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Original article

Evaluation of Diabetic Cardiac Autonomic Neuropathy in Libyan Patients: Cross-Link with Biochemical and Clinical Risk Factors

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Abstract
Diabetic cardiac autonomic neuropathy (DCAN) is a significant condition that affects cardiovascular health worldwide and is associated with increased morbidity and mortality rates. Therefore, early detection and management of DCAN are crucial for reducing the risk of cardiovascular disease among individuals with T2DM. Identifying this disorder can enhance patient outcomes and quality of life by minimizing the chances of serious complications. This cross-sectional study aims to identify diabetic individuals with DCAN and to investigate its relationship with various risk factors, including hyperglycemia, the duration of diabetes, the presence of peripheral somatic neuropathy, and diabetic microvascular complications. The study included 261 patients with T2DM, comprising 61.5% females and 38.5% males. Participants underwent cardiovascular testing and clinical evaluations to identify cases of cardiac autonomic neuropathy. Out of the 261 randomly selected patients, 82 were diagnosed with DCAN, resulting in a prevalence rate of 31.4%. The average age for female patients was 57.5 ± 0.7 years, while for male patients, it was 56.3 ± 1.2 years from the total recruited patients. In addition, there is a strong association between DCAN and clinical and biochemical parameters such as lipid profile, duration of diabetes, poor diabetic control, and presence of microalbuminuria in patients with DCAN and above 60 years old, compared to younger patients. The study highlighted a strong association between DCAN and factors such as poor glycemic control, prolonged diabetes duration, and the presence of chronic microvascular complications, including neuropathy, retinopathy, and nephropathy. These findings emphasize the importance of raising awareness and proactively assessing Libyan patients who are at risk for cardiovascular autonomic neuropathy. This is crucial to reduce the likelihood of recurrent acute cardiac complications, especially in patients undergoing emergency surgery without a prior diagnosis. It is vital to recognize this risk.
Keywords. Type 2 Diabetes Mellitus, Pulse Rate, Metabolic Syndrome, Blood Pressure.

Introduction

Diabetic cardiac autonomic neuropathy (DCAN) significantly increases morbidity and mortality rates in individuals with T2DM. This condition is associated with several serious complications, including (i) cardiovascular disorders such as arrhythmias and silent myocardial infarctions [1,2]; (ii) gastrointestinal issues like gastroparesis, painless nocturnal diabetic diarrhea, and gustatory hyperhidrosis; and (iii) disorders in the genitourinary problems, including erectile dysfunction and retrograde ejaculation. These complications can greatly diminish patients' quality of life [3,4]. The prevalence of diabetic autonomic neuropathy increases with the prolonged duration of T2DM. Studying this condition is essential for several reasons. First, it helps us understand the underlying mechanisms that lead to these complications, which can inform the development of targeted therapies and preventive measures [5]. Second, early identification of autonomic nerve damage can improve patient outcomes by enabling timely interventions and better disease management [6]. Finally, research in this area can help prevent severe complications that may require extensive medical treatment. Additionally, this study can enhance the quality of life for diabetic patients by promoting lifestyle modifications and optimizing treatment options to minimize the impact of this condition [7].

The parasympathetic vagus nerve is particularly vulnerable to early damage for several reasons. Firstly, as one of the longest nerves in the body, it extends from the brainstem to the abdomen, making it more susceptible to injury under certain pathological conditions. A significant contributor to this vulnerability is sustained hyperglycemia, which is commonly observed in individuals with diabetes. Elevated glucose levels can lead to various vascular complications, including decreased blood flow and reduced oxygen delivery to tissues, resulting in ischemic changes. Ischemia occurs when the blood supply to an area is inadequate, leading to tissue damage and the release of inflammatory mediators. These mediators can negatively impact nerve tissues, especially in cases of poorly managed diabetes.

