SUBCLINICAL DIAGNOSIS OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES: PREVALENCE, SEVERITY, CORRELATIONS WITH TIME, METABOLIC AND VASCULAR FACTORS

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ABSTRACT

Objective: To diagnose cardiovascular autonomic neuropathy in the general population of type 2 diabetes in our geographical area and determine its prevalence, severity and correlation with time, metabolic and vascular factors.

Patients and method: 212 type 2 diabetic patients (49% men), ages 20-80 years (mean age: 52+-5.10 years) were examined by 5 autonomic reflex tests: 1. deep breathing test 2. Valsalva test; 3. heart rate response during stand test; 4. orthostatic blood pressure response; 5. dyastolic blood pressure response during isometric exercise.

Cardiovascular autonomic neuropathy (CAN) was defined by at least 2 abnormal results. Total vegetative score was also calculated, associating to each test a conventional value of 0/0.5/1 and severity stages were defined.

Results: The overall prevalence of CAN was high (62,26%). CAN was clinically evident in 3% of patients only. Early and mild forms were predominant. CAN correlated well with: age, disease duration, HbA1C, body mass index (BMI), systolic blood pressure and did not correlate with gender.

Conclusion: Autonomic impairment is an early finding in type 2 diabetes which may go unnoticed long before clinical history is positive. Active diagnosing CAN by autonomic function tests in its subclinical phase would enable a closer metabolic control and prevent further deterioration.

Key words: diabetic autonomic neuropathy, cardiovascular autonomic neuropathy, autonomic function tests

BACKGROUND

One of the most important forms of diabetic autonomic neuropathy (DAN) is cardiovascular autonomic neuropathy (CAN) which not only impairs the quality of life, but also results in a 5 times increase in mortality (1).

As clinical symptoms of CAN develop only late in its evolution, active diagnosis is recommended in its subclinical phase, autonomic function tests being a validated method (2). Nonetheless, the presence of suggestive symptoms can only make a probable diagnosis that should be confirmed by autonomic function tests.

The wide ranges (1%-90%) of CAN prevalence as reported by different authors (25.3%, (3), 16.6% (4), 16.7% (5), 66% (6), 50% (7), 54% (8), 34% (9), 30% (10), 63% (11) was attributed to differences in:

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selection criteria, algorythms of definition, different normative values and to confounding variables like: age, gender, height, diabetes duration, diabetes type, glycemic control (3, 12).

OBJECTIVE

To asses the prevalence and severity of cardiovascular autonomic neuropathy in the general population of type 2 diabetes and to identify its correlation with time (age, disease duration), metabolic (glycemic control, BMI) and vascular factors (systolic blood pressure).

PATIENTS AND METHOD

212 type 2 diabetic patients (49% men), ages 20-80 years (mean age: 52+-5.10 years) and 100 healthy controls were submitted to 5 autonomic reflex tests: 1. deep breathing test (heart rate response during deep breathing HRDB) 2. Valsalva test (Valsalva ratio); 3. heart rate response during stand test (the 30/15 ratio); 4. orthostatic blood pressure response (orthostatic systolic blood pressure); 5. dyastolic blood pressure response during isometric exercise. Patients both with and without autonomic symptoms were included.

Patients with end-stage organ failure (renal and heart failure, coronary heart disease, prolipherative retinopathy) and with nondiabetic causes of autonomic dysfunction (pure autonomic failure, multiple system atrophy, other autonomic neuropaties, hypovolemia, medication with autonomic influence, endocrine disease) were excluded.

Cardiovascular autonomic neuropathy (CAN) was defined by ≥ 2 abnormal values (1abnormal test was diagnosed as "borderline").

Giving each test a conventional value of 0/0.5/1 according to a normal/borderline/abnormal value, the total vegetative score and different stages of severity of CAN were defined: absent (score=0-0.5), possible (score=1-1.5), definite (score=2-4), severe (score=4.5-5).

RESULTS

The values of autonomic function tests are shown in Tabel 1.

Prevalence of abnormal/borderline/normal values are shown in Tabel 2.

TABEL 2. *Prevalence of abnormal responses in autonomic function tests*

HR_{BD}	Normal	32	15,09
	Borderline	64	30,19
	Ab normal	116	54,72
	Total	212	
		No cases	%
30/15	Normal	88	41,51
	Borderline	32	15,10
	Ab normal	92	43,39
	Total	212	100,00
VR	Normal	134	63,21
	Borderline	28	13,21
	Ab normal	50	23,58
	Total	212	100,00
Orthost BP	Normal	128	60,37
	Borderline	12	5,67
	Ab normal	72	33,96
	Total	212	100,00
Isometric BP	Normal	76	35,85
	Borderlin	56	26,41
	Ab normal	80	37,74
	Total	212	100,00

All 5 autonomic function tests scored statistically different in patients comparatively to controls (α=0.05).

