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dr.Yenny Y <yennyfarmako@trisakti.ac.id>

Invitation to review a manuscript for Scientific Reports from Dr Valenti

1 message

Scientific Reports <do-not-reply@springernature.com> Fri, Jun 5, 2026 at 2:50 PM
To: yennyfarmako@trisakti.ac.id

Invitation to review "Determinants of Excretory Autonomic Dysfunction: The Role of Lipid-Lowering Drugs, Vegetable Intake, and Smoking in Type 2 Diabetes Mellitus in Zanzibar"

Should you accept to review this manuscript, your report would be due within 10 days.

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We have received a manuscript for Scientific Reports that we think falls within your area of expertise. Our reviewers are integral to ensuring we have the highest-quality publication.

We would greatly appreciate it if you could let us know if you are available to review by accepting or declining the invitation link below.

Title: Determinants of Excretory Autonomic Dysfunction: The Role of Lipid-Lowering Drugs, Vegetable Intake, and Smoking in Type 2 Diabetes Mellitus in Zanzibar

Abstract: Introduction: Excretory Autonomic Dysfunction (EAD) is a common complication of Type 2 Diabetes Mellitus (T2DM) that affects quality of life, leading to loss of control of the bladder, difficulty passing urine, and complete emptying of the bladder. However, its prevalence and risk factors remain underexplored, particularly in low-resource settings like Zanzibar. This study aimed to determine the prevalence of EAD and its association with pharmacological, clinical, and lifestyle factors among T2DM patients in Zanzibar.
Methods: A cross-sectional study was conducted among 364 patients with type 2 diabetes mellitus (T2DM) attending outpatient clinics in Zanzibar. Participants were recruited from local healthcare facilities, and data were collected using structured interviews. Excretory dysfunction symptoms were assessed using the excretory subdomain of the Composite Autonomic Symptom Score-31 (COMPASS 31). Descriptive and inferential statistical analyses were conducted to determine the prevalence and identify factors associated with EAD.
Results: The prevalence of EAD was 24.5% (n=89) out of 364 participants. A history of cigarette smoking was significantly associated with increased risk of EAD (AOR= 4.13, 95% CI: 1.46–11.67, p=0.007). Patients who reported consuming vegetables rarely or only one portion per day had a higher risk of EAD (AOR = 3.86, 95% CI: 1.67–8.89, p=0.002). Regarding the type of medication, the use of lipid-lowering drugs was associated with a higher risk of EAD (AOR = 4.21, 95% CI: 1.83–9.67, p = 0.001). Other variables, including age and BMI, did not show statistically significant associations.
Conclusion: EAD was found to be common for patients with type 2 diabetes in Zanzibar. In this study, dietary, lifestyle, and the type of medication used played a major role in EAD. Factors such as cigarette smoking, low vegetable intake, and the use of lipid-lowering medications were significantly associated with increased risk of EAD. Therefore, routine screening and targeted interventions are warranted to prevent mortality and improve the quality of life. Further study may be needed to explore the neurological effects of lipid-lowering therapies in diabetic patients.
Keywords: Excretory Autonomic Dysfunction, Excretory Autonomic Neuropathy, Bladder Dysfunction, Type 2 Diabetes Mellitus, COMPASS 31, Zanzibar.

Authors: Hassan Haji, Ramla Ali, Ahmed Khamis, Reuben Mutagaywa, Kaushik Ramaiya, Fredirick Mashili

We hope to hear from you soon.

Kind regards,

Vitor Valenti
Editorial Board Member
Scientific Reports

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Determinants of Excretory Autonomic Dysfunction: The Role of Lipid-Lowering Drugs, Vegetable Intake, and Smoking in Type 2 Diabetes Mellitus in Zanzibar

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Commented [Y1]: In the validation of the COMPASS-31 questionnaire by Sletten et al. (2012), the subdomain you used was referred to as the Urinary Domain, not Excretory. The use of "Excretory" can be confusing to readers because excretion also includes the digestive/defecation system. Please consider changing the term Excretory Autonomic Dysfunction (EAD) to Urinary Autonomic Dysfunction (UAD).

add study design at the end of the title

Abstract

Introduction: Excretory Autonomic Dysfunction (EAD) is a common complication of Type 2 Diabetes Mellitus (T2DM) that affects quality of life, leading to loss of control of the bladder, difficulty passing urine, and complete emptying of the bladder. However, its prevalence and risk factors remain underexplored, particularly in low-resource settings like Zanzibar. This study aimed to determine the prevalence of EAD and its association with pharmacological, clinical, and lifestyle factors among T2DM patients in Zanzibar.

Methods: A cross-sectional study was conducted among 364 patients with type 2 diabetes mellitus (T2DM) attending outpatient clinics in Zanzibar. Participants were recruited from local healthcare facilities, and data were collected using structured interviews. Excretory dysfunction symptoms were assessed using the excretory subdomain of the Composite Autonomic Symptom Score-31 (COMPASS 31). Descriptive and inferential statistical analyses were conducted to determine the prevalence and identify factors associated with EAD.

Results: The prevalence of EAD was 24.5% (n=89) out of 364 participants. A history of cigarette smoking was significantly associated with increased risk of EAD (AOR= 4.13, 95% CI: 1.46–11.67, p=0.007). Patients who reported consuming vegetables rarely or only one portion per day had a higher risk of EAD (AOR = 3.86, 95% CI: 1.67–8.89, p=0.002). Regarding the type of medication, the use of lipid-lowering drugs was associated with a higher risk of EAD (AOR = 4.21, 95% CI: 1.83–9.67, p = 0.001). Other variables, including age and BMI, did not show statistically significant associations.

Conclusion: EAD was found to be common for patients with type 2 diabetes in Zanzibar. In this study, dietary, lifestyle, and the type of medication used played a major role in EAD. Factors such as cigarette smoking, low vegetable intake, and the use of lipid-lowering medications were significantly associated with increased risk of EAD. Therefore, routine screening and targeted interventions are warranted to prevent mortality and improve the quality of life. Further study may be needed to explore the neurological effects of lipid-lowering therapies in diabetic patients.

Keywords: Excretory Autonomic Dysfunction, Excretory Autonomic Neuropathy, Bladder Dysfunction, Type 2 Diabetes Mellitus, COMPASS 31, Zanzibar.

Introduction

Excretory autonomic dysfunction (EAD) is a common but frequently under-recognized complication of diabetes mellitus. This condition results from autonomic neuropathy that impairs the neural control of bladder sensation and contractility [1]. As a manifestation of diabetic autonomic neuropathy, EAD disrupts normal bladder function, leading to difficulty initiating urination, a persistent sensation of incomplete bladder emptying, and, in severe cases, loss of bladder control [2], which significantly affects patients' quality of life [3].

Bladder dysfunction is a major component of EAD, which occurs in up to 50% of individuals with diabetes [4, 5]. It results from damage to both the sympathetic and parasympathetic nerves, which are essential for coordinated bladder control [6]. In particular, parasympathetic fibers from the S2–S4 spinal segments mediate detrusor muscle contraction via activation of muscarinic cholinergic receptors [6, 7]. When these fibers are damaged, as commonly observed in diabetes patients, they experience diminished bladder contractility (detrusor areflexia), leading to impaired voiding [7, 8].

Over time, cumulative nerve and vascular damage lead to further deterioration of bladder function. Damage to the small blood vessels supplying the bladder and urethra is common in diabetes. This reduces bladder sensation and smooth muscle contractility, and ultimately increases the risk of urinary retention and renal complications [9, 10]. This is compounded by reduced contractile responses to stimuli such as carbachol or potassium chloride (KCl), reflecting compromised muscle and neurotransmitter function [1, 11].

The reported prevalence of EAD varies widely, ranging from 25% to 90%, depending on the population studied and diagnostic criteria [12, 13]. Several studies also indicated that overactive bladder (OAB) and related symptoms are more prevalent in individuals with type 2 diabetes than in the general population, including in insulin-treated women and diabetic children aged 11 to 17 years [14-16]. In addition, other large epidemiological studies, such as the Nurses' Health Study of 1996 and 2000, have shown that diabetes is an independent risk factor for loss of control of the bladder, with a 17 to 50% increased risk [17]. While some strategies, such as scheduled voiding after every 2-4 hours, may help reduce incontinence risk [18]. Nearly 37–50% of diabetic patients continue to experience bladder dysfunction symptoms [12]. If left uncontrolled, EAD can lead to complications such as urinary tract infections and secondary excretory dysfunction [28, 29].

