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The Prevalence of Cardiovascular Autonomic Neuropathy among Long Term TypeII Diabetes Mellitus

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KEY WORDS:
Cardiovascular autonomic neuropathy , typeII diabetes mellitus and cardiovascular autonomic reflex tests.

ABSTRACT
Background: Worldwide, the prevalence of diabetes mellitus is considerably high. Cardiovascular autonomic neuropathy (CAN) is a severe complication of the advance stage of diabetes. More than 50% of diabetic patients diagnosed with peripheral neuropathy will have CAN, with clinical manifestations including tachycardia, severe orthostatic hypotension, syncope, and physical exercise intolerance.
Aime : The study aimed to evaluate the prevalence of cardiovascular autonomic neuropathy 1-in long term type ll diabetic patients

Materials and Methods: A case control study to sample of 88 patients with long term T2DM were collected from the department of medicine at Salah-Aldeen General Hospital, Tikrit-Iraq. Assessment of cardiovascular autonomic neuropathy by cardiovascular autonomic reflex test (CARTs).
Results: The results show cardiovascular autonomic neuropathy is common among the people with T2DM (84.1%). The longer duration of the disease and fibrinogen level becomes an independent factor of CAN incidences. Study revealed that the lymphocyte levels in uncontrolled T2DM patients with CAN are lower than without CAN.
The study conclude that cardiovascular autonomic neuropathy was common in long term T2DM.

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1-INTRODUCTION

Worldwide, the prevalence of T2DM is considerably high. One of the most serious and costly chronic diseases in the world with increased in the Incidence considerably over the past 30 years, and forecasts indicate that these numbers will continue to increase significantly (1). Cardiovascular autonomic neuropathy (CAN), which is common in individuals with T2DM and can cause cardiovascular diseases (CVD) and CVD-related mortality, is an underdiagnosed risk factor for CVD. (2). Several factors influence the likelihood of getting autonomic dysfunction in diabetes poor glycemic management, disease duration, hypertension, dyslipidemia, and obesity are recognized risk factors for CAN (3).

Clinical manifestations of CAN include resting tachycardia, exercise intolerance, impaired heart rate variation (HRV) (4). Intraoperative and perioperative cardiovascular instability, orthostatic hypotension (5).

2-Aime

The study aimed to evaluate the prevalence of cardiovascular autonomic neuropathy in long term type ll diabetic patients

3-MATERIALS AND METHODS

This study was conducted in the medical department at Salah-Aldeen General Hospital in Tikrit, Iraq, from the first of March 2021 to the end of December 2022. Samples of T2DM were taken from the outpatient and inpatient clinic medicine department for a case control study. After receiving their consent for our project, the patients were interviewed using a special questionnaire, all participants were instructed to abstain from tea, coffee ingestion, as well as energy drinks and exercise for 24 hours prior to testing by cardiovascular autonomic reflex tests (CARTs).

2-1. Inclusion criteria

1-T2DM.
2-Duration of illness ≥10 years.

2.2. Exclusion criteria

1-T1DM 2-T2DM less than10 years. 3-Congestive heart failure, cardiac arrhythmias, and any other chronic systemic diseases like chronic kidney diseases. 4-Participants who were taking alpha- or beta-blockers, calcium channel blockers, anticholinergics, sedatives, antidepressant agents were exclude 5- Participants with evidence of proliferative retinopathy were excluded from the Valsalva maneuver.

