



## Prevalence of Cardiovascular Autonomic Neuropathy among Type 2 Diabetic Patients in Erbil City

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### Abstract

**Background and objectives:** Type 2 diabetes affects over 500 million people worldwide. Damage to the autonomic nerve fibers that innervate the heart and blood vessels is known as cardiac-autonomic-neuropathy. It is usually an overlooked, significant diabetic complication. The aim of this study was to assess the prevalence of cardiac-autonomic-neuropathy, analyze its risk factors.

**Methods:** This cross-sectional study was carried out at the outpatient clinic for the Diabetes Center from October 2022 to April 2023 in Erbil, Iraq. Thorough physical examination was done in order to identify patients with and without cardiac-autonomic-neuropathy. Detailed history and blood workup were taken into consideration to find risk factors of cardiac-autonomic-neuropathy.

**Results:** The prevalence of cardiac-autonomic-neuropathy among the study population was 29.7%. Among the cardiac-autonomic-neuropathy patients, 53.3% were female and 45.5% were male. Patients with cardiac-autonomic-neuropathy had a higher HbA1c level (p-value <0.05). Moreover, patients with cardiac-autonomic-neuropathy were found to have lower total cholesterol, high-density and low-density lipoprotein, and (p-value >0.05). Our results show that being on oral hypoglycemic agent, being underweight or overweight are significant predictors of cardiac-autonomic-neuropathy (p-value <0.05). Moreover, we found that the odds of cardiac-autonomic-neuropathy decrease with increasing high-density lipoprotein (p-value <0.05); and the odds increase with increasing glycosylated hemoglobin and fasting blood sugar (p-value <0.05).

**Conclusion:** The current study demonstrates that the development of Cardiovascular Autonomic Neuropathy can be significantly affected by poor glycemic control, high-density lipoprotein level, and the mode of treatment for diabetes control.

**Keywords:** Cardiovascular-autonomic-neuropathy, HbA1c, Type 2 Diabetes

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## Introduction

Diabetes is a chronic illness marked by high blood sugar levels and impaired fat and protein metabolism. Cells in the body can't efficiently use the generated insulin, or the pancreas isn't producing any insulin, leading to elevated blood sugar levels.<sup>1</sup> Obesity and an unhealthy lifestyle have become more common around the world, leading to the high and rising disease burden associated with diabetes all around the world. Diabetes is classified into two types: type 1 and type 2. Type 2 accounts for the vast majority of diabetic people (>85%).<sup>2</sup> Furthermore, thirty million people in the USA and over five hundred million people around the world have type 2 diabetes, with a yearly prevalence of roughly 1.5 million cases.<sup>3</sup> The most prevalent age groups for type 1 diabetes are children, adolescents, and young adults; however, the specific cause is unknown. Type 2 diabetes risk factors are better understood. Despite the fact that there is a large genetic component, risk factors such as age, overweight, obesity, and inactivity are present in the majority of cases.<sup>1</sup> The chronic microvascular and macrovascular effects of diabetes are generally distinct from one another, with the first one being much more common than the latter. In contrast to macrovascular complications, which include cardiovascular disease, stroke, and peripheral arterial disease (PAD), microvascular complications include nephropathy, retinopathy, and neuropathy.<sup>4</sup> The most common diabetes complications are a group of clinical syndromes caused by damage to the peripheral and autonomic nervous systems. Distal symmetric polyneuropathy is the most prevalent type of diabetic neuropathy, which typically affects limbs. Other diabetes-related diffuse neuropathies can occur, including a constellation of autonomic neuropathies such as cardiac autonomic neuropathy, gastrointestinal dysmotility, diabetic cystopathy, and