The vagus nerve plays a crucial role in regulating various autonomic functions, including heart rate, digestion, and respiratory rate. These functions are essential for maintaining homeostasis and ensuring proper physiological performance. However, individuals with diabetes often experience subacute inflammation and oxidative stress, which can further compromise nerve health [7,8]. Oxidative stress occurs when there is an imbalance between free radicals and antioxidants in the body, resulting in cellular damage. This condition can not only worsen damage to the vagus nerve but also affect other peripheral somatic nerves. Therefore, individuals with T2DM need to manage their blood sugar levels and address inflammation to protect their nervous tissue health.

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Diabetic cardiac autonomic neuropathy (DCAN) is often undiagnosed in individuals with diabetes because it may not present any symptoms in its early stages. This condition involves damage to the autonomic nerves that control involuntary bodily functions, which can significantly affect a patient's quality of life and overall health. Timely diagnosis and intervention are crucial in preventing severe complications and improving health outcomes [9].

The diagnostic process for diabetic cardiovascular autonomic neuropathy (DCAN) includes several important steps: (i) identifying signs of sinus tachycardia at rest or the presence of nocturnal palpitations along with clinical symptoms of dizziness and/or syncope; and (ii) detecting orthostatic hypotension, which is characterized by a decrease in systolic blood pressure of ≥20 mmHg or a decrease in diastolic blood pressure of ≥10 mmHg when transitioning from a supine to an upright position [10]; and (iii) using standard electrocardiographic (ECG) recordings to assess R–R intervals during controlled deep breathing (one minute at a rate of six breaths per minute). The average R–R interval values for both the inspiration and expiration phases are used to calculate the expiration/inspiration (E/I) ratio [11], with a reference mean E/I ratio of less than 1.1 (95% Confidence Interval: 1.21–1.32) [12].

Grasping the influence of elevated blood sugar on the vagus nerve and its role in wider diabetic complications is crucial for creating treatment strategies aimed at mitigating these effects. This study emphasizes the significance of early detection of Diabetic Cardiovascular Autonomic Neuropathy (DCAN) to minimize morbidity and mortality. Additionally, it explores the connections between DCAN and various clinical factors, including Body Mass Index (BMI), hyperlipidemia, metabolic syndrome, duration of diabetes, and insulin resistance, which often coexist with the vascular and nerve complications associated with diabetes mellitus.

Methods

Study design and subjects

This research is a prospective cross-sectional study involving 261 individuals (62% female and 38% male) aged between 34 and 80 years. Data were collected from the Libyan patients and all of them gave their written consent to participate in the study after reading an information sheet for this study. The ethical approval was obtained from the Diabetic Hospital ethical committee and all saved data were stored confidentially. This questionnaire gathered comprehensive information on medical and biochemical parameters. Participants were excluded from the study based on the following criteria: (i) individuals younger than 16 years or older than 80 years; (ii) pregnant women; and (iii) individuals with hyperthyroidism or who are on adrenergic or anticholinergic medication (iv) individuals who had not fasted for 10 to 12 hours before laboratory investigations, as this could affect the results of metabolic assessments.

Clinical characteristics

A clinical examination was performed on all patients, which involved gathering a thorough medical history to identify any signs of autonomic neuropathy. The assessment included evaluations of body temperature, pupil reactions to light, accommodative reflexes, oral health, skin condition (wet or dry), and any retinal changes observed via ophthalmoscopy. Additionally, blood pressure and pulse rates were recorded in both supine and standing positions to assess for postural hypotension, resting tachycardia, and heart rate variations while sitting or standing. A neurological evaluation was conducted for all patients to identify signs of peripheral neuropathy and involvement of the autonomic nervous system. Each participant underwent several tests: Complete Blood Count (CBC), Fasting Blood Sugar (FBS), HbA_{1c}, urine microalbuminuria, and a lipid profile. Blood pressure was measured twice with a mercury sphygmomanometer using an appropriately sized cuff after a 10-minute rest. For diabetic patients without complications, normal blood pressure is defined as BP ≤ 130/80 mmHg. Diabetic cardiac autonomic neuropathy (DCAN) is diagnosed when two or more autonomic function tests show irregularities. These tests include: (i) a decrease in systolic blood pressure (SBP) of ≥ 25 mmHg upon standing from a supine position within 2 to 3 minutes; (ii) an expiration/inspiration (E/I) ratio of the R-R interval ≤ 1.1; and (iii) the presence of nocturnal sinus tachycardia (heart rate > 100 beats per minute).