CAN was a frequent finding in the general population of type 2 diabetes, its prevalence was 62.26% (Fig. 1).

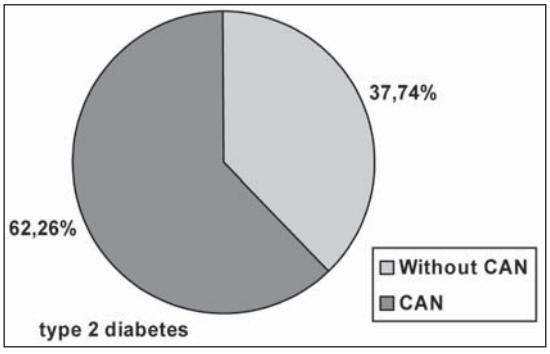

FIGURE 1. *Prevalence of CAN diagnosed by autonomic function tests*

TABEL 1*. Values of autonomic function tests*

	Min	Max	Media	Median	SD	Variation	Coef. Var.
HR_{DB}	1.04	30.23	10.637	9.575	6.572	43.198	61.8
30/15	0.85	1.35	1.076	1.06	0.091	0.008	8.5
VR	1	2.36	1.277	1.17	0.235	0.055	18.4
Orthost BP	-50	40	-8.015	-10	16.799	281.529	209.3
Isometric BP	-41	53	11.592	12.5	11.456	131.239	98.8

The distribution of patients in severity groups shows the preponderence of mild and definite forms (2 or 3 abnormal responses), comparative to severe forms (4 or 5 abnormal results) (Fig. 2).

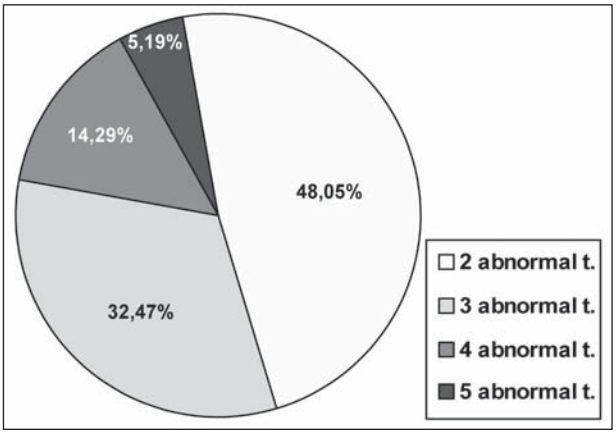

FIGURE 2. *Prevalence of abnormal tests among patients with CAN*

Distribution of cases according to different age groups is shown in Tabel 3.

TABEL 3. *Distribution of CAN according to diabetes duration*

Disease duration	Total number	CAN	
		No cases	%
< 5 years	88	42	47.72
5-10 years	74	48	64.86
11-20 years	50	42	84.00
>20 years	0	0	0
Total	212	132	62.26

CAN was preponderent in all age groups, except the 20-30 years age group (Fig. 3).

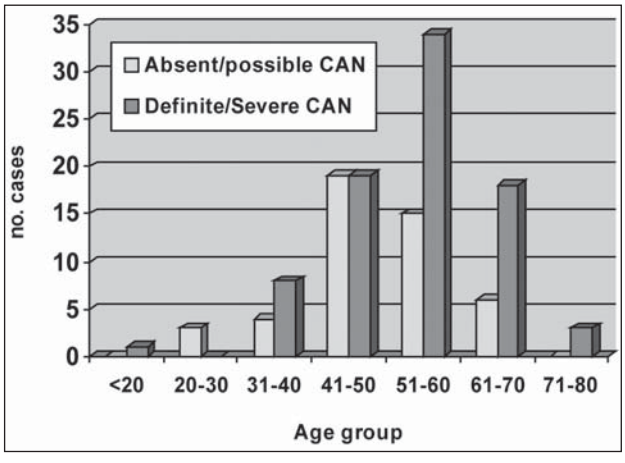

FIGURE 3. *Distribution of CAN according to different age groups*

We did not find any significant correlation with gender(p=0.5064) (Fig. 4).