Table (1) Cardiovascular autonomic reflex tests (CARTs): (6)

Test	Technique	Normal response and value
Heart rate variability (HRV)	With the patient at rest and supine, HR is monitored by ECG while the patient breath in and out at 6 breath per minute, paced by metronome or similar device	A difference in HR of >15 beats per minute is normal and <10beats per minute is abnormal. The lowest normal value for the expiration- to- inspiration ratio of the R-R interval decreases with age,
HR response to standing	During continuous ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing	Normally, a tachycardia is followed by reflex bradycardia. The 30:15 ratio should be >1.03, borderline 1.01-1.03
HR response to the valsalva maneuver	The subject forcibly exhales into the mouthpiece of a manometer to 40 mmHg for 15sec. a during ECG monitoring	Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in BP with release. The normal ratio of longest R-R to shortest R-R is>1.2, borderline 1.11-1.2
Systolic BP response to standing	Systolic BP is measured in the supine subject. The patient stands and systolic BP is measured after 2min	Normal response is a fall of <10mmHg, borderline fall is a fall of 10-29 mmHg and abnormal fall is a decrease of >30 mmHg
Diastolic BP response to isometric exercise	The subject squeezes a handgrip by dynamometer to establish a maximum. Grip is the squeeze at 30% maximum for 5 min	The normal response for diastolic BP is a rice of >16mmHg in the other arm, borderline 11-15 mmHg

HR= Heart rate, Bp=Blood pressure, HRV= Heart rate variability

4-Results

4-1-Prevalence of Cardiovascular Autonomic Neuropathy in T2DM Patients

Figure (1) shows that people with diabetes were classified according to the cardiac autonomic reflex tests into those with CAN 74(84.1%), and just 14(15.9%) without CAN.

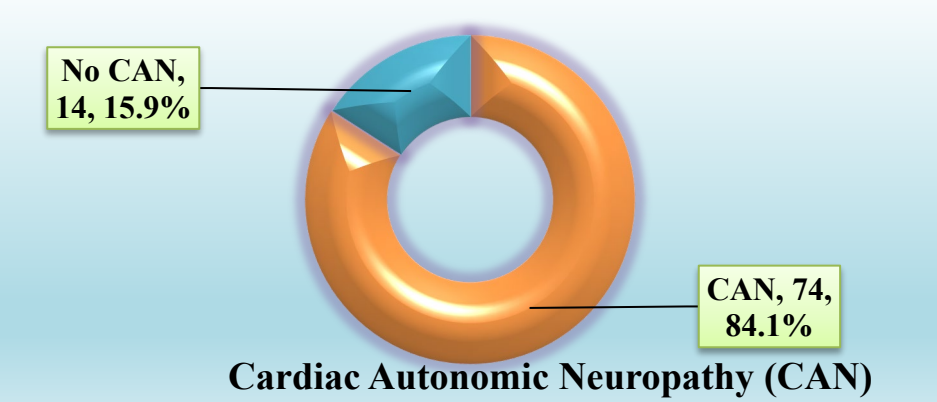

Figure (1)Prevalence of Cardiovascular Autonomic Neuropathy in T2DM

4-2. Characteristic of the T2DM Participant include CAN and without CAN

Concerning the CAN and without CAN There was no significant of a difference in age, BMI, WHR, but significant difference present in the duration (years)of illness which was longer in CAN group.

Table (2) Characteristic of the Participant Diabetes in relation to CAN and without CAN

Variable	**CAN n=74**	**without CAN n=14**	**P value**
Age (years)	55.9±8.5	52.3±7.5	0.144
Disease Duration(years)	14.7±4.9	12.0±1.9	0.046*
BMI (Kg/m^2)	29.70±4.92	27.31±3.88	0.089
WHR	1.035±0.22	1.006±0.058	0.6301
The data are present as Mean ± SD			

CAN=Cardiovascular autonomic neuropathy, BMI= body mass index, WHR=waist hip ratio

4-3. Blood Profile in Diabetics with and without CAN

Regarding to Hemoglobin, HbA1C, HCT, WBC, Lymphocytes, NLR and PWR that did not show statistically significant differences between the two groups. On the other hand, Platelets and Fibrinogen show significant increase in CAN group, while Neutrophils count was significantly increase in patient without CAN.