EAD is also common in the general population, especially among the elderly [1], but diabetes significantly increases both its incidence and severity. EAD has received less attention than autonomic dysfunction in other domains, such as the cardiac and gastrointestinal systems, especially in low-resource countries like Zanzibar, where diagnostic and preventive treatments are restricted. Previous studies have found several determinants of EAD, such as longer duration of diabetes mellitus, body mass index (BMI), and current smoking [17, 19]. A study from Ying Wang *et al* reported that EAD was associated with age and Blood Haemoglobin A1c (HbA1c) [20]. However, the previous studies differ from this study because we applied COMPASS 31 in determining the EAD and its determinants.

This study seeks to assess the prevalence and determinants of EAD among T2DM patients attending tertiary hospitals in Zanzibar. This was done by using the modern version of the Composite Autonomic Symptom Score (COMPASS 31). This study also evaluated key bladder symptoms to provide contextually relevant data for improved clinical strategies. The findings of this study are important in understanding EAD patterns, which will help inform public health responses, enhance diabetes care, and improve quality of life.

Methods

Study Design and Setting

A cross-sectional study was carried out at Zanzibar's Mnazi Mmoja Hospital (MMH) diabetic clinic. This referral hospital receives 223 outpatients and 81 inpatients every day, mostly from the Unguja Urban and West Region. It is among Zanzibar's four referral hospitals and serves as the only tertiary referral hospital in the area, as well as the local hospital for Unguja Island.

The hospital’s uptake area covers a mixed population from urban and peri-urban districts of Unguja, as well as rural patients referred from peripheral health facilities within Unguja. Most patients attending the clinic belong to low-to-middle income households and rely primarily on public health services where consultations and basic laboratory tests are subsidized. Diabetes care in Zanzibar is primarily guided by the Ministry of Health’s NCD Desk Guidelines.

Participants and recruitment

This study was conducted at the Endocrinology Department from 20th December 2023 to 20th March 2024. A systematic random sample strategy was used to enroll 364 patients with type 2 diabetes mellitus (T2DM) who met the inclusion criteria and were above 18 years of age.

This study was conducted at the Endocrinology Department from 20th December 2023 to 20th March 2024. A systematic random sampling strategy was used to enroll 364 patients with type 2 diabetes mellitus (T2DM) who were permanent residents of Zanzibar and diagnosed with type 2 diabetes, receiving at least one anti-diabetic medication. The study was carried out at Mnazi Mmoja Referral Hospital.

Commented [Y2]: how do you handle missing data in your analysis of this study

Commented [Y3]: This paragraph same with line no 92,93 ?

Commented [Y4]: Provide a participant flowchart to clarify the sample inclusion/exclusion process

Commented [Y5]: add the sample size calculation formula that bases the sample size N=364

Inclusion criteria

- Adults (≥18 years) diagnosed with Type 2 Diabetes Mellitus
- Permanent residents of Zanzibar
- Currently taking at least one prescribed anti-diabetic drug

Exclusion criteria

- Serious comorbid illnesses affecting autonomic function, including severe liver disease and chronic kidney disease.
- Current pregnancy or postpartum period <12 weeks, to avoid potential effects of pregnancy and gestational diabetes.

Data collection tool and procedure

Sociodemographic, lifestyle, and disease-related information were gathered using a structured questionnaire (Attachment 1). To ensure participants fully understood the questions, the instrument was provided in Swahili, the main language spoken in the region. Prior to data collection, participants were briefed on the study objectives and gave informed consent. Trained research assistants, including nurses, a clinical officer, and a physician, conducted the interviews. For accuracy, self-reported diabetes treatment histories were checked against clinic records. The data collection process was overseen by the principal investigator (HTH) and the research team to ensure protocol adherence and data quality.

115 **Anthropometric and physical activity measurements**

116 Height (cm), weight (kg), and waist and hip circumferences (cm) were measured for all
117 participants. Body mass index (BMI) was determined using the standard formula (weight ÷
118 height²) and categorized per World Health Organization (WHO) standards [21], see **Table 1**:

119 **Table 1: Body Mass Index (BMI) Categories According to WHO Classification**

Commented [Y6]: No need in Table form

BMI Category	Range (kg/m²)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25–29.9
Obesity	≥30

120 Abdominal obesity was defined as a waist circumference ≥88 cm for women and ≥102 cm for
121 men [22]. Blood pressure was measured while participants were seated using an automated
122 upper arm sphygmomanometer (CH-456, CITIZEN SYSTEMS JAPAN CO., LTD).
123 Hypertension was defined as systolic/diastolic pressure >140/90 mmHg or use of
124 antihypertensive medication [21, 23]. Metabolic equivalent task (MET) values for participants'
125 physical activities were computed from the Kobo questionnaire tool for every degree of
126 physical activity [24].

127 **Biochemical measurements**

128 An automated high-performance liquid chromatography analyzer (Cobas Integra 400, Roche
129 Diagnostics, Basel, Switzerland) was used to measure haemoglobin A1c (HbA1c) in
130 compliance with the Diabetes Control and Complications Trial (DCCT) guidelines at Lancet
131 Laboratories. Glucose fasting levels were also monitored to make sure there were no
132 hypoglycemic episodes before or during the tests. Other biochemical parameters measured
133 included S-Urea and S-Creatinine levels. The measurements were carried out in accordance
134 with standard operating procedure.

135 **Measurement of Excretory Autonomic Function**

136 The measurement of excretory autonomic dysfunction (EAD) in this study was conducted
137 using the Composite Autonomic Symptom Score 31 (COMPASS 31) questionnaire
138 (Attachment 1), which is a validated tool designed to assess autonomic dysfunction across
139 multiple domains [25]. Specifically, for EAD, COMPASS 31 focuses on symptoms related to

excretory autonomic function, including loss of control of the bladder, difficulty passing urine, and completely emptying the bladder [26]. These symptoms are indicative of underlying autonomic nervous system involvement in regulating the excretory system. The COMPASS 31 questionnaire was given by qualified healthcare experts during in-person interviews. Each symptom is first rated according to its frequency and intensity to determine the EAD. The overall excretory subdomain score within COMPASS 31 follows the impact of the total score

Excretory autonomic dysfunction was assessed using the COMPASS-31 questionnaire, a standardized and validated tool used to measure symptoms across major autonomic domains [25]. Specifically, for EAD, COMPASS 31 focuses on symptoms related to excretory autonomic function, including loss of control of the bladder, difficulty passing urine, and completely emptying the bladder [26]. These symptoms are indicative of underlying autonomic nervous system involvement in regulating the excretory system. The COMPASS 31 questionnaire was given by qualified healthcare experts during in-person interviews. Each symptom is first rated according to its frequency and intensity to determine the EAD. The overall excretory subdomain score within COMPASS 31 follows the impact of the total score.

Scoring of Excretory Autonomic Function by using COMPASS 31

The excretory subdomain of the COMPASS-31 questionnaire includes 3 questions that assess bladder function and related autonomic symptoms. These symptoms are: loss of control of the bladder, difficulty passing urine, and complete emptying of the bladder. Each response is scored and weighed, and the total score for this subdomain is obtained by summing the weighed scores of all three items. Higher scores reflect more severe excretory autonomic dysfunction. This technique offered a standardized way to evaluate and classify excretory autonomic dysfunction in individuals with diabetes. Other researchers have already employed this strategy, such as Sletten *et al* [26].

Loss of bladder control, difficulty passing urine, and incomplete bladder emptying had cumulative scores of 0 (Never), which indicates the absence of EAD, 1-3 (Mild), 4-6 (Moderate), and 7-9 (Severe), which indicate its prevalence. This approach assists in assessing the extent of autonomic dysfunction, impacting the excretory system to facilitate diagnosis and treatment.

Statistical Analysis

The data were imported into a Microsoft Excel datasheet and evaluated using Statistical Software for Data Science (STATA) version 17 and R-Studio version 4.5.1. Categorical variables were represented by frequency and percentage. The Chi-square test was used as the significance test for categorical variables. Continuous variables with a normal distribution were represented by the mean and standard deviation. We started by providing an overview of each participant's traits. The percentage of patients who met the EAD criteria was then calculated to determine the prevalence of EAD. All variables examined in the bivariate logistic regression were entered into a multivariate logistic regression model using a forward stepwise approach. The final adjusted odds ratios (AORs) were derived from this multivariable model, and statistical significance was set at $p < 0.05$.