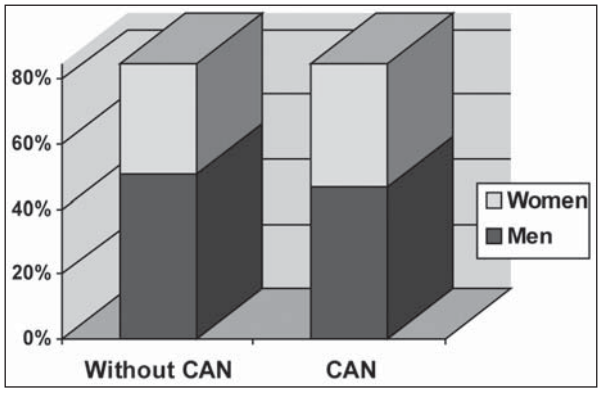

FIGURE 4. *CAN was equally distributed according to gender*

There was a linear positive correlation between the total number of abnormal responses and age (p=0.05) and diabetes duration (p=0.01) (Fig. 5 and Fig. 6).

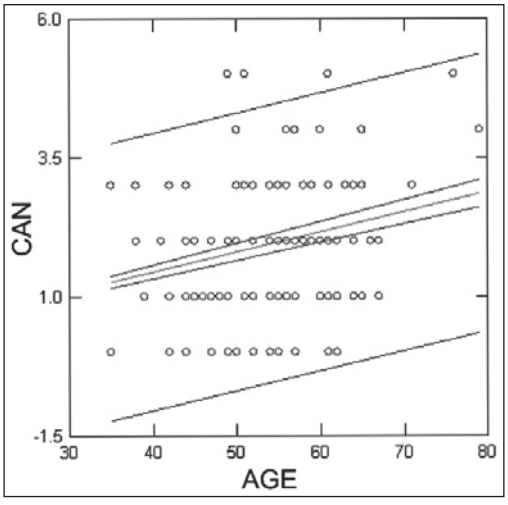

FIGURE 5. *The total number of abnormal tests increased with age*

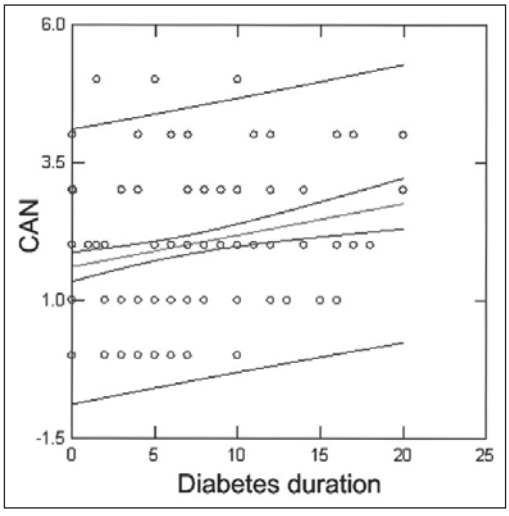

FIGURE 6. *The total number of abnormal results increased with diabetes duration*

Unaffected patients were predominant in the 0-5 years group only, although CAN had a high prevalence in this group (47.74%).

In all the other age groups (>5 years duration) the number of patients with CAN exceeded the number of unaffected patients and disease duration >5 years was highly associated with the presence of CAN(p=0.0002) (Fig. 7).

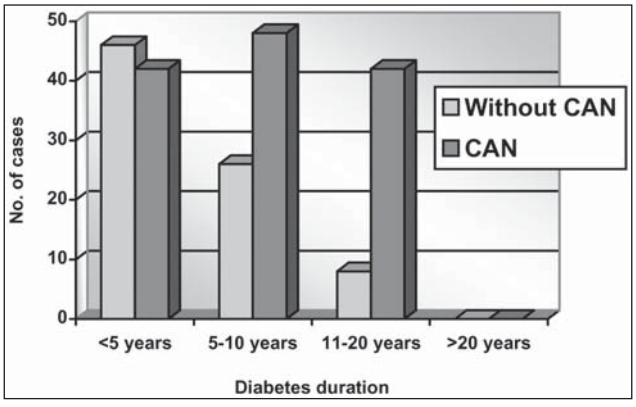

FIGURE 7. *CAN patients are predominant beggining from a disease duration of >5 years*

Distribution of CAN according to BMI is shown in Tabel 4.

The proportion between CAN/without CAN was not significant in normal and overweighted patients, while CAN was definitely predominant in obese patients (Fig. 8).