impotence.<sup>5</sup> Cardiovascular autonomic neuropathy (CAN) is caused by damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in a disruption in heart rate control and vascular dynamics. It is one of the most often overlooked and significant sequelae of diabetes.<sup>6</sup> The frequency of CAN varies substantially according to the diagnostic procedures utilized, the population analyzed, and the stage of the disease. According to previous research, the prevalence of CAN in type 1 diabetes patients ranges from 17% to 90%, and in type 2 diabetes patients, the prevalence ranges from 27.5% to 73%.<sup>7</sup> Approximately 7% of people with DM type 1 or type 2 have developed CAN at the time of diagnosis, and the risk is thought to increase by roughly 6% and 2% per year in type 1 and type 2, respectively. Additional risk factors for developing CAN include poor glycemic control, aging, obesity, smoking, hypertension, distal polyneuropathy, nephropathy, and retinopathy. Hyperglycemia is the main contributor to the pathogenic process that results in CAN, which is triggered by intricate interactions involving numerous processes and pathways that ultimately induce neuronal ischemia and neuronal death.<sup>7</sup> While resting tachycardia and a fixed heart rate are late symptoms in diabetic patients with vagal dysfunction, changes in HRV are the initial signs of CAN. The average resting heart rate is between 90 and 100 beats per minute, often rising up to 130 beats per minute.<sup>8</sup> Orthostatic hypotension is defined by the American Academy of Neurology as a physical finding that appears three minutes after standing and causes a systolic blood pressure drop of at least 20 mm Hg or a diastolic blood pressure drop of at least 10 mm Hg.<sup>9</sup> The purpose of this study was to assess the prevalence of CAN, analyze its risk factors, and discover the link between CAN and other type 2





diabetes microvascular and macrovascular problems.

### Patients and methods

This cross-sectional study was carried out at the Diabetes Center outpatient clinic in Erbil, Iraq. Patients were recruited from October 2022 to April 2023. A total of 101 cases with type 2 diabetes mellitus were enrolled in this study. The Study was Approved by the ethics committee of Kurdistan Higher Council of Medical Specialties. Inclusion criteria were patients of both genders, their ages equal or more than 18 years old, previously diagnosed as type 2 diabetes mellitus according to ADA criteria;<sup>10</sup> Exclusion criteria were Type 1 DM, congenital heart disease, pregnancy, chronic kidney disease, malignancy, heart failure, chronic liver disease, anemia, atrial fibrillation (AF), taking beta blocker drugs or sympathomimetic drugs, patients on pacemakers, patients with a past medical history of hypertension, or those who were taking antihypertensive medications. Data collection Patient interviews were held in the outpatient clinic of the diabetes center, with ethical considerations performed, informed consent taken verbally, and a comprehensive history taken, including history of current smoking, duration of diabetes, type of treatment, glycemic control, and chronic complications. After 15 minutes of rest, a thorough physical examination was done, including vital signs, peripheral pulse assessment, and systemic CVS examination. Orthostatic blood pressure was taken after 3 minutes of standing, BMI was calculated and classified according to WHO classification, and a clinical neurological sensory examination and deep tendon reflexes was done. After an overnight fast of at least 8 hours, venous blood was collected in the morning for testing fasting blood sugar, CBC, serum triglyceride, HDL, LDL, total cholesterol, and HbA1c by the immunoassay method, neuropathy was diagnosed based on clinical criteria suggested by Tesfaye et al.'s

criteria for probable neuropathy, which is defined as any two or more of the following symptoms and signs neuropathy: 1) neuropathic symptoms, 2) decreased distal sensation, or 3) unequivocally diminished or absent ankle reflexes. Moreover, an ophthalmology consultation was requested for screening for retinopathy. According to the Asian Association for the Study of Diabetes (AASD), a diagnosis of CAN was made by the presence of either resting tachycardia or orthostatic hypotension, or both together; resting tachycardia is regarded as  $PR \geq 100$  BPM, and orthostatic hypotension is diagnosed by a systolic blood pressure fall of at least 20 mm Hg or a diastolic blood pressure decrease of at least 10 mm Hg within 3 minutes of standing.<sup>8</sup>

The information was recorded on a prepared questionnaire. For data entry Microsoft excel worksheet (Excel 2010) was utilized. The statistical program Statistical Package for Social Sciences (SPSS, IBM, Chicago) version 23.0 was used to analyze the collected data. Continuous data were presented in the form of mean and standard deviation, whereas categorical variables were displayed in frequencies and percentages. For outcome-predicting variables, binary logistic regression analysis (odds ratio (OR)) was used, and the 95% confidence interval (CI) was calculated using standard statistical techniques. Any value of  $p < 0.05$  was considered significant.