Human Ethics and Consent to Participate

The International Council for Harmonization (ICH), the Declaration of Helsinki, the Guidelines for Good Clinical Practice (GCP), and, where applicable, the principles of Good Clinical and Laboratory Practices (GCLP) were among the relevant national and international ethical guidelines and regulations that were strictly adhered to during the study's execution. The Muhimbili University of Health and Allied Sciences Institution Review Board (reference number MUHAS-REC-02-2023-1528) and the Zanzibar Health Research Ethics Committee (ZAHREC), reference number ZAHREC/05/ST/DEC/2023/184, both granted ethical approval. All participants provided written informed consent before enrolment. Participants' confidentiality was ensured by assigning unique identification codes at the time of data collection and removing all personally identifying information from the research dataset.

Results

Table 2 shows that the mean age of participants was 56.0 ± 10.9 years, with 28 (7.7%) aged <40 years, 202 (55.5%) aged 40–60 years, and 134 (36.8%) aged >60 years. Regarding the history of cigarette smoking, 27 participants (7.4%) reported a positive history, while 337 (92.6%) had never smoked. Use of lipid-lowering drugs was reported in 46 participants (12.6%), compared to 318 (87.4%) who did not use these medications. Vegetable intake data indicated that 211 participants (58%) consumed vegetables rarely or only 1 portion per day, whereas 153 (42%) consumed ≥2 portions daily.

Commented [Y7]: The duration of diabetes is the most powerful and fundamental predictor for the development of autonomic neuropathy and has already been mentioned in the Introduction and Discussion sections, but why does this variable not appear at all in Table 2, Table 3, or in the multivariate regression model as a control variable?

199 **Table 2: Characteristics of study participants (N=364)**

Variables	Mean (SD)	Frequency(N)	Percent (%)
Age [years]	56.0 (10.9)		
<40		28	7.7
40 - 60		202	55.5
>60		134	36.8
Sex			
Male		121	33.2
Female		243	66.8
Body Mass Index (kg/m²)	28.3 (6.4)		
Under weight		11	3.0
Normal		105	28.9
Overweight		131	36.0
Obese		117	32.1
History of cigarette smoking			
Yes		27	7.4
No		337	92.6
Occupation			
Unemployed		154	42.3
Self Employed		102	28.0
Privately Employed		13	3.6
Government Employed		32	8.8
Retired		63	17.3
Followers of the diet recommendation			
Never		339	93.1
Strictly follows		1	0.3
Often		8	2.2
Rarely		13	3.6
Occasionally		3	0.8
Use of Oral hypoglycemic & Insulin			
Yes		23	6.3
No		341	93.7

Insulin Only				
Yes		268	73.6	
No		96	26.4	
Known renal disease				
No		20	5.5	
Yes		344	94.5	
Portion of fruits taken per day				
Rarely or 1 portion			255	70.1
2 portions and above			109	29.9
Portion of vegetables taken per day				
Rarely or 1 portion			211	58
2 portions and above			153	42
Serum Urea (mmol/L)	5.6 (1.9)			
Normal		320	87.9	
Abnormal		44	12.1	
Serum Creatinine (mmol/L)	73.9 (11.8)			
Normal		273	75.0	
Abnormal		91	25.0	
Hypertensive Status				
Normal		58	15.9	
Hypertensive		306	84.1	
Glucose fasting (mmol/L)	9.9 (5.8)			
Normal		83	22.8	
Abnormal		281	77.2	
History of Drinking Alcohol				
Yes		8	2.2	
No		356	97.8	
Use of lipid-lowering drugs				
Yes		46	12.6	
No		318	87.4	
B-HbA1c (DCCT)	7.3 (2.8)			
Normal		170	46.7	
Abnormal		194	53.3	

Table 2: Characteristics of study participants (N=364)

Commented [Y8]: • In the Exclusion criteria section, you stated that patients with chronic kidney disease were excluded from the study.
• However, Table 2 states: Known renal disease -> Yes: 344 (94.5%). If 94.5% of your sample had kidney disease, you have violated the study's exclusion criteria. Please clarify the exclusion criteria for the definition of chronic kidney disease.

Abbreviations: B-HbA1c (DCCT) – Blood Haemoglobin A1c based on Diabetes Control and Complications Trial standard [27].

Table 3 presents the background characteristics of T2DM patients with and without excretory autonomic dysfunction recruited from selected hospitals in Zanzibar. The majority of patients in both groups were aged between 40 and 60 years, with no statistically significant difference in age distribution ($p = 0.671$). A history of cigarette smoking was reported more frequently among patients with excretory dysfunction (14.6%) compared to those without dysfunction (5.1%), showing a statistically significant association ($p = 0.002$). In terms of dietary habits, most patients with dysfunction reported consuming fruits rarely or only one portion daily (82.0%) compared to those with normal function (66.2%) ($p = 0.007$). Similarly, low vegetable intake was observed in 75.3% of the dysfunction group versus 52.4% of the normal group ($p < 0.001$). The use of lipid-lowering drugs was also more common among patients with excretory dysfunction (21.3%) compared to those without (9.8%), and this difference was statistically significant ($p = 0.004$) (**Table 3)**.

Renal Profile and Glycemic Parameters of participants

Results presented in **Table 3** show the renal and metabolic markers, revealing varied patterns among participants with and without excretory autonomic dysfunction. The proportion of patients with known renal disease was slightly lower among those with dysfunction (3.4%) compared to the normal group (6.2%), but no statistically significant difference was observed ($p = 0.311$). However, a significant difference was observed in serum urea levels, where 95.5% of the dysfunction group had abnormal S-Urea results, compared to 85.5% in the normal group ($p = 0.011$). Regarding serum creatinine, abnormal values were recorded in 27.0% of participants with dysfunction and 24.4% of those without, showing no significant variation between the groups ($p = 0.622$). Fasting blood glucose levels were abnormal in the majority of both groups, with 83.1% in the dysfunction group and 75.3% in the normal group, though the difference was not statistically significant ($p = 0.123$). Similarly, abnormal HbA1c levels were recorded in 57.3% of patients with dysfunction and 52.0% of those without, with no significant association noted ($p = 0.383$).

Table 3: Percentage of patients with their excretory status in Zanzibar (N=364)

Variables	Category	Normal (n=275)		Dysfunction (n=89)		All (N=364)		P-value
		n	%	n	%	N	%	

Age [years]	Below 40	22	8.0	6	6.7	28	7.7	
	40 - 60	149	54.2	53	59.6	202	55.5	
	Above 60	104	37.8	30	33.7	134	36.8	0.671
Sex	Male	88	32.0	33	37.1	121	33.2	
	Female	187	68.0	56	62.9	243	66.8	0.376
***Body Mass Index* (kg/m²)**	Under Weight	10	3.6	1	1.1	11	3.0	
	Normal	85	30.9	20	22.5	105	28.8	
	Overweight	94	34.2	37	41.6	131	36.0	
	Obese	86	31.3	31	34.8	117	32.1	0.226
History of Cigarette Smoking	Yes	14	5.1	13	14.6	27	7.4	
	No	261	94.9	76	85.4	337	92.6	**0.002**
Occupation Status	Unemployed	123	44.7	31	34.8	154	42.3	
	Self Employed	76	27.6	26	29.2	102	28.0	
	Privately Employed	6	2.2	7	7.9	13	3.6	
	Government Employed	24	8.7	8	9.0	32	8.8	
	Retired	46	16.7	17	19.1	63	17.3	0.094
Followers of the diet recommendation	Never	261	94.9	78	87.6	339	93.1	
	Strictly follows	0	0.0	1	1.1	1	0.3	
	Often	5	1.8	3	3.4	8	2.2	
	Rarely	8	2.9	5	5.6	13	3.6	
	Occasionally	1	0.4	2	2.2	3	0.8	0.075
Use of Oral hypoglycemic & Insulin	Yes	17	6.2	6	6.7	23	6.3	
	No	258	93.8	83	93.3	341	93.7	0.850
Use of Insulin only	No	69	25.1	27	30.3	96	26.4	
	Yes	206	74.9	62	69.7	268	73.6	0.329
Known renal disease	Yes	17	6.2	3	3.4	20	5.5	
	No	258	93.8	86	96.6	344	94.5	0
Portion of fruits taken per day	Rarely or 1 portion	182	66.2	73	82	255	70.1	
	2 portions and above	93	33.8	16	18	109	29.9	**0.007**

Commented [Y9]: it seems your labels are mixed up (the correct ones are Yes = 20, No = 344). Please recheck the variable known renal disease in Table 2

Portion of vegetables taken per day	Rarely or 1 portion	144	52.4	67	75.3	211	58	
	2 portions and above	131	47.6	22	24.7	153	42	**<0.001**
Serum Urea (mmol/L)	Normal	235	85.5	4	4.5	239	64.8	
	Abnormal	40	14.5	85	95.5	125	35.2	**0**
Serum Creatinine (mmol/L)	Normal	208	75.6	65	73.0	273	75.0	
	Abnormal	67	24.4	24	27.0	91	25.0	0.622
Hypertensive status	Normal	46	16.7	12	13.5	58	15.9	
	Hypertensive	229	83.3	77	86.5	306	84.1	0.467
Glucose fasting (mmol/L)	Normal	68	24.7	15	16.9	83	22.8	
	Abnormal	207	75.3	74	83.1	281	77.2	0.123
History of Drinking Alcohol	Yes	6	2.2	2	2.2	8	2.2	
	No	269	97.8	87	97.8	356	97.8	0.970
Usage of lipid-lowering drugs	Yes	27	9.8	19	21.3	46	12.6	
	No	248	90.2	70	78.7	318	87.4	**0.004**
B-HbA1c (DCCT)	Normal	132	48.0	38	42.7	170	46.7	
	Abnormal	143	52.0	51	57.3	194	53.3	0.383

Commented [Y10]: Please recheck the "All" column in the Serum Urea variable. It says the total Normal = 239 (64.8%) and Abnormal = 125 (35.2%). If 239/364 is 65.6%, and 125/364 is 34.3%. Please recalculate.