Laboratory measurements

Blood samples were collected from the Diabetic Centre in Tripoli between November 2022 and December 2023. All biochemical parameters, including fasting blood sugar, HbA_{1c}, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG), were measured using the COBAS Integra 400 Plus analyzer from Roche Diagnostics in Basel, Switzerland. In addition, the TyG index will be calculated to identify patients with insulin resistance especially patients who have metabolic syndrome.

Statistical analyses

Data collected were systematically recorded using a structured questionnaire. Statistical analyses were conducted utilizing SPSS software (version 24 for Windows, IBM Corporation, New York, USA) and GraphPad

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Prism (version 6). The t-test and Fisher's exact test were applied to assess the correlation between key risk factors in diabetic patients with and without diabetic cardiac autonomic neuropathy (DCAN). Furthermore, logistic regression analysis was performed to identify significant predictors associated with the progression of DCAN. A p-value of <0.05 was considered indicative of statistical significance.

Results

In this study, 261 patients with T2DM were recruited. Among the participants, 62% were female, while 38% were male. The average age was 57.5 years (± 0.7) for females and 56.3 years (± 1.2) for males. Detailed demographic and clinical characteristics for both genders are summarized in Table 2. A significant proportion of patients were obese and demonstrated high levels of LDL, and low levels of HDL with P<0.002 and P≤ 0.0004 in females compared to males, respectively.

In this study, diabetic cardiac autonomic neuropathy (DCAN) was detected in 40 individuals under the age of 60, based on the cardiac autonomic tests explained by Ewing et al. (1978) [12]. All of these younger patients also presented with diabetic retinopathy. Additionally, DCAN was identified in 44 patients over the age of 60, of whom 33 had retinopathy and 44 exhibited polyneuropathy. A statistically significant difference was observed in the duration of diabetes between the two age groups: younger patients had a mean diabetes duration of 12.3 years (± 1.1), compared to 17 years (± 1.2) in older patients (P < 0.01).

Table 2. Clinical characteristics and biochemical parameters related to the risk factors of participants of type 2 diabetes in this study.

Clinical characteristics	Diabetes mellitus type 2		P value
	Female patients	Male patients	
Numbers (n)	162 (62%)	99 (38%)	N/A
Age (yrs)	57.5 ± 0.7	56.3 ± 1.2	0.4
BMI (Kg/m^2)	34.5 ± 0.4	30.1 ± 0.4	<0.0001
FBS (mg/dl)	171.7 ± 5.7	158.6 ± 5.7	0.13
Duration of diabetes (yrs)	10.1 ± 0.6	10.4 ± 0.7	0.76
HbA_{1c} (%)	8.4 ± 0.1	8.2 ± 0.2	0.32
Total cholesterol (mg/dl)	193.0 ± 3.8	169.2 ± 4.8	0.0001
LDL (mg/dl)	118.6 ± 3.1	103.3 ± 3.5	<0.002
HDL (mg/dl)	48.4 ± 1.1	42.5 ± 1.1	0.0004
Triglyceride (mg/dl)	156.5 ± 5.9	143.0 ± 9.1	0.19
LDL/HDL ratio (%)	2.6 ± 0.08	2.5 ± 0.09	0.42
*TyG index	5.0 ± 0.02	4.9 ± 0.03	<0.005
Incipient diabetic nephropathy (n)	71	49	N/A
Microalbuminuria (mg/dl)	37.6 ± 2.0	40.4 ± 2.7	0.4
Macroalbuminuria (mg/dl)	0	0	NA

*Data represented as number (n), percentage (%), and mean ± SEM. Regarding *Triglyceride-glucose (TyG) index indicates insulin resistance if it is >4.49.*

