prevalence remain limited but consistently indicate a high burden. A study in Uganda among ambulatory diabetic patients reported a 52.2% prevalence, aligning closely with the current findings and suggesting that resource-constrained settings may experience elevated rates due to suboptimal glycemic management and delayed diagnosis. Another African investigation in Nigeria found a 26.9% prevalence of CAN, though this was lower, potentially reflecting variations in patient selection or diagnostic thresholds(32).

Locally in Ethiopia, published evidence on CAN is sparse, with one review noting an absence of comprehensive data on its prevalence among diabetic patients. However, related studies on diabetic neuropathy report rates of 31–73% for cardiac autonomic involvement in type 2 diabetes, and a 48.3% prevalence among those with diabetic peripheral neuropathy. The 66.1% prevalence observed here is toward the higher end of these estimates, possibly due to the inclusion of both type 1 and type 2 diabetes patients and a focus on those with established disease. This suggests that CAN may be more pervasive in Ethiopian diabetic populations than previously documented, warranting increased attention in local clinical guidelines(29,39).

The high prevalence in this study may be explained by factors such as prolonged hyperglycemia, as evidenced by three-month average FBS 64.8%, and the predominance of type 2 diabetes (67.1%), which is often associated with metabolic comorbidities exacerbating autonomic damage. Without ECG, inter-observer variability rises, potentially leading to false positives (overdiagnosis). Compared to global and regional figures, these results highlight a potentially greater CAN burden in this Ethiopian cohort, emphasizing the need for context-specific interventions.

6.2 Factors Associated with Cardiovascular Autonomic Neuropathy

Multivariable logistic regression identified female sex, unemployment, longer diabetes duration (≥10 years), poor glycemic control (FBS > 130 mg/dl), and hypertension as independent risk factors for CAN, with adjusted odds ratios of 1.8, 2.24, 6.56, 4.5, and 2.82, respectively. Associations with residence, type of diabetes, body mass index (BMI), and diabetic retinopathy were significant in crude analyses but attenuated after adjustment.

The strong link between diabetes duration and CAN is consistent with worldwide literature, where prevalence increases progressively with time since diagnosis, from approximately 7% at onset to over 50% after 15 years. In African contexts, such as Uganda, longer duration has similarly been implicated as a key correlate. Locally, Ethiopian studies on diabetic neuropathy echo this, with incidence proportions rising significantly in patients with extended disease courses. This association likely reflects cumulative hyperglycemic neurotoxicity, leading to progressive autonomic nerve degeneration(15,26,27).

Poor glycemic control emerged as the most potent independent factor, aligning with global evidence that elevated FBS levels accelerate microvascular complications, including CAN. Meta-analyses worldwide confirm that hyperglycemia is a primary driver, with intensive control reducing CAN risk

by up to 60% in intervention trials. In Africa, likely due to inconsistent HbA1c testing, suboptimal FBS—often due to limited access to monitoring and therapy—has been associated with higher neuropathy rates, as seen in Ugandan, Tanzania & South African cohorts. Ethiopian data on diabetic complications further support this, with poor control predicting neuropathy progression. The high proportion of participants with suboptimal FBS (64.8% of those tested) in this study underscores a critical gap in local diabetes management(40,41).

Hypertension's independent association with CAN corroborates international findings, where it contributes to endothelial dysfunction and autonomic imbalance. Global studies report 2–4-fold increased odds in hypertensive diabetic patients, while African research in Nigeria links it to a 2.4-fold risk for neuropathy. In Ethiopia, comorbid hypertension in diabetic populations has been tied to elevated complication rates, reinforcing the need for integrated cardiovascular risk management(27,32).

Several studies have documented sex differences in diabetic autonomic and peripheral neuropathic complications, with women showing distinct autonomic dysfunction patterns and, in some settings, worse outcomes compared with men. In addition, socioeconomic disadvantage, including unemployment, has been associated with higher prevalence of diabetic neuropathy, possibly reflecting reduced healthcare access, suboptimal chronic disease management, and increased psychosocial stress. These factors may contribute to the observed higher prevalence of CAN among female and unemployed patients in our study(42).

