



Research Article

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Determination of Diabetes-associated Cardiovascular Autonomic Neuropathy Risk Factors among Insulin and Non-insulin Dependent Diabetics

Ibrahim Abdulsada¹, Zain Alabdeen Obaid², Farah Almerza³, Mays Alwaeli⁴, Anmar Al-Elayawi⁵, Taha Al-Dayyen⁶, Harir Al-Tuhafy⁷

¹ Senior house officer at Al-Sader Teaching Hospital, Iraq

² Junior resident at Al-Qasim General Hospital, Iraq

³ Junior resident at Al-Haydaria General Hospital, Iraq

⁴ Psychiatry resident at Al-Rashad Hospital for mental health, Iraq

⁵ Final-year medical student at Kufa University, Iraq

⁶ Junior resident at Al-Iraqia University Hospitals, Iraq

⁷ Senior house officer at Baybukht Primary Healthcare Center, Iraq

Abstract

Cardiovascular autonomic neuropathy (CAN) is a microvascular consequence characterized by the dysfunction of cardiovascular autonomic regulation in individuals diagnosed with diabetes, in the absence of any other underlying causes. This cross-sectional study was carried out in Baghdad City, Iraq in order to assess the risk factors of diabetes-associated cardiovascular autonomic neuropathy among insulin and non-insulin dependent diabetics. from January 20th 2023 to August 1st 2023. The mean age of studied patients was 48 years and the mean duration of diabetes was 15 years. 99 of diabetic patients were males and 64 of them were females; 94 were IDDM and 66 were NIDDM patients. In NIDDM patients, autonomic neuropathy was substantially correlated with retinopathy ($P < 0.001$), with a greater frequency of retinopathic individuals (82%) in the autonomic neuropathy group. There was a strong relationship between blood pressure and almost every test in both types of diabetes. In this clinic-based investigation, it is clear that autonomic neuropathy is related to microvascular diabetes sequelae, such as retinopathy and nephropathy in IDDM. In IDDM, there is evidence that glycemic control is important, but in NIDDM, additional variables than metabolic control could be important. However, data suggest a connection between autonomic neuropathy and blood pressure. Longitudinal and epidemiological research are required to better understand the association between cardiovascular risk factors and autonomic neuropathy, as well as the pathophysiology, prognosis, and prognostic implications of autonomic neuropathy.

Keywords: Autonomic neuropathy, Non-insulin dependent diabetes mellitus, Insulin dependent diabetes mellitus, Urine albumin excretion, Cardiovascular autonomic neuropathy.

INTRODUCTION

Cardiovascular autonomic neuropathy (CAN), a microvascular consequence that only affects people with diabetes, is described as the impairment of cardiovascular autonomic regulation [1]. Although some studies suggest that CAN may be present in newly diagnosed diabetic patients, the percentage is much lower, and it is associated with a longer duration of the illness [2]. American Diabetes Association (ADA) recommendations encourage additional assessment of diabetic individuals presenting characteristic CAN symptoms such as dizziness, weakness, palpitations, and syncope that occurs upon standing in order to rule out other possible causes. This is particularly essential if individuals have microvascular/neuropathic problems or are unaware of their hypoglycemia [3]. CAN often first detects parasympathetic activity in the vagus nerve since it is the longest parasympathetic autonomic nerve in the body [4]. Resting tachycardia and an overall reduction in parasympathetic tone are brought on by vagus nerve damage. The parasympathetic function is measured using the Valsalva maneuver, deep breathing, and posture adjustments (such as rising from a sitting to a standing position) [1]. Compared to sudomotor testing, these measurements of cardiovascular and adrenergic function are supported by greater data [4]. CAN's clinical signs and symptoms change as the condition becomes worse. Cardiovascular stress testing is indicated before commencing an exercise program since reduced cardiac output, blood pressure, and heart rate are the causes of exercise intolerance [5]. Severe may present as orthostatic hypotension and sympathetic cardiac denervation. Orthostatic hypotension is thought to affect 6% to 32% of DM patients. In addition to objective criteria such as a 20 mm Hg drop in blood pressure, various symptoms such as