Additionally, patients under 60 with diabetic cardiovascular autonomic neuropathy (DCAN) showed significantly elevated triglyceride levels and a higher triglyceride glucose index compared to their older counterparts. The older group's triglyceride levels averaged 173.2 mg/dl (± 12.8), while the younger group had an average of 141.2 mg/dl (± 11.5), with a significance level of P < 0.05. The triglyceride glucose index was statistically insignificant with 5.1 (± 0.05) for the younger group and 5.0 (± 0.05) for the older group (P > 0.1). Among the DCAN patients, various retinal changes were noted: 15.6% had macular edema, 23.4% had non-proliferative diabetic retinopathy (NPDR), and 31.2% exhibited proliferative diabetic retinopathy (PDR). The remaining 25% showed no retinal changes, although most patients had uncontrolled diabetes, indicated by mean HbA_{1c} levels exceeding 9.2%. Furthermore, 100% of older patients with polyneuropathy were diagnosed with DCAN. Postural hypotension and the E/I ratio were positively identified in 32.2% of all participants in the study. A statistically significant difference was found in systolic blood pressure between supine and standing positions for both males and females, with p-values of < 0.0001 for females and < 0.0004 for males, as illustrated in Figure 1 and Table 3.

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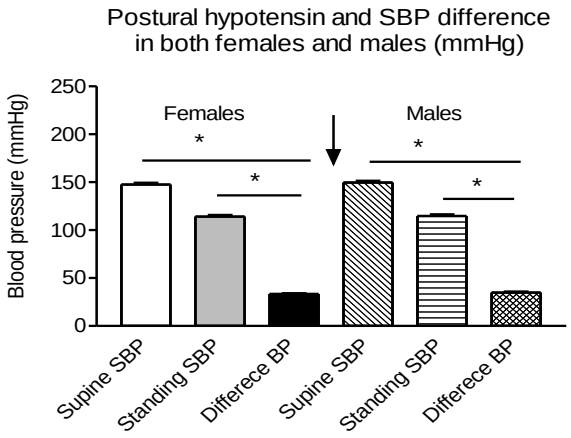

Figure 1. Blood pressure readings between supine and standing positions.

This study highlights the strong correlation between the duration of diabetes, fasting blood sugar, and glycated hemoglobin (HbA_{1c}) in females, as depicted in Figures 2A and 2B. Notably, this correlation is absent in males. These findings pertain to the total cases of T2DM, both with and without diabetic cardiac autonomic neuropathy, underscoring potential gender differences in the impact of diabetes on metabolic markers.

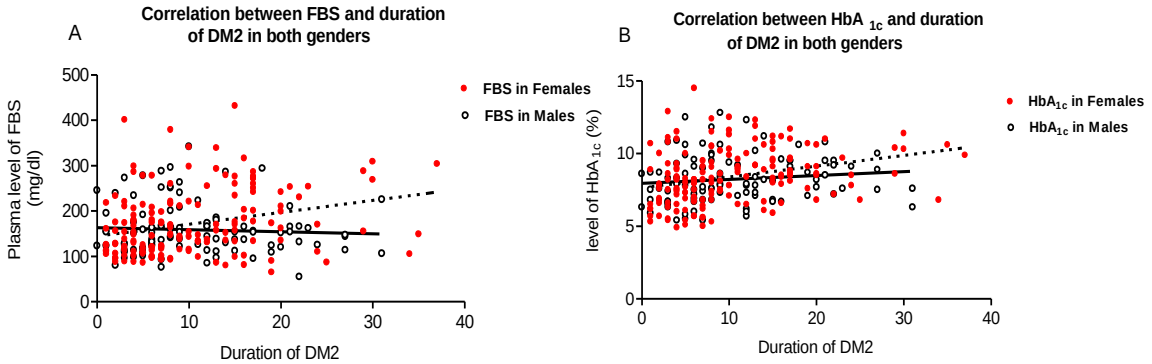

Figure 2. Correlation between fasting blood sugar (2A), glycated hemoglobin (2B), and the duration of diabetes in female patients

Figure 3 illustrates a significant positive correlation between the mean Expiratory/Inspiratory (E/I) ratio and the duration of diabetes, with an r^2 value of 0.056 and a p-value of < 0.05, as detailed in section 3A. Additionally, there is a significant negative relationship between the difference in systolic blood pressure (SBP) when in a supine position versus a standing position (indicative of postural hypotension) and the duration of diabetes, with an r^2 value of 0.073 and a p-value of <0.025, as described in Figure 3B.