Crude associations with older age, type of diabetes and BMI, retinopathy, which lost significance post-adjustment, are nonetheless supported by global evidence linking advanced age, obesity, and microvascular damage to CAN. Their attenuation here may indicate mediation through duration and glycemic control.

6.3 Clinical Implications and Limitations

These findings imply that CAN screening should be prioritized in diabetic patients with prolonged disease, poor control, or hypertension, potentially reducing associated morbidity such as silent ischemia and arrhythmias. The high prevalence signals an urgent need for enhanced diabetes care in Ethiopia, focusing on modifiable risks.

Limitations include;

- The cross-sectional design, which precludes causality inference.
- Manual testing lowers precision, especially for HR-based tests (e.g., deep breathing or heart rate response to standing), due to human error in timing or detecting subtle changes.
    - Increased risk of misclassification and bias.
    - Results may not align with studies using standardized ECG-based protocols.
    - In low-resource studies, manual methods are validated but show lower reproducibility than automated batteries.
- The exclusion of CVD was based solely on prior diagnosis; therefore, undiagnosed cases may have been included, potentially biasing the prevalence estimates.
- Lack of standard screening and diagnostic methods for diabetic microvascular complications may under-estimate the numbers.
- Missing HbA1c, LDL, HDL and total cholesterol data for greater than two-thirds of participants:
    - Fasting blood sugar for glycemic control, is less reliable than HbA1c for long-term assessment. Without HbA1c, one cannot reliably assess the relationship between glycemic variability or poor control and DCAN prevalence/severity. Its absence could lead to over- or underestimation of other factors like hypertension's role.
    - Similarly, lipids are independent risk factors for CAN and related cardiovascular outcomes; missing them prevents adjustment for dyslipidemia as a confounder, potentially inflating associations with other variables like disease duration or age.
- The hospital-based sample may not generalize to community settings, and reliance on self-reported data introduces recall bias.

Strengths comprise:

- Large sample (392),
- Inclusion of both type 1 and type 2 DM,
- As the first study on DCAN at our hospital, this work fills a critical gap in local evidence,
- Using digital platform (Kobo-Toolbox) for data collection for the first time,
- Discovering associations between DCAN and female sex, as well as unemployment, is a fresh contribution that could spark further investigation into social determinants of health in diabetes complications,

- The transparency about missing data (e.g., on HbA1c and lipids) strengthens ethical reporting and could inform policy on data completeness in diabetic registries,
- Multivariable adjustment for confounders.

Recommendations

Based on the study findings and integrated literature, the following recommendations are proposed to address the high burden of CAN in diabetic populations:

For Hospital;

Routine Screening and Early Detection: Implement systematic CAN screening using Ewing's battery for diabetic patients, particularly those with ≥10 years' duration, FBS >130, or hypertension. This aligns with global guidelines from the American Diabetes Association, which advocate autonomic testing in high-risk groups, and should be adapted for Ethiopian healthcare settings to facilitate early intervention. Female sex and unemployed individuals should also be prioritized.

Optimization of Glycemic and Blood Pressure Control: Prioritize intensive management of hyperglycemia and hypertension through accessible monitoring, affordable medications, and patient education programs. Evidence from worldwide trials, such as the Diabetes Control and Complications Trial, demonstrates that tight control halves CAN progression; similar strategies in Africa have shown feasibility in reducing complications.

Integrated Diabetes Care Programs: Develop multidisciplinary clinics in Ethiopia focusing on comprehensive risk factor modification, including lifestyle interventions for physical activity and weight management, given the study's favorable lifestyle profile but persistent CAN risk. Local health authorities should collaborate with international bodies to enhance resource availability.

For Researchers: Conduct longitudinal studies in Ethiopia to establish CAN incidence, type-specific differences, and intervention efficacy. Comparative research across African regions could elucidate contextual factors, addressing the current data paucity noted in local reviews.