*Corresponding author:
Dr. Ibrahim Abdulsada
Senior house officer at Al-Sader
Teaching Hospital, Iraq
Email: hkmeded20@gmail.com

dizziness, syncope, visual abnormalities, frequent falls, and nocturnal hypertension caused by a paradoxical increase in sympathetic tone may be found in CAN [1,4]. CAN in DM provides a higher risk of silent ischemia, perioperative death, and severe morbidity. Glycemic management to delay development and symptomatic therapy of orthostatic hypotension are the mainstays of current CAN treatment [6].

METHODOLOGY

A cross-sectional study was undertaken in Baghdad, Iraq, between January 20 and August 1st, 2023, to assess the risk factors for diabetes-associated cardiovascular autonomic neuropathy in both insulin-dependent and non-insulin-dependent diabetics. Each diabetic patient informedly agreed to participate in the experiment. The research is being conducted in the outpatient diabetes clinic of Baghdad Medical City, which is a component of a network of academic hospitals in Bab Al-Moatham, Baghdad, Iraq.

Participants in the research were 48 years old on average, and they had diabetes for an average of 15 years. 99 men and 64 women with diabetes were diagnosed with IDDM and 66 with NIDDM, respectively. The average body mass index was 25 kg/m², and below-average BMIs were seen in 29% of patients and 71% of patients, respectively. 45% of patients acknowledged to smoking, and 4% to drinking too much. Table 1 shows that 26% of patients have been given a hypertension diagnosis.

The chi-squared test was used to categorize variables, and the analysis of variance (ANOVA) and T-test were performed to assess if the means were statistically significant. To connect numerous variables, an analysis of linear regression was used. The data was analyzed using SPSS software, version 26 (IBM Corp., Armonk, New York). A significant value was considered to be $P < 0.05$. To measure autonomic function, four cardiovascular tests were employed, including postural hypotension, the Valsalva maneuver, lying to standing, and deep breathing.

RESULTS

When compared to NIDDM patients without autonomic neuropathy, individuals with autonomic neuropathy were found to be substantially older. Between NIDDM patients with and without autonomic neuropathy, there were no differences in gender, diabetes duration, body mass index, HbA1c, blood creatinine, cholesterol, HDL, or triglycerides. There was no connection between autonomic neuropathy and smoking, diabetes, or peripheral vascular disease. Contrarily, it had a marginally positive correlation with alcohol addiction ($P = 0.03$).

Despite no statistically significant difference in the proportion of hypertension patients across the groups, systolic blood pressure was somewhat higher in NIDDM patients with autonomic neuropathy compared to those without.

Autonomic neuropathy and retinopathy were significantly correlated in NIDDM patients ($P < 0.001$), with retinopathic people being more common (82%) in the autonomic neuropathy group. Contrary to what was seen in individuals with IDDM, autonomic neuropathy was not associated with nephropathy, and the 24-hour UAE was the same in patients with NIDDM who had autonomic neuropathy and those who did not (Table 2).

Age or gender did not vary between IDDM patients with autonomic neuropathy and those without. Patients with autonomic neuropathy had considerably longer-lasting diabetes and higher HbA1c levels than those without it, despite having a lower BMI. Serum lipid levels in IDDM patients with and without autonomic neuropathy were comparable. Smoking was common among IDDM patients, both neuropathic and non-neuropathic. Despite the fact that hypertension was not significantly more common in neuropathic IDDM patients than

in non-neuropathic individuals, blood pressure readings in those with neuropathy were notably higher.

Peripheral vascular disease and autonomic neuropathy were related ($P = 0.04$). Additionally, there was a significant correlation ($P = 0.03$) between autonomic neuropathy and retinopathy. Retinopathy impacted 73% of individuals with autonomic neuropathy but only 52% of those without autonomic neuropathy. Despite this, there was no conclusive evidence linking autonomic neuropathy to nephropathy. In addition, individuals with neuropathy had substantially greater 24-hour UAE compared to patients without neuropathy ($P < 0.001$) (Table 2).