### Results

One hundred and one patients were enrolled in this trial. Their ages ranged from 22 to 67 years old. The mean age of patients was  $50.2 \pm 8.9$  years. Among them, 46 were male and 55 were female. Sociodemographic characteristics are exhibited in Table (1). The prevalence of cardiac autonomic neuropathy (CAN) among the study population was 29.7%. Among the CAN patients, 53.3% were female and 45.5% were male. Patients were divided into two groups: those who did

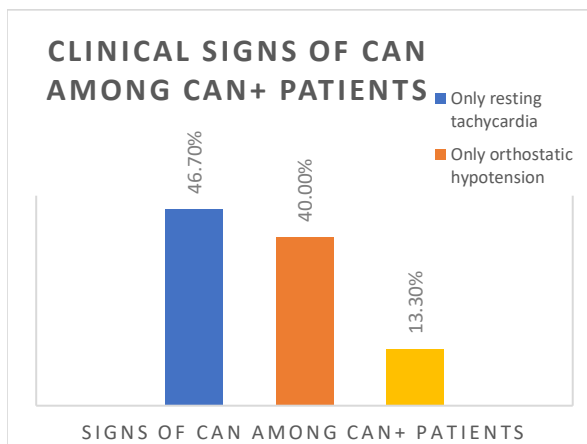




not have CAN (Group 1: CAN—) and those who did (Group 2: CAN+). Most of our CAN+ patients only had resting tachycardia (46.7%), followed by only orthostatic hypotension (40%) and combined resting tachycardia with orthostatic hypotension (13.3%) respectively. the clinical signs of CAN are shown in Figure (1).

**Table (1):** Sociodemographic information of the studied population

Variables		
Mean age		50.2 ± 8.9
Gender	Male	46 (45.5%)
	Female	55 (54.5%)
Marital status	Single	1 (1%)
	Married	95 (95%)
	Divorced/Widowed	5 (5%)
BMI	Underweight	5 (5%)
	Normal	37 (36.6%)
	Overweight	33 (32.7%)
	Obese	26 (25.7%)
Smoking status	Smoker	16 (15.8%)
	Non-smoker	85 (84.3%)



**Figure (1):** Clinical signs of Cardiac Autonomic Neuropathy among our CAN+ patients

Regarding the biochemical profile of patients with CAN compared to patients without CAN we found that patients with CAN had a higher fasting and random blood sugar levels, and higher HbA1c, but lower total cholesterol, HDL, and LDL levels. Table (2) displays the clinical and biochemical traits sorted by the existence of cardiac autonomic neuropathy.

**Table (2):** Clinical and biochemical characteristics of the subjects

Variables		Total (n=101)	Group 1: CAN— (n=71)	Group 2: CAN+ (n=30)	p-value
Age (in years)		50.2 ± 8.9	49.9 ± 8.6	50.9 ± 9.7	0.617
Gender	Male	46 (45.5%)	32 (45.1%)	14 (46.7%)	0.883
	Female	55 (54.5%)	39 (54.9%)	16 (53.3%)	
Duration of DM	<5years	36 (35.6%)	28 (39.4%)	8 (26.7%)	0.221
	>5years	65 (64.4%)	43 (60.6%)	22 (73.3%)	
BMI	Underweight	5 (5%)	1 (1.4%)	4 (13.3%)	0.019
	Normal	37 (36.6%)	31 (43.7%)	6 (20%)	
	Overweight	33 (32.7%)	21 (29.6%)	12 (40%)	
	Obese	26 (25.7%)	18 (25.4%)	8 (26.7%)	
Resting blood pressure	Systolic BP (mmHg)	142.4 ± 12.7	140.8 ± 21	146.3 ± 18.2	0.216
	Diastolic BP (mmHg)	87 ± 9.5	87.1 ± 9	89.2 ± 10.3	
Orthostatic blood pressure	Systolic BP (mmHg)	140.9 ± 21.2	142.4 ± 21.6	137.3 ± 20.2	0.264





	Diastolic BP (mmHg)	91.4 ± 11.2	92.5 ± 9.9	88.5 ± 13.6	0.1
Resting HR		88.5 ± 12.7	82.3 ± 7.9	100.8 ± 13.4	0.000
Fasting blood sugar (mg/dl)		187.5 ± 74.4	186.25 ± 77.4	190.5 ± 67.9	0.795
Random blood sugar (mg/dl)		272.6 ± 111.1	266.7 ± 108.6	286.6 ± 117.6	0.413
HbA1c (%)		8.7 ± 1.9	8.4 ± 1.8	9.5 ± 2.1	0.007
Total cholesterol		176.6 ± 54	179.2 ± 46.7	170.4 ± 68.7	0.457
LDL		112.6 ± 34.4	114.3 ± 32.2	108.9 ± 39.5	0.475
HDL		36.9 ± 10.1	38.1 ± 9.9	34 ± 10.1	0.06
Triglyceride		216.7 ± 116.9	219.6 ± 119	209 ± 113.4	0.705
Mode of treatment	Insulin	11 (10.9%)	5 (7%)	6 (20%)	0.087
	Oral hypoglycemic agent	60 (59.4%)	47 (66.2%)	13 (43.3%)	
	Combined Insulin and OHA	19 (18.8%)	13 (18.3%)	6 (20%)	
	None	11 (10.9%)	6 (8.5%)	5 (16.7%)	
Ischemic heart disease	Yes	3 (3%)	2 (2.8%)	1 (3.3%)	1.000
	No	98 (98%)	69 (97.2%)	29 (96.7%)	
Smoking status	Smoker	16 (15.8%)	11 (15.5%)	5 (16.7%)	1.000
	Non-smoker	85 (84.3%)	60 (84.5%)	25 (83.3%)	