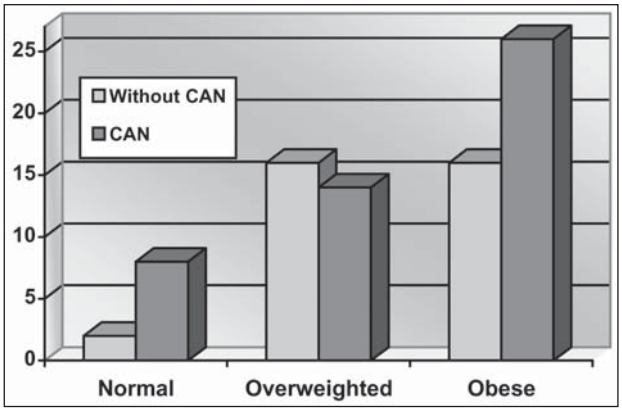

FIGURE 8. *Distribution of cases according to BMI*

We found a positive correlation between definite/severe forms of CAN (score≥2) and BMI≥30 kg/m^2 (p=0.00063), while the correlation between CAN and BMI ≥25 kg/m2 was not significant (p=0.6206).

The prevalence of HbA1C in different stages of CAN severity shows a strong association between HbA1C >8% and definite/severe CAN (p=0.006) (Fig. 9).

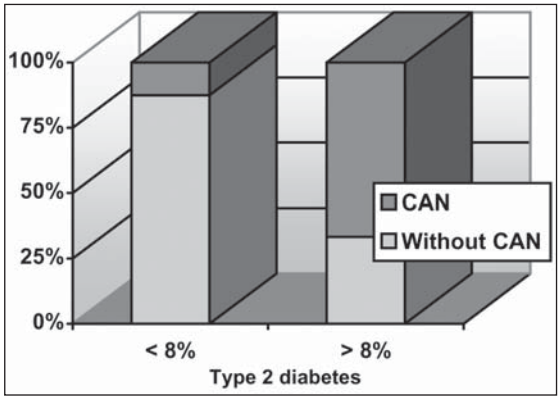

FIGURE 9. *Prevalence of CAN according to HbA1 C*

There was a positive correlation between CAN and systolic blood pressure (p=0.001), as it is shown in (Fig. 10).

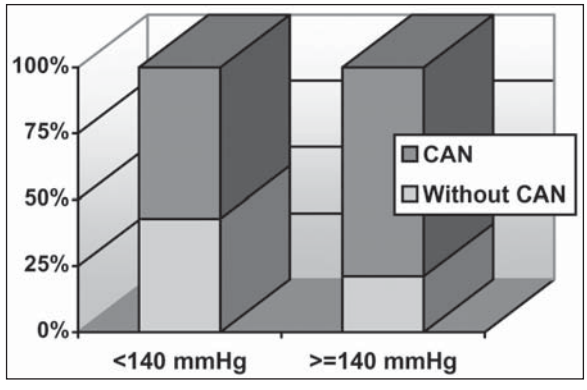

FIGURE 10. *Prevalence of CAN according to blood pressure*

DISCUSSION

Our reported prevalence of CAN (62.26%) was similar to other studies (63% reported by Valensi) (12), 59% reported by Dyck (11).

TABEL 4. *Distribution of severity stages according to BMI*

BMI	CAN				Total
	Absent	Possible	Definite	Severe	
18.5-24.9	2	8	22	2	34
kg/m^2	5.88%	23.53%	64.70%	5.88%	100.0%
25-29.9	14	26	40	6	86
kg/m^2	16.38%	30.23%	46.51%	6.98%	100.0%
? 30 kg/m^2	4	14	66	8	92
	4.35%	15.22%	71.74%	8.69%	100.0%
Total	20	48	128	16	212

Although HbA1C <7% is the value considered to define a good metabolic control, our cases requested the value of 8% to mark the limit between the groups.

As long as metabolic and ischemic factors had been identified in the pathogenesis of CAN (Vinik) (13), the good correlation that we found with age, disease duration BMI, chronic glycemic control and systolic blood pressure was expected and was similar to other studies Latini (14), Tesfaye (15). We did not find any correlation with gender, although there are studies which report an increased prevalence of CAN in men (The CARDIA Study) (16) or in women May (17).

CONCLUSION

Autonomic impairment is an early and frequent finding in type 2 diabetes.

It correlates well with age, disease duration, BMI, HbA1C and systolic blood pressure.

CAN should be actively diagnosed beggining from its subclinical phase long before clinical signs of autonomic dysfunction become obvious. The great proportion of affected patients in the group <5 years of diabetes duration leads to the statement that screening for CAN should be done in the moment of diagnosis in type 2 diabetes.

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