Blood pressure was significantly linked with almost all tests in both types of diabetes. In IDDM and NIDDM, systolic and diastolic blood pressure were especially strongly linked with deep breathing, postural hypotension, and autonomic score. Only IDDM 24h UAE was substantially correlated with autonomic score and deep breathing.

There was still a link between the IDDM autonomic score and body mass index, HbA1c, and systolic blood pressure in this model. There were also associations between deep breathing and systolic blood pressure, lying to standing and HbA1c, the Valsalva method and body mass index, and postural hypotension and body mass index. There was a significant relationship between the autonomic score and systolic blood pressure in NIDDM, as well as age and deep breathing, and the Valsalva maneuver and retinopathy (Table 3).

In both IDDM and NIDDM, age was associated to deep breathing and the transition from laying to standing. Only in IDDM were the parameters for body mass index, glycosylated hemoglobin, and duration of diabetes substantially associated to cardiovascular testing. Deep breathing, the autonomic score, and the Valsalva maneuver in particular were related to how long the sickness lasted. The autonomic score and the body mass index were negatively connected, whereas the Valsalva maneuver and the body mass index were favorably correlated.

Only in NIDDM patients were cholesterol levels shown to be favorably correlated with autonomic score and weakly adversely correlated with the Valsalva maneuver. Only in individuals with IDDM did triglyceridemia have an adverse relationship with deep breathing. There was no connection between the tests and daily cigarette use (Table 4).

DISCUSSION

Four cardiovascular tests were identified in individuals with IDDM and NIDDM, and their clinical and pathophysiology correlations were assessed. In 16% of IDDM patients and 10% of NIDDM patients, we discovered autonomic neuropathy. This prevalence is comparable to William's et al. estimate (17%) [9].

Our diabetic group cannot be regarded as a retrospective sample of the whole diabetes community since we evaluated people who were recruited from a diabetic clinic. The prevalence of diabetic neuropathy may have been overestimated due to a selection bias. In reality, epidemiological population-based research such as Cristian et al. [10] with 126 diabetes individuals found a lower prevalence.

Between IDDM and NIDDM patients, there was no difference in the prevalence of autonomic neuropathy. Cardiovascular testing or autonomic neuropathy and gender were not related in this research. Previous research showed that female gender was independently linked with lower heart rate variation in IDDM patients [8] and that cardiovascular tests were unrelated to gender in normal people [7].

Table 1: Clinical and Sociodemographic Features of Patients with IDDM and NIDDM (N=160)

Variables	IDDM	NIDDM
N	94	66
Age (years)	41.7 ± 11.3	55.1 ± 8.3
Gender (M:F)	54:43	45:21
Body Mass Index	24.1 ± 3.6	26.1 ± 3.2
Diabetes Duration (years)	17.6 ± 8.4	14.1 ± 8.1
HbA1c (%)	9.1 ± 2.0	9.1 ± 1.7
Serum Creatinine (mg/dl)	0.96 ± 0.6	0.99 ± 0.2
Cholesterol (mg/dl)	189.7 ± 52.4	199.8 ± 47.1
HDL (mg/dl)	53.1 ± 17.3	41.2 ± 12.3
Triglycerides (mg/dl)	116.9 ± 57.4	159.3 ± 115
UAE 24h (µg/min)	14.2 ± (0.9-457)	4.4 (0.1-361)
Retinopathy (%)	64	47
Nephropathy (%)	46	15
Peripheral Vascular Disease (%)	16	8
Systolic BP (mmHg)	138.2 ± 22.6	140.3 ± 20.1
Diastolic BP (mmHg)	83.7 ± 12.1	82.4 ± 10.9
Hypertension (%)	18	32
Smokers (%)	42	31
Alcohol Abuse (%)	2	4

UAE: urine albumin excretion; %: percent; M: male; F: female; BP: Blood Pressure; N: Study Sample