Prevalence and severity of symptomatic profile in EAD

Excretory autonomic dysfunction was identified in 89 patients (24.5%) of the 364 subjects that were assessed. Patients with EAD had a considerably higher prevalence of excretory symptoms than people with normal function. Loss of bladder control was a common dysfunction, affecting 62 out of the 89 participants with dysfunction. The results showed that 21 participants (24.1%) had severe symptoms, while 41 participants (47.1%) had mild symptoms. This implies that a significant proportion of patients have difficulties maintaining bladder control. Furthermore, this study found that difficulty in passing urine was reported by 53 participants (59.5%) with excretory dysfunction. About 28 patients (32.2%) had mild symptoms, 11 (12.6%) had moderate symptoms, and 14 (16.1%) suffered from severe difficulty. In terms of bladder emptying, 43 participants (49.4%) experienced a complete inability to empty the bladder, as shown in **Table 4**.

Table 4: Prevalence and severity of symptomatic profile of Excretory autonomic dysfunction (EAD) among T2DM patients in Zanzibar

Excretory autonomic status		Total (N=364)	Dysfunction (n=89)		Normal (n=275)	
		N	n	%	n	%
Lost control of the bladder	Never	302	27	28.7	275	100
	Mild	41	41	47.1	0	0
	Moderate	0	0	0.0	0	0
	Severe	21	21	24.1	0	0
Difficulty passing urine	Never	311	36	39.1	275	100
	Mild	28	28	32.2	0	0
	Moderate	11	11	12.6	0	0
	Severe	14	14	16.1	0	0
Completely emptying the bladder	Never	44	46	50.6	275	100
	Mild	0	0	0.0	0	0
	Moderate	0	0	0.0	0	0
	Severe	43	43	49.4	0	0
Total (N=364)			**89**		**275**	

Commented [Y11]: Table 4. The variable Completely emptying the bladder in the Never row, is written as a total of 44. If added up from the Dysfunction (n=46) + Normal (n=275) columns, the result is 321. Check the calculation results again.

Risk factors of excretory autonomic dysfunction (EAD)

The multivariate logistic results identified three significant risk factors independently associated with EAD in this study. Cigarette smoking emerged as a strong determinant, with smokers having over four times higher odds of experiencing EAD compared to non-smokers (AOR = 4.13, 95% CI: 1.46–11.67, p = 0.007). Low vegetable intake was another key determinant; individuals who consumed rarely or only one portion per day had significantly higher odds of EAD than those consuming two or more portions daily (AOR = 3.86, 95% CI: 1.67–8.89, p = 0.002). Additionally, using lipid-lowering drugs was associated with a higher risk of EAD (AOR = 4.21, 95% CI: 1.83–9.67, p = 0.001) (**Table 5**).

Table 5: Multivariate analysis of factors associated with Excretory dysfunction

VARIABLES	CATEGORY	COR (95% CI)	P-value	AOR (95% CI)	P-value
Age [years]	Below 40	—		—	
	40 - 60	1.3(0.5-3.39)	0.586	1.32(0.44-3.97)	0.621

	Above 60	1.06(0.39-2.85)	0.912	0.76(0.23-2.52)	0.662
Sex	Male	—		—	
	Female	0.8(0.48-1.32)	0.377	1.12(0.41-3.08)	0.823
	Under Weight	—		—	
	Normal	2.35(0.28-19.46)	0.427	1.4(0.15-12.99)	0.765
Body Mass Index (kg/m²)	Overweight	3.94(0.49-31.84)	0.199	2.88(0.32-25.79)	0.345
	Obese	3.6(0.44-29.33)	0.231	2.64(0.28-24.72)	0.394
History of cigarette smoking	No	—		—	
	Yes	3.19(1.43-7.08)	**0.004**	4.13(1.46-11.67)	**0.007**
	Unemployed	—		—	
	Self Employed	1.36(0.75-2.46)	0.314	1.24(0.58-2.65)	0.579
Occupation Status	Privately Employed	4.63(1.45-14.76)	**0.010**	4.09(0.9-18.12)	0.063
	Government Employed	1.32(0.54-3.23)	0.539	1.82(0.61-5.38)	0.280
	Retired	1.47(0.74-2.9)	0.271	2.05(0.81-5.21)	0.129
	Never	—		—	
Followers of the diet	Often	2.01(0.47-8.59)	0.347	1.94(0.33-11.5)	0.468
recommendation	Rarely	2.09(0.67-6.58)	0.207	2.81(0.78-10.1)	0.113
	Occasionally	6.69(0.6-74.79)	0.123	3.05(0.18-52.5)	0.442
Oral hypoglycemic &	Yes	—		—	
Insulin	No	0.91(0.35-2.39)	0.850	2.72(0.72-10.2)	0.139
Insulin only	No	—		—	
	Yes	0.77(0.45-1.3)	0.330	0.6(0.31-1.17)	0.133
Known renal disease	Yes	—		—	
	No	1.89(0.54-6.6)	0.319	3.21(0.77-13.3)	0.109
Portion of fruits taken per day	Rarely or 1 portion	2.33(1.28-4.23)	**0.005**	1.28(0.51-3.20)	0.599

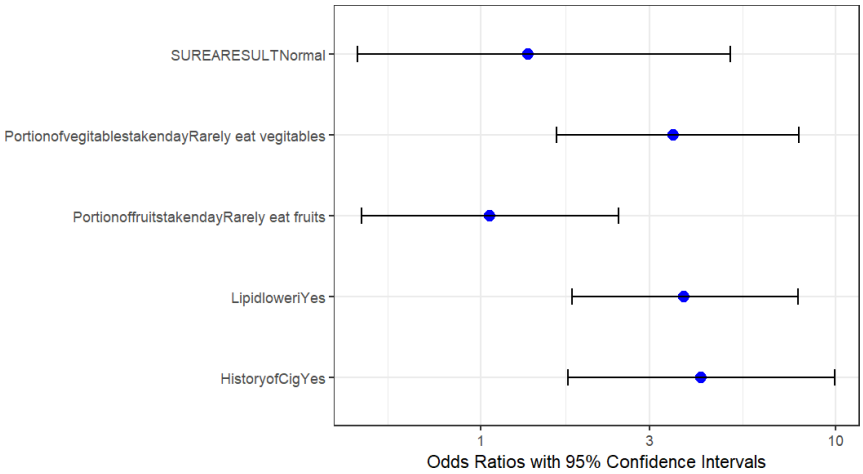
	2 portions and above	—		—	
Portion of vegetables taken per day	Rarely or 1 portion	2.77(1.62-4.73)	**0.001**	3.86(1.67-8.89)	**0.002**
	2 portions and above	—		—	
S-urea (mmol/L)	Normal	—		—	
	Abnormal	0.28(0.1-0.8)	**0.017**	0.88(0.24-3.13)	0.843
S-creatinine (mmol/L)	Normal	—		—	
	Abnormal	1.15(0.67-1.97)	0.622	1.11(0.39-3.12)	0.840
Hypertensive status	Normal	—		—	
	Hypertensive	1.29(0.65-2.56)	0.468	1.15(0.51-2.58)	0.740
Glucose fasting (mmol/L)	Normal	—		—	
	Abnormal	1.62(0.87-3.01)	0.126	1.07(0.52-2.21)	0.848
History of Drinking Alcohol	Yes	—		—	
	No	0.97(0.19-4.9)	0.971	0.64(0.09-4.59)	0.664
Usage of lipid-lowering drugs	No	—		—	
	Yes	2.49(1.31-4.74)	**0.005**	4.21(1.83-9.67)	**0.001**
B-HbA1c (DCCT)	Normal	—		—	
	Abnormal	1.24(0.77-2.01)	0.384	0.98(0.54-1.76)	0.946

OR=odd ratio; CI=Confidence interval. The first category listed under each variable is the reference group in the regression analysis.