Table (3) shows the prevalence of other microangiopathies such as neuropathy was found in 60% of cardiac autonomic neuropathy patients ( $p>0.667$ ) and retinopathy was found in (53.3%) of cardiac autonomic neuropathy patients.

**Table (3):** The Prevalence of other microangiopathies among the subjects

Variables	CAN— (n=71)	CAN+ (n=30)	p-value
Peripheral neuropathy	47 (66.2%)	18 (60%)	0.667
Retinopathy	34 (47.9%)	16 (53.3%)	0.650

Multiple logistic regression analysis was performed based on the presence of cardiac autonomic neuropathy, as the dependent variable showed that being underweight and

overweight were independently associated with cardiac autonomic neuropathy. As well as higher HDL and HbA1c, being on an oral hypoglycemic agent was also independently associated with cardiac autonomic neuropathy. Our data shows that the odds of CAN decrease with an increase in HDL and increase with an increase in HbA1c. Moreover, compared to patients with normal weight, the odds of CAN increase when the patient is under-weight or overweight. Lastly, patients on OHA are less likely to have CAN compared to those who do not receive any treatment. Table (4) demonstrates the results of two models of binary logistic regression





**Table (4):** Binary logistic regression analysis for evaluating predictors of cardiac autonomic neuropathy

Variables	Odds ratio (OR)	95% CI	p-value	
<b>Model 1</b>				
Age	1.004	0.945-1.068	0.888	
Gender (Female vs. Male)	1.091	0.406-2.934	0.862	
Duration of DM (>5 years vs <5 years)	0.526	0.151-1.829	0.312	
Mode of treatment	Insulin vs. No Rx	1.474	0.183-11.842	0.715
	OHA vs. No Rx	0.206	0.043-0.983	0.048
	Combined Insulin and OHA vs. No Rx	0.383	0.066-2.240	0.287
BMI	Underweight vs. Normal	25.648	1.794-366.672	0.017
	Overweight vs. Normal	4.909	1.294-18.621	0.019
	Obese vs. Normal	3.383	0.847-13.519	0.085
<b>Model 2</b>				
Fasting blood sugar	0.986	0.973-1.000	0.05	
Random Blood sugar	1.006	0.997-1.015	0.183	
HbA1c	1.719	1.199-2.466	0.003	
T. cholesterol	1.000	0.983-1.02	0.970	
LDL	0.990	0.965-1.02	0.449	
HDL	0.941	0.894-0.990	0.018	
Triglyceride	1.000	0.996-1.005	0.921	

## Discussion

There are numerous risk factors associated with the development of CAN in diabetic patients; those that are mentioned in the literature include older age, hypertension, dyslipidemia, a longer duration of diabetes, poor glycemic control, and obesity. The prevalence of CAN among the study population was 29.7%; this is much lower than Bhuyan et al.'s and Birajdar et al.'s studies<sup>11,12</sup> in which the prevalence of CAN was 70% and 58%, respectively. We believe that the reason for this difference is the variability of diagnostic criteria. In our study, the criteria that we defined for the diagnosis of CAN were different from other studies in which they also identified patients in the early CAN stage, in contrast to our study, where we only extracted patients who had clear signs of CAN that usually occur in later stages. Hence, some cases that are in the early