Table 2: Clinical Parameters for Diabetic Cardiac Autonomic Neuropathy Patients with and Without IDDM and NIDDM

Variables	IDDM Patients			NIDDM Patients		
	With AN	Without AN	P-value	With AN	Without AN	P-value
N	28	46		16	28	
Age (years)	42.4 ± 13.5	38.1 ± 10.9	N.S.	57.9 ± 7.7	49.9 ± 9.9	0.01
Gender (M:F)	14:12	25:21	N.S.	14:4	17:9	N.S.
BMI	20.7 ± 3.0	23.3 ± 3.4	0.05	26.7 ± 5.1	24.2 ± 3.1	N.S.
Diabetes Duration (years)	21.3 ± 9.1	17.3 ± 8.2	0.04	13.5 ± 8.1	14 ± 6.2	N.S.
HbA1c (%)	10.0 ± 2.3	7.9 ± 1.9	N.S.	8.3 ± 1.7	8.9 ± 1.9	N.S.
Insulin Dose (U/Kg)	0.81 ± 0.3	0.81 ± 0.3	<0.001	0	0	N.S.
Serum Creatinine (mg/dl)	1.2 ± 0.9	0.92 ± 0.31	N.S.	1.1 ± 0.3	0.9 ± 0.2	N.S.
Cholesterol (mg/dl)	197.5 ± 38.4	191.0 ± 41.2	N.S.	219 ± 55	184.7 ± 42.8	N.S.
HDL (mg/dl)	58.3 ± 17.4	51.7 ± 15.3	N.S.	39.8 ± 10.1	40.7 ± 12.8	N.S.
Triglycerides (mg/dl)	121.1 ± 53.8	109.1 ± 53.1	N.S.	181.2 ± 79.1	166.1 ± 154.3	N.S.
UAE 24h (µg/min)	102.6 (6.7-463)	9.17 (0.9-134)	<0.001	18.7 (0.9-190.4)	4.6 (0.4-351)	N.S.
Retinopathy (%)	73	52	0.03	82	24	<0.001
Nephropathy (%)	59	41	N.S.	33	7	N.S.
Peripheral Vascular Disease (%)	22	2	0.04	0	6	N.S.
Systolic BP (mmHg)	148.3 ± 26.9	126.1 ± 15.1	0.01	144.1 ± 21.4	127.3 ± 19.3	0.02
Diastolic BP (mmHg)	94.8 ± 16.2	81.5 ± 8.4	0.005	88.2 ± 11.1	78.7 ± 12.1	N.S.
Hypertension (%)	27	11	N.S.	44	23	N.S.
Smokers (%)	44	36	N.S.	34	31	N.S.
Alcohol Abuse (%)	11	2	N.S.	13	0	0.03

UAE: urine albumin excretion; %: percent; M: male; F: female; BP: Blood Pressure; N: Study Sample

Table 3: Cardiovascular tests' univariate associations with clinical and metabolic markers in IDDM patients

Variables	Autonomic Score		Deep Breathing		Lying to Standing		Valsalva Maneuver		Postural Hypotension	
	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value
Age	0.15	0.28	-0.32	0.001	-0.07	0.521	0.04	0.625	-0.01	0.87
BMI	-0.28	0.021	-0.03	0.87	0.23	0.065	0.23	0.055	-0.1	0.06
Diabetes Duration	0.27	0.021	-0.25	0.007	-0.18	0.154	-0.24	0.051	0.04	0.65
HbA1c	0.44	<0.001	-0.38	<0.001	-0.36	0.005	-0.43	<0.001	0.33	0.007
Cholesterol	0.05	0.72	-0.22	0.08	0.2	0.51	-0.12	0.55	0.03	0.76
Triglycerides	0.03	0.78	-0.27	0.01	0.13	0.23	-0.01	0.97	0.06	0.61
UAE 24 h	0.52	<0.001	-0.36	0.03	-0.30	0.24	-0.33	0.05	0.33	0.12
Systolic BP	0.25	0.07	-0.41	<0.001	-0.07	0.57	-0.03	0.84	0.37	<0.001
Diastolic BP	0.22	0.09	-0.38	<0.001	-0.05	0.57	-0.03	0.91	0.34	<0.001
Smoking	0.05	0.81	-0.04	0.73	-0.22	0.09	-0.16	0.31	0.15	0.25

r: Pearson's correlation coefficient; UAE: urine albumin excretion; BP: Blood Pressure; BMI: body mass index