For MOH: Advocate for national guidelines incorporating CAN awareness in diabetes training for healthcare providers. Public health campaigns should emphasize modifiable risks, drawing from successful African models in Uganda to improve outcomes.

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Annexes

Annex I: English version of the Information sheet and Consent form

Part One: English Version of the Information Sheet

Hello! Good [morning/afternoon].

My name is _____, and I am a data collector for Dr. Gadisa Tadese Urgesa, a resident physician in Internal Medicine. We are conducting a study on: "Assessment of Cardiovascular Autonomic Neuropathy in patients with Diabetes at Arsi University Referral & Teaching Hospital, Ethiopia."

Your participation is voluntary, but your input is valuable in understanding this condition better.

What Will Happen?

- You will answer questions about your medical history, lifestyle, and symptoms (30-40 mins).

- No harmful procedures—just simple, non-invasive tests in a private setting.

- You can skip any question or stop anytime.

Benefits

- Helps doctors and policymakers improve early detection & care for diabetic patients.

- You may learn more about diabetic complications.

Confidentiality

- Your identity & responses will never be shared.

- Reports will only show group data, not individual details.

Safety Measure

- Strict hygiene protocols (handwashing).

- Safe disposal of medical waste.

- Any concerning findings will be referred for proper care.

Contact for Questions

Dr. Gadisa Tadese

0925337214 | gadisatadese5@gmail.com

Part II: Consent Section

I understand the purpose of this study, the interview process, possible risks, benefits, and how my responses will be kept confidential. I agree to participate in the interview and answer all questions.

Do you agree to participate?

☐ Yes (Proceed to consent form)

☐ No (Thank you—interview ends here)

Participant's Name & Signature: _____ (or thumbprint)

Interviewer's Name & Signature: _____

Supervisor's Name & Signature: _____

Interview Time: Start: _____ End: _____

Status: ☐ Completed ☐ Partially Completed

Annex II: Amharic version of the information sheet and consent form

ክፍል አንድ - የመረጃ ሉህ የአማርኛ ስሪት

ሰላም፡ እንደምን አደራችሁ

በመጀመሪያ እንኳን በሰላም መጡ። እራሴን ለማስተዋወቅ : ስሜ ---------- የዶክተር ጋዲሳ ታደሰ ኡርጌሳ የውሂብ ሰብሳቢ ነኝ። እሱ በውስጠኛ ሕክምና (Internal Medicine) የትምህርት ዲፕሎማ በማግኘት ላይ ያለ ተማሪ ነው። ዛሬ እዚህ የመጣሁት በአርሲ ዩኒቨርሲቲ ሪፈራል እና የትምህርት ሆስፒታል፣ አሰላ፣ ኢትዮጵያ የሚገኙ የስኳር በሽተኞች ውስጥ የልብ እና የደም አተሮች አውቶኖሚክ ኔውሮፓቲ (Cardiovascular

Autonomic Neuropathy) እና ከእሱ ጋር የተያያዙ ምክንያቶች ግምገማ የሚለውን ርዕስ በተመለከተ ውሂብ ለመሰብሰብ ነው።

በጥናቱ ላይ ተጨማሪ ማብራሪያ መጠየቅ የሚፈልጉ ከሆነ የዚህ ጥናት ዋነኛ መርማሪ ዶክተር ጋዲሳ ታደሰ ኡርጌሳን ማነጋገር ይችላሉ::

በሞባይል ስልክ ቁጥር 0925337214 በኩል, ወይም የኢሜይል አድራሻ gadisatadese5@gmail.com።

ክፍል II - የስምምነት ቅጽ የአማርኛ ስሪት

የጥናቱ ዓላማ ፣ የአሠራር ሂደቶች ፣ አደጋዎች እና ምቾት ፣ የጥናቱ ጥቅሞች እና የምላሾች ምስጢራዊነት በተመለከተ በተሰጠኝ መረጃ መሠረት ቃለ በጥናቱ ለመሳተፍ ተስማምቻለሁ።

የተሳታፍው ስም እና ፊርማ፣

የመረጃ ሰብሳቢው ፊርማ

Annex III: Afan Oromo version of the information sheet and consent form

Odeeffannoo Waliigalaa

Kaadhimamaa/tuu keenya ati akka gaaffii fi deebii waa’ee midhamuu sirna narvii kan onnee kan dhukkuba sukkaraatiin walqabate dhufu irratti waliin taasisuuf carraan isin qaqabeera,irratti hirmaachuuf eeyyamamoodhaa?