Table (3) - Blood Profile in Diabetics with and without CAN

Variable	CAN n=74	Without CAN n=14	P value
HbA1C (%)	9.800 (6.0-12.9)	8.900 (6.1-10.3)	0.061
Hemoglobin (g/dL)	12.300 (9.4-17.2)	12.450 (11.0-16.0)	0.653
HCT (%)	38.250 (29.40-57.60)	38.350 (34.50-43.80)	0.898
WBC (10^9/L)	9.900 (3.2-20.3)	11.050 (7.9-28.9)	0.079
Platelets (x10^{12}/L)	276.000 (133-468)	231.500 (98-393)	0.011*
Lymphocytes (10^9/L)	2.850(1-32)	3.950(2.9-21.8)	0.233
Neutrophils (10^9/L)	4.450 (1.3-10.7)	5.400 (2.3-17.4)	0.018*
Neut/Lym Ratio	1.360 (0.063-3.240)	1.530 (0.180-2.940)	0.820
Platelets/WBC Ratio	19.340 (8.000-81.56)	23.360 (6.57-5.32)	0.804
Fibrinogen (mg/dL)	287.000 (158-389)	204.000 (202-318)	0.04*
The data are present as Mean ± SD and (Range) or median and (Range)			

4-4. Characteristic of the Biochemical Investigation in CAN and without CAN Groups

Renal function test and lipid profile results in diabetes with and without CAN, show no significant different.

Table(4) Biochemical Profile in Diabetes According to CAN

Variable	CAN n=74	without CAN n=14	P value
Blood urea (mg/dl)	36.000 (28-128)	33.000 (30-39)	0.208
Serum creatinine (mg/dl)	0.900 (0.40-3.80)	0.92 (0.63-1.20)	0.531
Serum uric acid (mg/dl)	5.7±0.8	5.4±0.6	0.294
Total cholesterol (mg/dl)	194.8±41.0	198.1±31.9	0.774
Triglycerides (mg/dl)	202.000 (162-308)	193.000 (94-610)	0.191
HDL (mg/dl)	26.5±3.7	31.5±12.1	0.132
LDL (mg/dl)	125.5±29.2	106.1±35.8	0.059
The data are present as Mean ± SD and (Range) or median and (Range)			

HDL=high density lipoprotein, LDL= low density lipoprotein

4-5. Blood Pressure and Resting Tachycardia (beat/min) in CAN and without CAN groups

In this study hypertension form (59.5%) in CAN and (57.1%) among without CAN groups, but neither systolic blood pressure nor diastolic blood pressure(mmHg) have significant difference between both groups. About resting tachycardia there is highly significant difference in CAN group (101.14±20.7) in compare to without CAN group (89.99±12.64).

TABEL (5) Blood Pressure and Resting Tachycardia in Diabetics with and without CAN

Variable	**CAN n=74**	**Without CAN n=14**	P -value
Resting tachycardia (beat/min)	101.14±20.7	89.99±12.64	0.008*
Systolic blood pressure(mmHg)	132.4±17.0	135.7±17.9	0.500
Diastolic blood pressure(mmHg)	79.8±11.5	81.4±9.3	0.609
Hypertension	44(59.5%)	8(57.1%)	0.872
The data are present as Mean±SD			

4-6. Cardiovascular Autonomic Reflex Tests Finding in CAN and without CAN groups

Summarizes the parameters of CARTs analysis in patient groups include CAN and without CAN of short-term recording (during resting) revealed :

Analysis for the parasympathetic system:* all the heart rate response to (E: I Ratio, and Valsalva Maneuver) show significantly lower in CAN when compared to without CAN,** while HR response to standing (30:15 Ratio) has no significant difference.

****Analysis for the sympathetic system*****:** The significant of BP response to sustained handgrip test (HGT) was low, while high BP response to stand in CAN group. It was obvious that Ewing score was significantly increase in CAN group.