CAN stage might have gone undiagnosed. In terms of gender, there is no significant difference between genders in the prevalence of CAN, male (53.3%) and female (46.7%) ( $p > 0.05$ ). This is in accordance with a study of 3007 diabetic patients, where it was reported that there was no difference in the prevalence of CAN between males and females (males 35% and females 37%). There is controversy regarding the impact of gender on CAN's epidemiology.<sup>13</sup> In contrast to our study, a number of other studies reported a higher frequency of CAN among women than men.<sup>14-16</sup> The mean age of patients with CAN was  $50.2 \pm 8.9$ , which is similar to Vashegahni et al.'s study ( $50.41 \pm 14.43$ ),<sup>17</sup> but lower than that reported in Bhuyun et al., and Dhumad et al.'s studies, where the mean age was  $55.6 \pm 10.3$  and  $53.79 \pm 6.66$ , respectively.<sup>11,18</sup> The research we conducted found no statistically significant difference in the mean age of patients with and without





CAN. This therefore indicates that there is no correlation between age and CAN. This is in accordance with AlOlaiwi et al., Vsheghani et al., Dhumad et al., and Pillai et al.'s studies, in which their findings also denoted no significant relationship between age and CAN.<sup>15,17,18,19</sup> In the current study, duration of diabetes >5 years was not found to be a significant predictor of CAN. This is in contrast to Bhuyun et al., Dhumad et al., and Ahire et al.'s studies, in which longer duration of diabetes was significantly associated with the development of CAN.<sup>11,18,20</sup> Dhumad et al. reported that the prevalence of CAN in diabetic patients is almost doubled when the duration of diagnosis is 6–10 years and more than 10 years in comparison to less than 5 years.<sup>18</sup> In our opinion, the reason for this difference is that many diabetic patients in our community are diagnosed in later stages due to a lack of a solid program for frequent check-ups of high-risk patients; therefore, patient histories are not entirely accurate, leading to inconsistent results. Another risk factor related to the development of CAN is poor glycemic control. The mean value of HbA1c in the patients in our study was  $9.5 \pm 2.1$ , and this finding was significant. This is similar to Dhumad et al.'s findings, in which the mean HbA1c of their CAN patients was reported to be  $9.025 \pm 1.37$ . However, their finding was statistically insignificant.<sup>18</sup> Furthermore, in the current study, we found that HbA1c is a highly significant predictor of CAN and that fasting blood sugar is also somewhat significant in the prediction of CAN. This is in accordance with Dhumad et al.'s study, where they reported that the frequency of CAN increased significantly with poor glycemic control and that HbA1c values appear to be associated with CAN.<sup>18</sup> However, Bhuyun et al.'s study revealed no significant association between HbA1c and CAN.<sup>11</sup> The mean HDL value of CAN patients was  $34 \pm 10.1$ , and this finding was

significant. The mean HDL level of CAN patients reported in Bhuyun et al.'s study is slightly higher ( $38.31 \pm 10.45$ ) but relatively similar to our finding.<sup>11</sup> In the current study, HDL was also found to be a significant predictor of CAN. Based on BMI categorization, we found that most of our CAN patients were in the overweight group (40%) followed by the obese group (26.7%), and this finding was highly significant. This observation was in accordance with Vasheghani et al.'s study, in which the mean BMI of CAN patients was significantly higher than that of patients without CAN.<sup>17</sup> However, our finding is in contrast with Bhuyun et al.'s findings, in which the mean BMI of their CAN patients was  $23.28 \pm 2.28$ , meaning they mostly belonged to the normal weight group.<sup>11</sup> When comparing underweight patients with normal-weight patients, underweight patients were more likely to have CAN than normal-weight patients. When overweight individuals were compared to normal-weight patients, overweight patients were shown to be more likely to have CAN, and these findings were highly significant. An interesting finding in our study was that, when comparing the mode of treatment with those who do not take any treatment, our data revealed that patients on OHA were significantly less likely to develop CAN compared to patients who are not on any medication. Other modes of treatment did not show a significant difference compared to no treatment. Vasheghani et al. reported no significant difference in the mode of treatment of patients with or without CAN.<sup>17</sup>

## Conclusion

The current study demonstrates that the development of CAN can be significantly affected by poor glycemic control, HDL level, and mode of treatment for diabetes. Due to the fact that this was a cross-sectional study, the duration of glycemic control wasn't apparent, and patient compliance with





treatment was not certain. Lastly, the prevalence of CAN changes from one study to another because it depends on multiple factors such as the definition of CAN, the diagnostic criteria, the study population, diagnostic methods, the severity of the symptoms, the duration of the disease, and the stage of the disease.

### Conflict of interest

The authors declare no conflict of interest

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