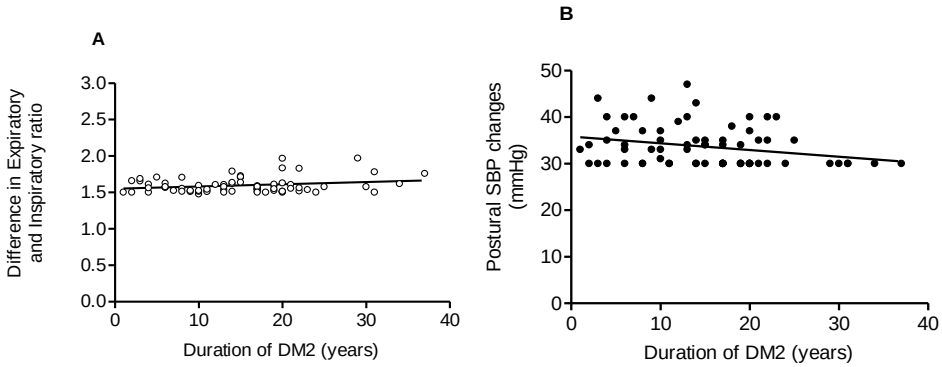

Figure 3. Correlation between the mean Expiratory/Inspiratory (E/I) ratio and the duration of diabetes

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Table 2. Clinical characteristics and biochemical parameters related to the risk factors of participants of diabetic type 2 diabetes in this study

Diabetes mellitus type 2						
Clinical and biochemical characteristics	**Patients without cardiac autonomic neuropathy**		**P value**	**Patients with cardiac autonomic neuropathy**		**P value**
	< 60 years old	**> 60 years old**		**< 60 years old**	**> 60 years old**	
Numbers (n)	113	64	NA	40	44	
Age (years)	49.3 ± 0.6	66.7 ± 0.8	P< 0.0001	52.3 ± 0.9	67.1 ± 0.8	P< 0.0001
BMI (Kg/m^2)	32.3 ± 0.5	32.4 ± 0.6	P> 0.6	34.4 ± 1.1	33.4 ± 0.8	P> 0.2
FBS mg/dl	160.7 ± 8.3	162.5 ± 7.9	P> 0.4	174.7 ± 10.2	181.4 ± 11.4	P> 0.8
Duration of diabetes (years)	6.4 ± 0.6	11.7 ± 1.0	P<0.0001	12.3 ± 1.1	17.0 ± 1.2	P< 0.01
HbA_{1c} (%)	8.0 ± 0.2	8.2 ± 0.2	P> 0.3	9.2 ± 0.3	8.6 ± 0.2	P> 0.09
Total cholesterol mg/dl	183.2 ± 4.6	177.7 ± 6.4	P> 0.5	189.3 ± 7.6	190.1 ± 7.6	P> 0.8
LDL mg/dl	112.5 ± 3.1	115.7 ± 4.5	P> 0.6	114.6 ± 4.9	127.3 ± 4.9	P> 0.06
HDL mg/dl	46.2 ± 1.4	47.6 ± 1.5	P> 0.4	45.6 ± 1.7	44.8 ± 1.6	P> 0.5
Triglyceride mg/dl	158.4 ± 9.0	132.4 ± 5.7	P> 0.05	173.2 ± 12.8	141.2 ± 11.5	P< 0.05
*TyG index	4.9 ± 0.03	4.9 ± 0.03	P> 0.5	5.1 ± 0.05	5.0 ± 0.05	P> 0.1
Diabetic nephropathy Microalbuminuria (mg/dl) Macroalbuminuria (mg/dl)	 14.3 ± 1.8 0	 27.0 ± 5.2 0	 P< 0.01 NA	 35.1 ± 2.0 0	 46.1 ± 3.4 0	P< 0.006
Diabetic neuropathy No neuropathy neuropathy	 50 (44.2%) 63 (55.8%)	 8 (86%) 56 (14%)	NA	 5 (13.2%) 35 (86.8%)	 0 44 (100%)	NA
Diabetic retinopathy No retinopathy (n) Retinopathy	 88 (77.9%) 25 (22.1%)	 29 (45.3%) 35 (54.7)	NA	 12 (%) 28 (%)	 11 (27%) 33 (73%)	NA