Table (6) Cardiovascular Autonomic Reflex Tests in CAN and without CAN

CARTs	**CAN n=74**	**Without CAN n=14**	**P value**
HR response (E: I Ratio)	3.900 (1.60-16.00)	8.00 (1.200-14.800)	0.0001*
HR response **(**30:15 Ratio)	0.940 (0.81-1.03)	0.990 (0.84-1.06)	0.163
HR response to Valsalva Maneuver (Valsalva Ratio)	1000 (0.70-1.70)	1.155 (0.95-1.80)	0.002*
BP response to sustained handgrip (mmHg)	16.250 (8.00-19.00)	16.500 (9.00-20.00)	0.038*
BP response to standing(mmHg)	10.000 (3.00-32.00)	9.000 (6.50-11.00	0.040*
Ewing Score	3.000 (2.5-4.0)	2.000 (1.5-2.5)	0.0001*
The data are present as median and (Range)			

HR = heart rate; E: I = expiration: inspiration; BP =blood pressure **,** CARTs= cardiovascular autonomic reflex tests

5-Discussion

5-1- Prevalence of Cardiovascular Autonomic Neuropathy in T2DM

In current study eighty-eight people with diabetes divided according to cardiac autonomic tests to CAN 74 (84.1%) and without CAN 14(15.9%), while other studies show CAN prevalence,39.1% (7),29.9% (8), (52.82%) (9).

CAN prevalence ranges from as low as 1% to as high as 90% in long standing DM (10) , (11). The prevalence of CAN in current study higher than other studies, this is because the patients of current study had long duration of T2DM (10-30y) and diabetes duration is a major risk factor for the development of CAN in patients with T2DM (12).

5-2- Characteristic of the T2DM Participant include CAN and without CAN:

The Age: The study concluded non-significant difference in the mean age of the diabetics with and without CAN, similar other studies done by Shah B *et al and* Jindal S *et al* (13), (14).

BMI and WHR: Absent BMI and WHR with CAN correlations may be explained by the fact that BMI quantifies general adiposity; although individuals who are overweight or obese are likely to have excess fat, BMI and WHR does not indicate how this fat is distributed in the body (15), (16). Have confirmed that WHR is a superior clinical measure for predicting all-cause and cardiovascular disease mortality.

The Duration: In present study, the prevalence of CAN increases as the duration of diabetes increases (10 years and more). In their studies done by Moningi S and Bhuyan *et al* (17), (18) have shown that the longer duration of diabetes mellitus is independently associated with CAN. The incidence of CAN was reported to be 2% annually in patients with T2DM(19).The prevalence increased from 9 to 31% 1 year later (20). In addition, Dimova R *et al* found that prevalence increased from 19.8% in pre-diabetics to 32.2% in newly diagnosed patients with T2DM (21), while the current study show higher percentage because illnesses duration of the sample already have 10 years or more that go with CAN was more common in those people with diabetes for over 10 years. (22). It is reported in this study that DM duration becomes an independent factor of CAN incidences.

5-3 Blood Profile in Diabetics with and without CAN

-Glycated hemoglobin: despite no significantly difference of HbA1C between the two groups in this present research but still high in the mean value of CAN patients this is probably due to use hypoglycemic treatment made HbA1C no so different. Other cause attributable to including GI autonomic neuropathy and delayed gastric emptying, it can be challenging to maintain glycemic control (23).

A mismatch between insulin delivery and glucose absorption may result from glycemic disturbances and GI dysmotility (24).

- Fibrinogen Level: There is high difference value between CAN and without CAN in this study. Hyperfibrinogenemia has been identified as a separate risk factor for cardiovascular disease and is an indicator of inflammatory vascular changes and endothelial dysfunction (25).

-WBC and Lymphocyte Count: lack of a significant correlation between CAN and without CAN in current study.