Table 4: Cardiovascular tests' univariate associations with clinical and metabolic markers in NIDDM patients

Variables	Autonomic Score		Deep Breathing		Lying to Standing		Valsalva Maneuver		Postural Hypotension	
	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value
Age	0.25	0.09	-0.40	<0.001	-0.31	0.02	-0.11	0.52	-0.21	0.05
BMI	-0.02	0.89	-0.09	0.55	-0.04	0.86	-0.18	0.17	-0.13	0.38
Diabetes Duration	-0.04	0.89	-0.17	0.25	-0.09	0.55	0.08	0.51	-0.08	0.65
HbA1c	-0.11	0.54	0.07	0.63	0.05	0.78	0.17	0.32	-0.06	0.71
Cholesterol	0.33	0.03	-0.14	0.34	-0.31	0.06	-0.32	0.03	0.04	0.87
Triglycerides	0.05	0.88	0.16	0.43	-0.02	0.98	-0.14	0.55	0.03	0.78
UAE 24 h	-0.04	0.88	0.15	0.43	-0.02	0.95	-0.13	0.51	0.21	0.26
Systolic BP	0.53	<0.001	-0.29	0.03	-0.33	0.02	-0.31	0.03	0.19	0.17
Diastolic BP	0.51	0.002	-0.14	0.34	-0.32	-0.031	-0.14	0.39	0.29	0.04
Smoking	0.06	0.81	-0.06	0.51	-0.09	0.56	-0.15	0.33	0.02	0.83

r: Pearson's correlation coefficient; UAE: urine albumin excretion; BP: Blood Pressure; BMI: body mass index

In NIDDM with autonomic neuropathy compared to those without, age was somewhat greater. In addition, the ratio of lying to standing was negatively associated to age in both IDDM and NIDDM patients, but only in NIDDM. In IDDM individuals with autonomic neuropathy compared to those without, the duration of diabetes was somewhat longer. Additionally, only in individuals with IDDM were autonomic score, the Valsalva maneuver, and deep breathing linked to the length of diabetes. These results are in line with previous research showing that autonomic function is only affected by the duration of diabetes in IDDM patients and not in NIDDM patients [11, 12], and that deep breathing and parasympathetically controlled heart rate tests, in particular, are age-dependent in both healthy and diabetic populations.

In line with past studies, IDDM patients with autonomic neuropathy had worse glycemic control than those without autonomic neuropathy [15]. When employing a multiple regression analysis, glycosylated hemoglobin was also connected to autonomic score and cardiovascular tests in IDDM patients. In contrast, as shown by Zander et al. and Kim et al. [16, 17], there was no correlation between HbA1c and autonomic neuropathy in NIDDM patients. This data together with the absence of a correlation with the length of the illness raises the possibility that variables other than glycemic management are involved in the onset of autonomic neuropathy in NIDDM.

We have discovered a strong connection between retinopathy and cardiovascular autonomic neuropathy in patients with both insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent

diabetes mellitus (NIDDM). This finding aligns with previous discoveries in IDDM [18]. But it is different from what was discovered in a prior research on NIDDM [19]. Although there was no notable correlation between autonomic neuropathy and nephropathy in either type of diabetes, our findings revealed a connection between albuminuria and autonomic score in IDDM patients with autonomic neuropathy. This suggests that the severity of autonomic damage is related to the extent of albumin excretion. In prior studies, a connection between microangiopathic effects and autonomic neuropathy was shown [20, 21, 22]. The discrepancy may be due to the varying levels of microalbuminuria between IDDM and NIDDM when considering the connection between autonomic neuropathy and 24-hour UAE. Contrary to what is commonly believed, microalbuminuria in individuals with non-insulin dependent diabetes mellitus (NIDDM) is more commonly associated with a systemic vascular problem rather than being seen as an early sign of diabetic nephropathy. Additionally, it is less frequently considered a risk factor for mortality [23]. Therefore, a connection between autonomic neuropathy and nephropathy is not necessarily excluded only because albumin excretion and autonomic neuropathy in NIDDM are unrelated.