*Data represented as number (n), percentage (%), and mean ± SEM. Regarding *Triglyceride-glucose (TyG) index indicates insulin resistance if it is >4.49.*

Table 3 Data of mean results ± standard error of mean for statistical analysis for postural hypotension, resting tachycardia, and E/I ratio refers to the ratio of the duration of the longest R-R interval (E) to the shortest R-R interval (I) during certain phases of heart rate variability.

Age of patients with diabetic cardiac AN	**Number of patients**	**Supine SBP mmHg**	**Standing SBP mmHg**	***P value***	**Mean pulse rate at rest**	**Mean RR interval (E/I) ratio**
Below 60 years	40	146.6 ± 2.1	113.2 ± 2.0	P< 0.0001	88.6 ± 2.0	0.96 ± 0.02
Above 60 years	44	148.4 ± 1.6	114.8 ± 1.5	P< 0.0001	88.4 ± 1.6	0.96 ± 0.01
P value					P=0.8	P= 0.0007

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Discussion

This study showed that patients' age over 60 years had DCAN more than those younger age groups this can be explained by the fact that with the progressing of age and duration of diabetes patients are more prone to develop cardiovascular autonomic neuropathy, this is similar to what was described by (Cameron et al; 1997 and Low et al; 1997) [13,14]. Therefore**,** older age is another risk factor, as aging alone can lead to decreased nerve regeneration and increased susceptibility to nerve damage.

Interestingly, Elevated blood glucose levels can lead to nerve damage over time. The HbA_{1c} level is often monitored, as consistently high levels indicate poor glycemic control, especially with increased diabetes duration, significantly increasing the susceptibility for DCAN, especially in females, as detected in this study. This is consistent with the findings of [15,16]. Additionally, these findings can be attributed to several factors: (i) the progressive nature of diabetes, which is linked to insulin resistance or a decrease in endogenous insulin production in type 2 diabetes, and (ii) females may experience unique metabolic changes, particularly during hormonal fluctuations related to the menstrual cycle, pregnancy, or menopause. These hormonal changes can affect insulin sensitivity and glucose tolerance, potentially worsening hyperglycemia over time.

The existence of various metabolic disorders and metabolic syndrome, characterized by obesity, hypertension, dyslipidemia, and insulin resistance in which can work synergistically to elevate the risk of DCAN [17]. These aspects of metabolic syndrome lead to oxidative stress and chronic low-grade inflammation, which can result in endothelial cell dysfunction and reduced blood flow to nerve cells [18_21]. This study found that a higher body mass index (BMI) is linked to the development of insulin resistance, which complicates glycemic control and raises the risk of complications related to autonomic neuropathy [22,23].

Cardiovascular autonomic neuropathy is frequently observed in diabetic patients experiencing microvascular complications, including those with somatic sensory, motor, and polyneuropathies, and we noted a significant prevalence of cardiovascular autonomic neuropathy, reaching 100% among older patients with peripheral polyneuropathy.

Given these findings, we suggest implementing bedside assessments to screen diabetic patients with neuropathy for early signs of cardiovascular autonomic neuropathy. Early detection could enhance better therapeutic management [24]. Furthermore, fundus examinations revealed changes linked to various stages of diabetic retinopathy, highlighting a higher prevalence of this condition. The increased occurrence of cardiovascular autonomic neuropathy in uncontrolled diabetic patients with retinopathy is consistent with these studies [24–26].