-Neutrophils Count: Although neutrophilia in diabetes was common because of functionally altered, due to exposure to the diabetic microenvironment, including changes to blood glucose as well as other factors. (26),but in current study is different in CAN group that lower count when compare with without CAN ,this probably due to co-infections: Viral, bacterial and parasitic infections ,Medications, nutritional deficiencies(27).

- Platelet Count: Study revealed that platelet count was significantly higher in CAN when compare with without CAN, like study (28), and increased Platelets activity have been reported in diabetics as demonstrated by increases in GPs IIb/IIIa, 1b-IX, and 1a/IIa , other factors, false increase of the platelet count can be observed in the presence of non-platelet particles (as small as platelets), such as fragmented erythrocytes, fragments of nucleated cells, bacteria, fungi, lipids, and cryoglobulins.(29).

5-4- Biochemical Investigation in CAN and without CAN Groups:

-Renal function: Although there was no significant difference, in serum creatinine and blood urea between CAN and without CAN patients, but the value of upper limit present in CAN patients, this gives ideas that renal impairment presents in CAN but cannot know the degree of that impairment without measure GFR.

-Lipids Profile: Dyslipidemia contributes to CAN in T2DM (30). But in the current study Lipids profile get no significant difference between CAN and without CAN, this probably because many of the participants used statin treatment, thus, serological CVD risk factors such as cholesterol, triglycerides, and HDL were within the normal ranges.

5-5- Resting Tachycardia and Blood Pressure:

- Resting Tachycardia: There is highly significant in CAN group in compare to without CAN group. One of the earliest signs of CAN is asymptomatic abnormalities in heart rate, which later progresses to resting tachycardia (90–130 bpm) (31). A fixed and unresponsive HR to breathing is associated with complete cardiac denervation and severe CAN (10). Therefore, resting HR can be used as a diagnostic and prognostic tool in patients with DM after excluding other causes of tachycardia (19). resting tachycardia is associated with an increased risk of death and CV complications (32).

-Systolic and Diastolic Blood Pressure (SBp and DBp**):** Although hypertension present in both CAN and without CAN 44(59.5%), 8(57.1%) respectively, but there was no significant difference between two groups of the diabetic patients regarding to SBp and DBp. Use of antihypertensive drugs in those diabetic patients may affect the current results.

5-6- Cardiovascular Autonomic Reflux Tests Finding in CAN and without CAN Groups:

According to the Ewing and colleagues' method, the gold standard to measure the CAN is cardiovascular autonomic reflex tests (33). The five tests reflect both arms of the sympathetic and parasympathetic nervous system, and a minimum of two abnormal tests define the presence of CAN in people with DM (34). The presence of CAN with two abnormal tests was linked to higher CVD mortality rates (2) Therefore, identifying risk factors associated with CAN may help health care professionals attenuate these factors and implement strategies to reduce future risk and mortality.

In the current study cardiovascular autonomic neuropathy was detected in approximately most patients with sympathetic involvement and in most patients with parasympathetic involvement, but with less frequency, this is contrast to what was mentioned in the literature, this may be due to that most patients in study had T2DM, with poor glycemic control and long duration of undiscovered DM, indicating that presence of autonomic symptoms indicate necessarily a severe form of cardiovascular autonomic neuropathy, this is consistent with Smith's findings(35),give idea that the rigid division of cardiovascular autonomic neuropathy into sympathetic and parasympathetic is not appropriate as both nerves are involved to differing degrees in most patients. Being rarely life threatening (as many doctors believe), the symptoms of cardiovascular autonomic neuropathy received little attention by researchers compared to other diabetic complications.

Conclusion

Cardiovascular autonomic neuropathy is common among the people with long standing T2DM that diagnosed by cardio vascular reflexes (Ewing's Test) .Duration of diabetes was independent risk factors for CAN.

The risk factors for diabetic cardiovascular autonomic neuropathy including significantly lower in neutrophils count while, Fibrinogen level and Platelets count were higher significant when compare with without CAN.

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