In IDDM patients with autonomic neuropathy, we identified a reduced BMI. This index showed a favorable relationship with the Valsalva maneuver and an independent, adverse relationship with autonomic score. The idea that those with neuropathic conditions had worse glycemic control and a lower BMI was disproved by the absence of a correlation between body mass index and HbA1c. The previous study found a positive association between the two variables in patients with

IDDM. However, this finding does not support the negative relationship between autonomic neuropathy and body mass index that was observed in a multiple regression analysis [24]. Additionally, there was no significant positive correlation found between body mass index and cardiovascular tests or autonomic neuropathy in patients with IDDM. Contrary to past results in people with non-diabetic obesity [25] and NIDDM [26].

In contrast to the people Rashid et al. [27] studied, who had coronary artery disease and could have been on cardiovascular drugs, our NIDDM patients were often younger, less fat, and free of cardiac disease. Thus, a link between obesity and autonomic neuropathy can only be shown in elderly people or those who have cardiovascular issues.

Smoking or the quantity of cigarettes smoked daily were not associated with autonomic neuropathy or cardiovascular tests in people with IDDM or NIDDM. Only IDDM patients—not NIDDM patients—were identified in prior research to have a link between smoking and peripheral neuropathy [28, 29, 30]. While smoking was not linked to autonomic neuropathy in individuals with IDDM who underwent a cross-sectional investigation [31].

Although hypertension was not linked to autonomic neuropathy in this investigation, neuropathic patients had higher blood pressure readings than non-neuropathic individuals. Patients with both IDDM and NIDDM exhibited similar symptoms. The majority of cardiovascular tests conducted in individuals with IDDM and NIDDM showed a correlation with both systolic and diastolic blood pressure. Notably, the association between the autonomic score and blood pressure was found to be stronger in individuals with NIDDM. There is a connection between hypertension and autonomic neuropathy in patients with insulin-dependent diabetes mellitus (IDDM). Hypertension may also increase the risk of developing autonomic neuropathy [25]. In a different research, hypertension in diabetic individuals was linked to an increased frequency of incorrect Valsalva maneuvers and cross correlation tests [32]. The importance of this findings is not immediately apparent. Nephropathy most likely represents the link between autonomic neuropathy and blood pressure in IDDM, but in NIDDM, the link between cardiovascular disease and neuropathy is less clear.

Patients with and without autonomic neuropathy did not have different blood lipid levels, according to our observations. Between cholesterol, triglycerides, and cardiovascular tests, there was only a small and weak connection that was not significant. Some researchers found a link between IDDM-related lipid abnormalities and autonomic neuropathy [33], while others hypothesized that controlling blood lipid levels would be more crucial than glucose levels for preventing the progression of autonomic neuropathy [34].

CONCLUSION

This clinic-based study establishes a clear link between autonomic neuropathy and microvascular diabetic complications, specifically retinal complications in both IDDM and NIDDM, as well as nephropathy in IDDM. In IDDM, there is evidence that glycemic control plays a significant impact, but in NIDDM, additional variables than metabolic control may be important. Contrarily, although there is evidence connecting autonomic neuropathy to blood pressure, there isn't a strong correlation to cardiovascular risk factors including obesity, smoking, or dyslipidemia. To further understand the pathophysiology and prognostic consequences of autonomic neuropathy and the link between cardiovascular risk factors and this condition, longitudinal and epidemiological studies are required.

Conflict of Interest

The authors declare no conflicts of interest.

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