Ashamaa harka fuune, maqaan koo ----------jedhama. Ani waa’ee qo’annoo mata dureen isaa hariiroo dhukkuba sukkaaraa fi midhamuu sirna nervii kan onnee gidduu jiru qo’atamu irratti gaaffii fi deebii isin wajjiin taasisuuf. Yeroo kamiyyuu gaaffii fi deebii addaan kutuuf mirga guutuu qabdu.

Kaayyoo qorannichaa, adeemsa gaaffii fi deebii sirriitti nan hubadha. Deebiiwwan kiyya iccitiidhaan eegamuu nan hubadha. Gaaffii fi deebii keessatti hirmaachuu fi gaaffiiwwan hunda deebisuuf nan walii gala.

Lakk. Kaardii----------

Maqaa fi mallattoo hirmaatichaa---------- ------- Iddoo hirmaataa----------

Lakk. Bilbilaa----------Mallattoo----------

Annex IV Data Extraction Checklist

Identification

- Patient ID: _____
- Data collector name / ID: _____

Informed Consent and Eligibility

- Are you willing to consent? ☐ Yes ☐ No
- Age ≥ 18 years: ☐ Yes ☐ No

Socio-demographic Data

- Age (years): _____
- Sex: ☐ Male ☐ Female
- Residence: ☐ Urban ☐ Rural

Occupation

- ☐ Government employee
- ☐ Unemployed
- ☐ Farmer
- ☐ Student

Marital Status

- ☐ Single ☐ Married ☐ Divorced ☐ Widowed

Religion

- ☐ Christian ☐ Muslim ☐ Other: _____

Ethnicity

- ☐ Oromo ☐ Amhara ☐ Tigre ☐ Others: _____

Monthly household income (ETB): _____

Economic status:

☐ Low (< 3,000 ETB / month)

☐ Middle (3,000 – 10,000 ETB / month)

☐ High (> 10,000 ETB / month)

Level of Education

- ☐ No formal education
- ☐ Primary school
- ☐ Secondary school
- ☐ College / University

Clinical Data

Diabetes-related Information

- Type of diabetes: ☐ Type 1 diabetes ☐ Type 2 diabetes
- Duration of diabetes (years): _____

Current Treatment for Diabetes

- ☐ Diet only
- ☐ Oral agents only
- ☐ Insulin only
- ☐ Combination (insulin + oral)

Diabetes-related Complications (doctor diagnosed)

(Check all that apply)

- ☐ Eye problems (diabetic retinopathy or vision changes)
- ☐ Kidney problems (kidney damage or protein in urine)
- ☐ Nerve problems (tingling, numbness, or pain in hands/feet)

- ☐ Heart problems (chest pain, heart attack)
- ☐ Stroke or TIA
- ☐ Poor blood flow to legs or feet (peripheral vascular disease)
- ☐ Foot ulcers or amputations
- ☐ None
- ☐ I don't know

Hypertension

- Ever diagnosed with high blood pressure? ☐ Yes ☐ No ☐ Not sure

If yes:

- Duration of hypertension (years): _____
- Currently taking antihypertensive medication? ☐ Yes ☐ No

Hypertension-related Complications

(Check all that apply)

- ☐ Stroke
- ☐ Heart failure
- ☐ Kidney problems
- ☐ Eye problems
- ☐ None

Dyslipidemia

- Ever diagnosed with dyslipidemia? ☐ Yes ☐ No

If yes:

- Duration of dyslipidemia (years): _____
- Currently on treatment (e.g., statins, diet)? ☐ Yes ☐ No