Classifying cardiovascular autonomic neuropathy into sympathetic and parasympathetic types may be misleading, as most patients experience a combination of nerve involvement. While the symptoms of this condition are generally not life-threatening, they have received less research focus compared to other diabetes-related complications.

Conclusion

Diabetic cardiac autonomic neuropathy is strongly associated with several risk factors that mainly arise from inadequate glycemic control and abnormal metabolic issues. Taking a comprehensive approach to address these factors can not only help prevent DCAN but also enhance overall cardiovascular health in individuals with diabetes. Consistent monitoring and proactive management are crucial for alleviating the impact of this serious condition.

Conflicts of Interest

The authors declared no conflict of interest.

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المستخلص

الاعتلال العصبي القلبي اللاإرادي السكري هو حالة مهمة تؤثر على صحة القلب والأوعية الدموية في جميع أنحاء العالم وترتبط بزيادة معدلات الاعتلال والوفيات. ولذلك، يعد الكشف المبكر عن اعتلال الأعصاب القلبية اللاإرادية السكري وعلاجه أمرًا بالغ الأهمية للحد من مخاطر الإصابة بأمراض القلب والأوعية الدموية بين مرضى السكري. يمكن أن يؤدي تحديد هذا الاضطراب إلى تحسين نتائج المرضى ونوعية حياتهم من خلال تقليل فرص حدوث مضاعفات خطيرة. تهدف هذه الدراسة المستعرضة إلى تحديد الأفراد المصابين بداء السكري الذين يعانون من الاعتلال العصبي القلبي اللاإرادي السكري والتحقيق في علاقته بعوامل الخطر المختلفة، بما في ذلك ارتفاع السكر في الدم، ومدة الإصابة بداء السكري، ووجود اعتلال الأعصاب الجسدية المحيطية، ومضاعفات الأوعية الدموية الدقيقة لمرضى السكري. شملت الدراسة 261 مريضًا بالسكري من النوع الثاني، منهم 61.5% من الإناث و38.5% من الذكور. خضع المشاركون لاختبارات القلب والأوعية الدموية والتقييمات السريرية لتحديد حالات الاعتلال العصبي القلبي اللاإرادي. من بين 261 مريضًا تم اختيارهم عشوائيًا، تم تشخيص 84 مريضًا بالاعتلال العصبي القلبي المستقل للقلب مما أدى إلى معدل انتشار بنسبة 32.2%. كان متوسط عمر المريضات الإناث 57.5 ±0.7 سنة، بينما كان متوسط عمر المرضى الذكور 56.3 ± 1.2 سنة من إجمالي المرضى الذين تم تجنيدهم. بالإضافة إلى ذلك، هناك ارتباطات قوية بين الاعتلال العصبي القلبي اللاإرادي السكري والمعايير السريرية والكيميائية الحيوية مثل ملف الدهون ومدة الإصابة بالسكري وضعف السيطرة على مرض السكري ووجود بيلة الألبومين الدقيقة لدى المرضى الذين يعانون من الاعتلال العصبي القلبي اللاإرادي السكري والذين تزيد أعمارهم عن 60 عامًا مقارنة بالمرضى الأصغر سنًا. سلطت الدراسة الضوء على وجود ارتباط قوي بين الاعتلال العصبي القلبي اللاإرادي السكري وعوامل مثل ضعف التحكم في نسبة السكر في الدم، ومدة مرض السكري الطويلة، ووجود مضاعفات مزمنة في الأوعية الدموية الدقيقة، بما في ذلك الاعتلال العصبي واعتلال الشبكية واعتلال الكلية. تؤكد هذه النتائج على ضرورة زيادة الوعي والتقييمات الاستباقية للمرضى الليبيين المعرضين لخطر الإصابة بالاعتلال العصبي اللاإرادي القلبي الوعائي، وذلك للحد من خطر تكرار المضاعفات القلبية حادة، خاصةً لدى المرضى الذين يخضعون لجراحة طارئة دون تشخيص مسبق. فمن الضروري إدراك هذا الخطر.

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