Figure 1: Odds ratio with 95% confidence intervals for medication, dietary, and lifestyle factors of EAD among type 2 diabetes patients in Zanzibar

Fig 1 below illustrates the impact of medication, dietary, and lifestyle factors on EAD in this study. Generally, the results show a high impact of cigarette smoking, followed by use of lipid-lowering drugs and vegetable intake.

Commented [Y12]: Figure 1 currently displays the raw variable names from statistical software (such as SUREARESULTNormal, LipidlowerYes, and HistoryofCigYes). Suggest changing the Y-axis labels to clean, formal text (e.g., History of Smoking, Low Vegetable Intake, Use of Lipid-Lowering Drugs)



Discussion

This study revealed a considerable prevalence of excretory autonomic dysfunction (EAD) among Type 2 Diabetes Mellitus (T2DM) patients attending tertiary hospitals in Zanzibar, with a notable percentage of 24.5%. Loss of bladder control was the most common symptom 62%, followed by difficulty voiding and incomplete emptying, confirming that EAD is a frequent complication. The analysis identified that usage of lipid-lowering drugs, a history of cigarette smoking, and the portion of vegetables taken per day were significantly associated with the presence of EAD. These findings show varying severity of excretory disturbances and underscore the need for routine screening.

The prevalence of EAD in this study aligns with global evidence of its common occurrence in diabetes. However, the incidence and long-term consequences of EAD in T2DM are not yet fully understood [28]. Although their tendency is most noticeable in bladder dysfunction, which can occur in 25%-75% of diabetics, and is one of the more prevalent signs of autonomic neuropathy [4, 29, 30]. Loss of control of the bladder was found to be quite severe in 15.4% of adult male T2DM patients and 43.2% of female T2DM patients aged 30–83 years [31, 32].

These findings highlight the need for medical professionals to take excretory symptoms into account when managing diabetes comprehensively, especially for patients taking lipid-lowering medications. Resolving these problems could improve the general clinical results and quality of life for patients with both excretory difficulties and T2DM.

The study found that the use of lipid-lowering medications was significantly associated with a higher risk of developing excretory autonomic dysfunction (EAD). However, this association should be interpreted with caution. Use of lipid-lowering therapy may indicate higher underlying cardiometabolic risk, and residual confounding may persist despite exclusion of severe comorbidities. While some observational studies, such as Callaghan et al., suggest that statins may affect neuronal health by altering lipid metabolism and potentially contribute to neuropathy [33]. High-quality evidence from narrative, systematic reviews, and meta-analyses does not support a causal link between statin therapy and autonomic or peripheral neuropathy [33-36].

Statins are widely recognized for their pleiotropic cardiovascular and neuroprotective effects [37, 38], including the potential modulation of sympathetic activity, rather than harm [39-42]. Therefore, although our findings indicate an association between lipid-lowering drugs and EAD in this population, causality cannot be inferred. Further studies in Zanzibar should carefully consider confounding factors and use longitudinal or interventional designs to clarify the direction of effect.

Smoking was significantly associated with an increased risk of excretory autonomic dysfunction (EAD) in T2DM patients. This aligns with evidence that tobacco exposure contributes to diabetic nerve injury through multiple pathogenic pathways [43]. Cigarette smoke contains thousands of oxidants and free radicals [44], which exacerbate oxidative stress, a central mechanism in the pathogenesis of diabetic neuropathy that damages both sensory and autonomic nerve fibers [45]. Smoking also induces endothelial dysfunction and impaired microvascular perfusion, reducing blood flow to nerve tissues and thereby promoting nerve ischemia and degeneration [46].

Autonomic neuropathy, including bladder dysfunction, is a common complication of DM and may be exacerbated by smoking-induced vascular and metabolic injury [11]. While quitting smoking reduces the risk of macrovascular and microvascular complications, evidence on its impact on diabetic neuropathy, particularly autonomic phenotypes such as EAD, remains limited and poorly investigated [47]. These findings support a biologically plausible link between smoking and impaired excretory autonomic function in T2DM. They also highlight the need for targeted smoking cessation as part of comprehensive DM care to prevent autonomic complications

In our study, T2DM patients with low vegetable intake had a higher risk of excretory autonomic neuropathy, whereas those consuming ≥2 portions per day appeared protected. This aligns with evidence that high adherence to vegetable-rich, plant-based diets is associated with significantly lower risk of diabetic polyneuropathy [48]. Mechanistically, vegetables and plant foods supply antioxidants, phytochemicals, and fiber that reduce oxidative stress and systemic inflammation, both implicated in diabetic nerve injury, and contribute to improved metabolic control, which may preserve autonomic neural integrity [49].

A 20-week randomized study demonstrated that a plant-based diet in patients with T2DM and painful neuropathy significantly improved pain, symptom scores, and nerve function, suggesting that diet quality directly affects nerve health [50]. Michael Klowak et al demonstrates that dietary lifestyle changes, especially those emphasizing plant-based whole foods, are associated with improvements in neuropathic pain and nerve function outcomes in chronic neuropathy [51]. Lindsay Zilliox et al. suggest that lifestyle and dietary interventions can both prevent diabetic neuropathy and improve outcomes in patients with established neuropathy, emphasizing their modifiable nature [52].

Although fruit intake was not significantly associated with EAD. Fruits are rich sources of dietary fiber, vitamins, and phytochemicals that have been inversely associated with markers of oxidative stress and inflammation in patients with T2DM, mechanisms implicated in nerve injury [27, 53]. A large prospective cohort analysis from the UK Biobank showed that higher fresh fruit intake was associated with lower risk of diabetes progression and complications, including diabetes complications overall [54].

Evidence from the EPIC-InterAct study also indicates that specific fruit and vegetable subtypes, such as green leafy vegetables, are inversely associated with T2DM risk, although total fruit or vegetable intake alone showed weaker associations [55]. Taken together, these data suggest that while whole fruit consumption may contribute to overall metabolic health, the specific relationship between fruit intake and excretory autonomic dysfunction remains to be clarified.

These findings have several clinical implications. The prevalence of EAD and the risk factors found highlight the necessity for routine EAD screening, particularly for patients who smoke cigarettes. When autonomic dysfunction is identified early, prompt therapies may be possible, which could stop the progression of symptoms and lessen the overall burden of the condition [56, 57]. Primary care physicians should implement comprehensive management plans. These

programs should include lifestyle changes, strict glucose control, focused interventions to address autonomic dysfunction, and routine monitoring of autonomic function.

Despite the relatively large sample size, the absence of a control group limits the ability to directly compare autonomic function between diabetic and non-diabetic populations. Longitudinal studies that track the progression of autonomic dysfunction and assess the impact of therapeutic interventions would provide more robust insights. In addition, the observed sex differences in prevalence may have been influenced by the biased sex distribution, with a higher proportion of female participants, which restricts the interpretability and generalizability of the findings. Although statistical adjustment for sex was applied to reduce this limitation, future studies should aim for a more balanced sex representation or consider reporting sex-specific outcomes to enhance the validity of comparisons. Excluding patients with significant comorbidities such as cardiovascular, kidney, or liver disease, as well as pregnant women, may reduce the generalizability of our findings to all patients with type 2 diabetes in Zanzibar, particularly those with multiple chronic conditions who are commonly seen in clinical practice.

Commented [Y13]: add an in-depth discussion of the potential recall bias resulting from self-completion of diet/smoking questionnaires, and how the direction and magnitude of this bias affects study results.

Conclusion

Excretory autonomic dysfunction (EAD) was shown to be highly prevalent 24.5% among patients with type 2 diabetes mellitus (T2DM) in Zanzibar. There were also notable correlations between EAD and cigarette smoking, low vegetable consumption, and the use of lipid-lowering drugs. These results highlight the significance of regular EAD screening and the application of lifestyle-based treatments, like quitting smoking and making dietary changes. The surprising association between lipid-lowering medications and EAD points to the need for more investigation into how they affect the nervous system. Considering limitations such as self-reported data and the absence of a control group, the study provides insightful information to direct future longitudinal studies in diabetic populations as well as therapeutic care.