HIV Status

- Ever tested for HIV?
    - ☐ Yes, tested positive

    - ☐ Yes, tested negative
    - ☐ No
- Currently on antiretroviral therapy (ART)? ☐ Yes ☐ No

Autonomic Neuropathy Symptoms

Cardiovascular-related Symptoms

(Check all that apply)

- ☐ Dizziness or lightheadedness on standing
- ☐ Fast or racing heartbeat at rest
- ☐ Difficulty exercising / early fatigue
- ☐ Fainting or near-fainting spells
- ☐ Palpitations
- ☐ Unexplained fatigue
- ☐ None of the above

Other Autonomic Symptoms

(Check all that apply)

- ☐ Bloating, nausea, or vomiting after meals
- ☐ Constipation or diarrhea
- ☐ Stool incontinence
- ☐ Urinary problems
- ☐ Erectile dysfunction (men only)
- ☐ Vaginal dryness or reduced sexual response (women only)
- ☐ Excessive or reduced sweating
- ☐ Trouble adjusting to darkness / light sensitivity
- ☐ None of the above

Lifestyle Factors

- Chews khat (chat)? ☐ Yes ☐ No

Smoking Status

- ☐ Never ☐ Former ☐ Current

Alcohol Use

- ☐ No
- ☐ Occasional
- ☐ Regular

Physical Activity Categories

☐ Low physical activity

- < 600 MET-minutes/week

☐ Moderate physical activity

600–2999 MET-minutes/week

- ≥150 minutes/week of moderate activity OR
- ≥75 minutes/week of vigorous activity OR
- Equivalent combination

☐ High physical activity

- ≥ 3000 MET-minutes/week
- High-volume or high-intensity physical activity

Anthropometric Measurements

- Weight (kg): _____
- Height (cm): _____
- Waist circumference (cm): _____

Laboratory Results

- HbA1c (%): _____
- Serum creatinine (mg/dL): _____
- LDL (mg/dL): _____
- Total cholesterol: _____
- HDL: _____
- Fasting blood sugar (FBS): _____

Consent for CARTs

- Are you willing to consent for CARTs? ☐ Yes ☐ No

Ewing's Battery Tests

- Resting pulse rate (beats/min): _____
- Resting systolic BP (mmHg): _____
- Resting diastolic BP (mmHg): _____
- Maximum heart rate during deep breathing (bpm): _____
- Minimum heart rate during deep breathing (bpm): _____
- Heart rate at 15th beat on standing (bpm): _____
- Heart rate at 30th beat on standing (bpm): _____
- Systolic BP after standing (within 3 minutes) (mmHg): _____
- Diastolic BP – baseline (before sustained handgrip) (mmHg): _____
- Diastolic BP – during sustained handgrip (mmHg): _____

CAN Categories

☐ No CAN (Normal autonomic function)

- All CARTs normal

☐ Early CAN

- One abnormal parasympathetic test

  (deep breathing or 30:15 ratio)

  Sympathetic tests normal

☐ Definite CAN

- Two or more abnormal parasympathetic tests

☐ Severe CAN

- Definite CAN PLUS abnormal sympathetic test (orthostatic hypotension).

Annex V: Declaration

Declaration of Investigator

I, the undersigned Internal Medicine Resident, declare that this thesis is my original work in partial fulfillment of the requirement for the Specialty Degree in Internal Medicine to my best knowledge.

Name of investigator: Dr. Gadisa Tadese (Internal medicine resident)

Signature: _____ Date; 27/1/2026

Declaration of Advisors

We, the undersigned Advisors, declare that this thesis is our original work in partial fulfillment of the requirement for the Specialty Degree in Internal Medicine for the stated student, to the best of our knowledge. We confirm that this proposal is ready for defense with our approval as the university advisor(s).

Date of Submission: 27/01/2026

Name of Advisors:	Signatures	Date
1.Mr. Kabtamu Tolosie		27/1/2026
2.Dr. Gutu Kebede		27/1/2026