Commented [Y14]: Your finding that lipid-lowering drugs (likely statins) increased the risk of urinary tract infections by 4.21-fold is a sensitive finding, and already explained in the discussion section that this is likely due to confounding by indication. It would be helpful to add a statement in the abstract and conclusion that this association requires cautious interpretation due to potential residual confounding.

Abbreviations

EAD: Excretory Autonomic Dysfunction

MMH: Mnazi Mmoja Hospital

T2DM: Type two Diabetes Mellitus

BMI: Body Mass Index.

OR: Odd ratio

COR: Crude odds ratio

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Consent for Publication

Not applicable

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

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REFERENCES

Commented [Y15]: Add the name of the funding institution or grant number.
If this is independent research without external funding, the sentence should be adjusted accordingly.

1. Golbidi S, Laher I: **Bladder dysfunction in diabetes mellitus**. *Frontiers in pharmacology* 2010, **1**:136.
2. Tarcan T, Choi H-P, Azadzoi KM: **Molecular regulation of concomitant lower urinary tract symptoms and erectile dysfunction in pelvic ischemia**. *International Journal of Molecular Sciences* 2022, **23**(24):15988.
3. Brown JS, Wessells H, Chancellor MB, Howards SS, Stamm WE, Stapleton AE, Steers WD, Van Den Eeden SK, McVary KT: **Urologic complications of diabetes**. *Diabetes care* 2005, **28**(1).
4. Goldman H, Appell R: **Voiding dysfunction in women with diabetes mellitus**. *International Urogynecology Journal* 1999, **10**:130-133.
5. Piętak PA, Rechberger T: **Overactive bladder as a dysfunction of the autonomic nervous system–A narrative review**. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2022, **271**:102-107.
6. Vinik AI, Maser RE, Mitchell BD, Freeman R: **Diabetic autonomic neuropathy**. *Diabetes care* 2003, **26**(5):1553-1579.
7. Andersson K-E: **Antimuscarinic mechanisms and the overactive detrusor: an update**. *European urology* 2011, **59**(3):377-386.
8. Gall A, Craggs M: **Autonomic nervous system dysfunction**. *Oxford Textbook of Neurorehabilitation* 2015:89.
9. Michel MC, Chess-Williams R, Hegde SS: **Are blood vessels a target to treat lower urinary tract dysfunction?** In., vol. 388: Springer; 2015: 687-694.
10. Levin RM, English M, Barretto M, Dubuc M, O'Connor L, Leggett R, Whitbeck C: **Normal detrusor is more sensitive than hypertrophied detrusor to in vitro ischemia followed by re-oxygenation**. *Neurourology and Urodynamics: Official Journal of the International Continence Society* 2000, **19**(6):701-712.
11. Agochukwu-Mmonu N, Pop-Busui R, Wessells H, Sarma AV: **Autonomic neuropathy and urologic complications in diabetes**. *Autonomic Neuroscience* 2020, **229**:102736.
12. Frimodt-Møller C: **Diabetic cystopathy: epidemiology and related disorders**. *Annals of internal medicine* 1980, **92**(2_Part_2):318-321.
13. Liu R-T, Chung M-S, Lee W-C, Chang S-W, Huang S-T, Yang KD, Chancellor MB, Chuang Y-C: **Prevalence of overactive bladder and associated risk factors in 1359 patients with type 2 diabetes**. *Urology* 2011, **78**(5):1040-1045.
14. Jackson RA, Vittinghoff E, Kanaya AM, Miles TP, Resnick HE, Kritchevsky SB, Simonsick EM, Brown JS, Health A, Study BC: **Urinary incontinence in elderly women: findings from the Health, Aging, and Body Composition Study**. *Obstetrics & Gynecology* 2004, **104**(2):301-307.
15. Kelly MS, Routh JC, Davis LG, Purves JT, Wiener JS, Maciejewski ML: **Lower urinary tract symptoms in older children with and without diabetes mellitus**. *Clinical pediatrics* 2018, **57**(13):1576-1581.
16. Bolgeo T, Maconi A, Bertolotti M, Roveta A, Betti M, Gatti D, Boccafoschi C: **Physiopathology of the diabetic bladder**. *Archivio Italiano di Urologia e Andrologia* 2020, **92**(4).
17. Lifford KL, Curhan GC, Hu FB, Barbieri RL, Grodstein F: **Type 2 diabetes mellitus and risk of developing urinary incontinence**. *Journal of the American Geriatrics Society* 2005, **53**(11):1851-1857.
18. Yuan Z, Tang Z, He C, Tang W: **Diabetic cystopathy: a review 综述: 糖尿病性膀胱病**. *Journal of diabetes* 2015, **7**(4):442-447.
19. Sampselle CM, Harlow SD, Skurnick J, Brubaker L, Bondarenko I: **Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women**. *Obstetrics & Gynecology* 2002, **100**(6):1230-1238.
20. Wang Y, Wang X, Liang S, Cai W, Chen L, Hu Y, Hao F, Ren W: **Predictive value of risk factors for bladder dysfunction in Chinese patients with type 2 diabetes mellitus: A case-control study**. *Neurourology and Urodynamics* 2023, **42**(8):1712-1721.

21. Khamis AG, Senkoro M, Mwanri AW, Kreppel K, Mfinanga SG, Bonfoh B, Kwesigabo G: **Prevalence and determinants of hypertension among pastoralists in Monduli District, Arusha region in Tanzania: a cross-sectional study**. *Archives of Public Health* 2020, **78**:1-12.
22. Twofoot MTM: **Clinical and experimental evidence for the pathological mechanisms underlying aspects of sexual dysfunction: Impact of adiposity and chronic kidney disease**: Queen's University (Canada); 2013.
23. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT: **Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure**. *hypertension* 2003, **42**(6):1206-1252.
24. Cleland CL, Hunter RF, Kee F, Cupples ME, Sallis JF, Tully MA: **Validity of the global physical activity questionnaire (GPAQ) in assessing levels and change in moderate-vigorous physical activity and sedentary behaviour**. *BMC public health* 2014, **14**:1-11.
25. Meling S, Tjora E, Eichele H, Ejskjaer N, Carlsen S, Njølstad PR, Brock C, Søfteland E: **The Composite Autonomic Symptom Score 31 Questionnaire: A Sensitive Test to Detect Risk for Autonomic Neuropathy**. *Journal of diabetes research* 2023, **2023**:4441115.
26. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W: **COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score**. In: *Mayo Clinic Proceedings: 2012*: Elsevier; 2012: 1196-1201.
27. Haji HT, Ebrahim A, Khamis AG, Ali RM, Ramaiya K, Mashili FL: **Associations of oral hypoglycemic use, fruit intake, and diabetes duration with gastrointestinal autonomic dysfunction in type 2 diabetes patients in Zanzibar**. *Scientific Reports* 2025, **15**(1):41643.
28. Braffett BH, Wessells H, Sarma AV: **Urogenital autonomic dysfunction in diabetes**. *Current Diabetes Reports* 2016, **16**:1-10.
29. Brown JS, Wessells H, Chancellor MB, Howards SS, Stamm WE, Stapleton AE, Steers WD, Van Den Eeden SK, McVary KT: **Urologic Complications of Diabetes**. *Diabetes Care* 2005, **28**(1):177-185.
30. Laumann EO, Paik A, Rosen RC: **Sexual dysfunction in the United States: prevalence and predictors**. *Jama* 1999, **281**(6):537-544.
31. Mahishale A, Ambre P, Kantanavar KA: **Prevalence of urinary incontinence in males with type 2 diabetes mellitus**. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 2019, **13**(5):2953-2956.
32. Nazzal Z, Khatib B, Al-Quqa B, Abu-Taha L, Jaradat A: **The prevalence and risk factors of urinary incontinence amongst Palestinian women with type 2 diabetes mellitus: A cross-sectional study**. *Arab journal of urology* 2020, **18**(1):34-40.
33. Pasha R, Azmi S, Ferdousi M, Kalteniece A, Bashir B, Gouni-Berthold I, Malik RA, Soran H: **Lipids, lipid-lowering therapy, and neuropathy: a narrative review**. *Clinical Therapeutics* 2022, **44**(7):1012-1025.
34. Lewandowski J, Symonides B, Gaciong Z, Siński M: **The effect of statins on sympathetic activity: a meta-analysis**. *Clinical Autonomic Research* 2015, **25**(2):125-131.
35. Antoniou GA, Fisher RK, Georgiadis GS, Antoniou SA, Torella F: **Statin therapy in lower limb peripheral arterial disease: systematic review and meta-analysis**. *Vascular Pharmacology* 2014, **63**(2):79-87.
36. Wannarong T, Chaikijurajai T, Preston DC, Naweera W, Sukpornchairak P, Ungprasert P: **Statins and the risk of polyneuropathy: A systematic review and two meta-analyses**. *Muscle & Nerve* 2022, **65**(1):120-125.
37. Gaist D, Jeppesen U, Andersen M, Garcia Rodriguez L, Hallas J, Sindrup SH: **Statins and risk of polyneuropathy: a case-control study**. *Neurology* 2002, **58**(9):1333-1337.
38. Nunley KA, Orchard TJ, Ryan CM, Miller R, Costacou T, Rosano C: **Statin use and cognitive function in middle-aged adults with type 1 diabetes**. *World journal of diabetes* 2017, **8**(6):286.

39. Wood WG, Eckert GP, Igbavboa U, Müller WE: **Statins and neuroprotection: a prescription to move the field forward**. *Annals of the New York academy of sciences* 2010, **1199**(1):69-76.
40. Morofuji Y, Nakagawa S, Ujifuku K, Fujimoto T, Otsuka K, Niwa M, Tsutsumi K: **Beyond lipid-lowering: effects of statins on cardiovascular and cerebrovascular diseases and cancer**. *Pharmaceuticals* 2022, **15**(2):151.
41. Zhao W, Xiao Z-J, Zhao S-P: **The benefits and risks of statin therapy in ischemic stroke: a review of the literature**. *Neurology India* 2019, **67**(4):983-992.
42. Westphal Filho FL, Moss Lopes PR, Menegaz de Almeida A, Sano VKT, Tamashiro FM, Gonçalves OR, de Moraes FCA, Kreuz M, Kelly FA, Silveira Feitoza PV: **Statin use and dementia risk: A systematic review and updated meta-analysis**. *Alzheimer's & Dementia: Translational Research & Clinical Interventions* 2025, **11**(1):e70039.
43. Clair C, Cohen MJ, Eichler F, Selby KJ, Rigotti NA: **The effect of cigarette smoking on diabetic peripheral neuropathy: a systematic review and meta-analysis**. *Journal of general internal medicine* 2015, **30**(8):1193-1203.
44. Valavanidis A, Vlachogianni T, Fiotakis K: **Tobacco smoke: involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenesis and synergistic effects with other respirable particles**. *International journal of environmental research and public health* 2009, **6**(2):445-462.
45. Figueroa-Romero C, Sadidi M, Feldman EL: **Mechanisms of disease: the oxidative stress theory of diabetic neuropathy**. *Reviews in Endocrine and Metabolic Disorders* 2008, **9**(4):301-314.
46. Roy B: **Pathophysiological mechanisms of diabetes-induced macrovascular and microvascular complications: the role of oxidative stress**. *Medical Sciences* 2025, **13**(3):87.
47. Walicka M, Krysiński A, La Rosa GRM, Sun A, Campagna D, Di Ciaula A, Dugal T, Kengne A, Le Dinh P, Misra A: **Influence of quitting smoking on diabetes-related complications: A scoping review with a systematic search strategy**. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 2024, **18**(5):103044.
48. Aminianfar A, Haghighat_Lari MM, Asoudeh F, Mirzae K, Qorbani M, Asadi S: **The association between Plant-Based Diets and Diabetic Polyneuropathy: a case-control study**. 2024.
49. Ansari P, Samia JF, Khan JT, Rafi MR, Rahman MS, Rahman AB, Abdel-Wahab YH, Seidel V: **Protective effects of medicinal plant-based foods against diabetes: a review on pharmacology, phytochemistry, and molecular mechanisms**. *Nutrients* 2023, **15**(14):3266.
50. Bunner A, Wells C, Gonzales J, Agarwal U, Bayat E, Barnard ND: **A dietary intervention for chronic diabetic neuropathy pain: a randomized controlled pilot study**. *Nutrition & diabetes* 2015, **5**(5):e158-e158.
51. Klowak M, Lau R, Mohammed MN, Birago A, Samson B, Ahmed L, Renee C, Meconnen M, Sam M, Boggild AK: **A Systematic Review of Dietary Lifestyle Interventions for Neuropathic Pain**. *Journal of Clinical Medicine* 2024, **13**(22):6766.
52. Zilliox LA, Russell JW: **Physical activity and dietary interventions in diabetic neuropathy: a systematic review**. *Clinical Autonomic Research* 2019, **29**(4):443-455.
53. Halvorsen RE, Elvestad M, Molin M, Aune D: **Fruit and vegetable consumption and the risk of type 2 diabetes: a systematic review and dose–response meta-analysis of prospective studies**. *BMJ nutrition, prevention & health* 2021, **4**(2):519.
54. Zheng G, Ran S, Zhang J, Qian AM, Hua J, Wang C, Vaughn MG, Tabet M, Lin H: **Fresh fruit, dried fruit, raw vegetables, and cooked vegetables consumption associated with progression trajectory of type 2 diabetes: a multi-state analysis of a prospective cohort**. *European Journal of Nutrition* 2024, **63**(5):1719-1730.
55. Cooper AJ, Forouhi NG, Ye Z, Buijsse B, Arriola L, Balkau B, Barricarte A, Beulens JW, Boeing H, Büchner FL: **Fruit and vegetable intake and type 2 diabetes: EPIC-InterAct prospective study and meta-analysis**. *European journal of clinical nutrition* 2012, **66**(10):1082-1092.

56. Erbas T: **Recognizing and treating diabetic autonomic neuropathy**. *Cleve Clin J Med* 2001, **68**(1):1.
57. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D: **Diabetic neuropathy: a position statement by the American Diabetes Association**. *Diabetes care* 2017, **40**(1):136.

Supporting information

S1 Fig. Odds ratio with 95% confidence intervals for medication, dietary and lifestyle factors of EAD among type 2 diabetes patients in Zanzibar.

S2 Questionnaire: Prevalence and factors associated with excretory autonomic neuronal dysfunction in patients with type 2 diabetic mellitus attending a tertiary hospital in Zanzibar.

UNIVERSITAS TRISAKTI

dr.Yenny Y <yennyfarmako@trisakti.ac.id>

Scientific Reports: Thank you for your review on " Determinants of Excretory Autonomic Dysfunction: The Role of Lipid-Lowering Drugs, Vegetable Intake, and Smoking in Type 2 Diabetes Mellitus in Zanzibar "

1 message

Scientific Reports <srep@nature.com> Sun, Jun 7, 2026 at 11:19 AM
To: yennyfarmako@trisakti.ac.id

Ref: "

Determinants of Excretory Autonomic Dysfunction: The Role of Lipid-Lowering Drugs, Vegetable Intake, and Smoking in Type 2 Diabetes Mellitus in Zanzibar

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Determinants of Excretory Autonomic Dysfunction: The Role of Lipid-Lowering Drugs, Vegetable Intake, and Smoking in Type 2 Diabetes Mellitus in Zanzibar

Feedback for the author(s)

Review file(s)

Review__EXCRETORY AUTONOMIC NEUROPATHY MANUSCRIPT.docx

Comments to the author(s)

This manuscript addresses a very important and contextual topic, particularly regarding autonomic complications in patients with type 2 diabetes mellitus (T2DM) in a sparsely studied region like Zanzibar. The use of a standardized instrument like the COMPASS-31 is also a strong plus.
Major revisions to this manuscript to ensure STROBE compliance and enhance the validity of this study are:Is the excretory terminology consistent with the urinary domain (COMPASS-31 QUESTIONNAIRE):

1. In the validation of the COMPASS-31 questionnaire by Sletten et al. (2012), the subdomain you used was referred to as the Urinary Domain, not Excretory (including urinary and defecation). Is the terminology used appropriate?
2. Add the study design (Cross-Sectional) to the Title.
3. Explain the sample size calculation in the Methods section.
4. Provide a participant flowchart to clarify the sample inclusion/exclusion process.
5. Explain the status or handling of missing data.
6. The duration of diabetes is the most powerful and fundamental predictor for the development of autonomic neuropathy and has already been mentioned in the Introduction and Discussion sections, but why does this variable not appear at all in Table 2, Table 3, or in the multivariate regression model as a control variable?
7. In the Exclusion criteria section, you stated that patients with chronic kidney disease were excluded from the study. However, Table 2 states: Known renal

disease -> Yes: 344 (94.5%). If 94.5% of your sample had kidney disease, you have violated the study's exclusion criteria. Please clarify the exclusion criteria for the definition of chronic kidney disease.
8. it seems your labels are mixed up (the correct ones are Yes = 20, No = 344). Please recheck the variable known renal disease in Table 2 and compare with Table 3
9. Table 3. Please recheck the "All" column in the Serum Urea variable. It says the total Normal = 239 (64.8%) and Abnormal = 125 (35.2%). If 239/364 is 65.6%, and 125/364 is 34.3%. Please recalculate.
10. Table 4. The variable, completely emptying the bladder in the Never row, is written as a total of 44. If added up from the Dysfunction (n=46) + Normal (n=275) columns, the result is 321. Check the calculation results again.
11. Figure 1 currently displays the raw variable names from statistical software (such as SUREARESULTNormal, LipidlowerYes, and HistoryofCigYes). Suggest changing the Y-axis labels to clean, formal text (e.g., History of Smoking, Low Vegetable Intake, Use of Lipid-Lowering Drugs)
12. In the limitation section, add an in-depth discussion of the potential recall bias resulting from self-completion of diet/smoking questionnaires, and how the direction and magnitude of this bias affects study results.
13. Your finding that lipid-lowering drugs (likely statins) increased the risk of urinary tract infections by 4.21-fold is a sensitive finding, and already explained in the discussion section that this is likely due to confounding by indication. It would be helpful to add a statement in the abstract and conclusion that this association requires cautious interpretation due to potential residual confounding.
Please find a complete comment on this manuscript review

Confidential feedback for the Editor

Your recommendation	• ***Revise***
Is the study design appropriate to answer the research question (including the use of appropriate controls), and are the conclusions supported by the evidence presented?	• ***Yes***
Are the methods sufficiently described to allow the study to be repeated?	• ***No, but these points can be addressed with revisions***
Comments	***- Explain the sample size calculation in the Methods section. - Provide a participant flowchart to clarify the sample inclusion/exclusion process. - Explain the status or handling of missing data.***
Is the use of statistics and treatment of uncertainties appropriate?	• ***No***

Comments

The statistics test use is correct, but the duration of diabetes is the most powerful and fundamental predictor for the development of autonomic neuropathy, and has already been mentioned in the Introduction and Discussion sections. Why does this variable not appear at all in Table 2, Table 3, or in the multivariate regression model as a control variable?

Has guidance been provided on how overstated claims should be rewritten?

- ***Yes, I have suggested how the text can be rewritten***

Is the presentation of the work clear?

- ***No, it needs some language corrections before being published***

Comments

Some revisions should be made, including recalculation result tables and then rewriting

---

Are the images in this manuscript (including electrophoretic gels and blots) free from apparent manipulation?

- ***I am not able to assess this***

Comments

Figure 1 currently displays the raw variable names from statistical software (such as SUREARESULTNormal, LipidlowerYes, and HistoryofCigYes). Suggest changing the Y-axis labels to clean, formal text (e.g., History of Smoking, Low Vegetable Intake, Use of Lipid-Lowering Drugs)

Confidential comments to the Editor

The author addresses a timely and vital subject by examining autonomic complications in T2DM patients within Zanzibar, a region where such data remains scarce.
A key strength of this work is its reliance on the standardized COMPASS-31 framework.
While the manuscript shows clear merit, I recommend a decision of major revision before it can be deemed acceptable for publication.

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REVIEWER CERTIFICATE

This certificate is awarded to

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in recognition of their contribution to

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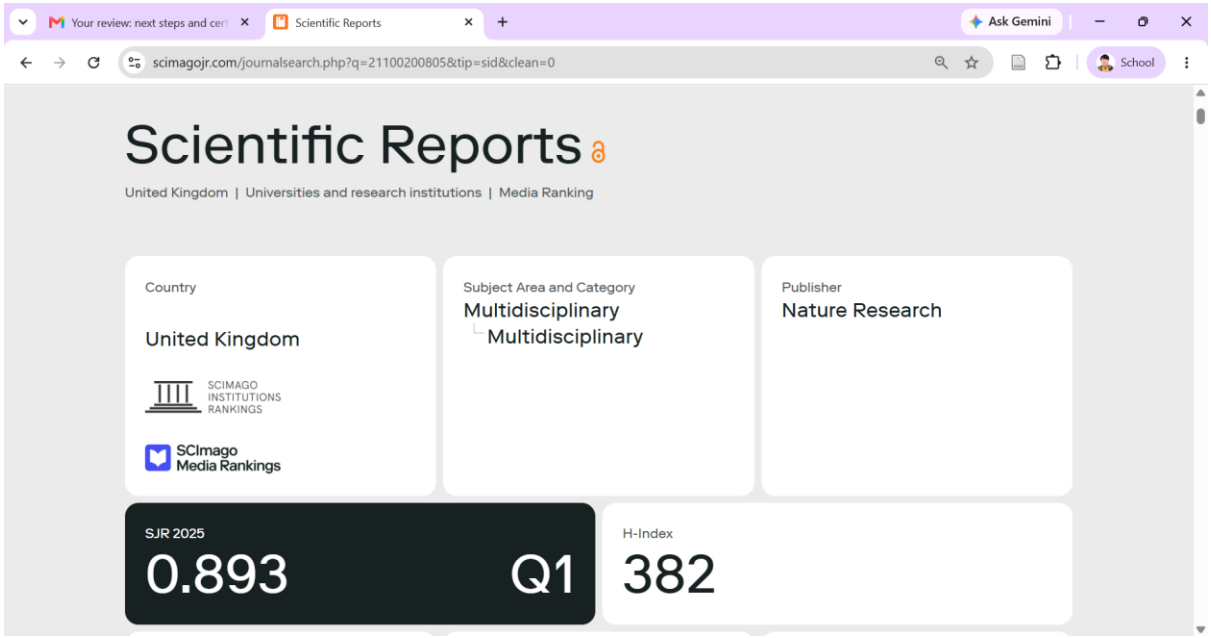
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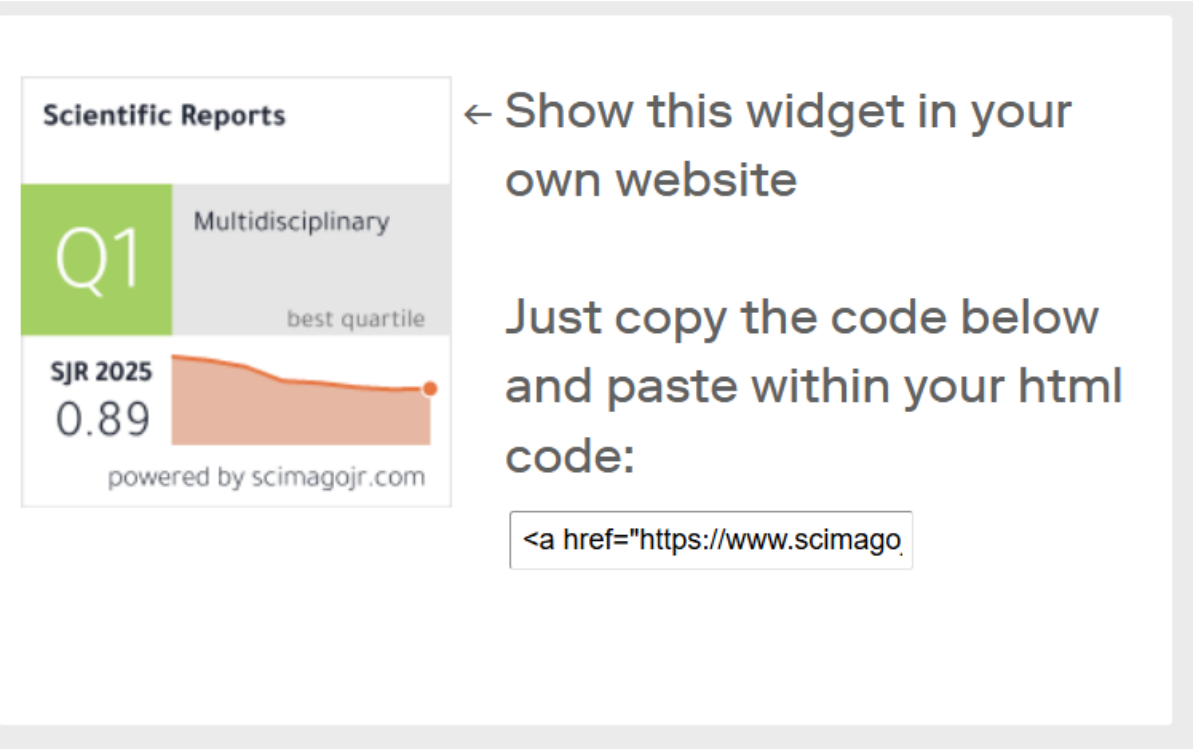
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