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The prevalence of cardiac autonomic neuropathy in pure type II diabetic patients

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Abstract
Cardiac autonomic neuropathy (CAN) has a negative effect on survival and quality of life in people with diabetes mellitus (DM) and is regarded as a subtype of the diabetic autonomic neuropathy. This type of neuropathy is the most prominent focusing because of its life threatening and the availability of the cardiovascular tests that can diagnose it. This study aims to determine the prevalence of CAN in patients with type 2 diabetes mellitus. This cross sectional study included 103 (56 males and 47 females) pure diabetic patients without hypertension or pre-diagnosis of ischemia. They had attended to the diabetic center in Marjan Medical City in Hilla from March 2013 to February 2014. The patients had undergone thorough assessments that included clinical (history and full examination). The study found that most of the diabetic patients presented with CAN (72.8%). Patients with CAN were older when compared to patients without CAN ($p<0.01$) and had longer duration of DM ($p<0.01$). The most abnormal sympathetic response was diastolic blood pressure response to hand grip while the most abnormal parasympathetic response was heart rate response to breathing. On contrary, the lowest abnormal response was found in postural blood pressure test. In conclusion, This study concludes that CAN is a common complication of type 2 diabetes that affected a large percentage of diabetic patients. The duration of the diabetes and the age of patients are important non modifiable risk factors for the development of CAN. Additionally, heart rate variability is considered as an important test for early detection of CAN.
Key words: Diabetes mellitus, Cardiac autonomic neuropathy, Cardiac autonomic reflex test.

Introduction

Cardiac autonomic neuropathy (CAN) is the most important and overlooked complication of diabetes mellitus (DM) and globally, it affects large amount of population. However, very limited researches in the world were present regarding the early cardiac autonomic complications (Deepak *et al.,* 2012). Furthermore, CAN is considered as one of the important causes of morbidity and mortality is in diabetic patients as it usually associated with a high risk of cardiac arrhythmias and sudden death that possibly is related to silent myocardial ischemia (Maser and Lenhard, 2005).
The reported prevalence of CAN varies greatly depending on the criteria used for its identification and about the population studied. Usually its prevalence ranges from as low as 2.5% of the primary prevention cohort in the Diabetes Control and Complications Trial (DCCT) to as high as 90% of patients with long-standing T1DM who were potential candidates for a pancreas transplantation (Rodica, 2010).

Materials and methods:

This cross sectional study included 103 (56 males and 47 females) pure diabetic patients without hypertenstion or predignosed ischemia. They had attended to the diabetic center in Marjan Medical City in Hilla from March 2013 to February 2014. Informed consent was obtained from all patients.

They were divided in to two groups according to the presence of autonomic neuropathy:
Group I: Seventy five patients with abnormal cardiac autonomic function test (42 males and 33 females) with a mean age 50.6 ± 7.8 years (mean ± SD).

Group II: Twenty eight with normal cardiac autonomic function test (14 males and 14 females) with a mean age of 45 ± 6 years (mean ± SD).

CARTs were performed in a time between (8.00 am – 1.00 pm) by the same operator and were analyzed by one investigator. According to Ewing's protocol cardiac autonomic neuropathy (CAN) was assessed by the five standard cardiovascular reflex tests; 3 for parasympathetic and 2 for sympathetic divisions (Ewing *et al*., 1985).

The parasympathetic functions were assessed by heart rate responses to deep breathing (R-R variation), to standing (30:15 ratio) and to Valsalva maneuver assessed automatically by Mortara ECG recordings. On the other hands, the sympathetic functions were mainly assessed by sustained handgrip test and by blood pressure responses to standing.

According to these five tests, cardiac autonomic function were classified into three categories (normal, borderline and abnormal) which were pointed as 0, 0.5 and 1, respectively (Bellavere *et al*., 1983) (Table 1). Cardiac autonomic neuropathy scores were classified as follows: CAN score 0 (total points 0), CAN score 1 (points 0.5-1.5), CAN score 2 (points 2-3), and CAN score 3 (points ≥ 3.5). CAN was considered absent, early, definite, or severe if the CAN scores were 0, 1, 2, or 3, respectively (Jung *et al*., 2012).

If two of these five test results were abnormal, the presence of cardiovascular autonomic neuropathy was assumed (Ziegler *et al*., 1992).

Table 1 Points for classification of CAN

Tests	Point 0	Point 0.5	Point 1
Hand grip test (DBP)	>16	11-15	<10
Standing BP (SBP)	<10	11-29	>30
Standing HR (30/15)	>1.04	1.03-1.01	<1
HR breathing (I-E)	>15	14-11	<10
HR valsalva (re/st)	>1.21	1.2-1.11	<1.1

Statistical analysis were performed using SPSS 17.0 (SPSS Inc, Chicago, IL, USA). Distribution of genotypes and alleles was compared by chi-square test. Clinical data were compared by one-way analysis of variance (ANOVA) and mean ±SD. Correlation between variables was tested by Spearman correlation coefficient. Statistical significance was defined as $P < 0.05$.

Results

The results of this study were shown and expressed as two groups; diabetic patients with cardiac autonomic neuropathy (CAN) and diabetic patients without CAN. There were no significant changes in gender, family history and history of the smoking between the study groups (P>0.05) (Table 2).

Table 2 Distribution of the study groups according to their demographic data.

Variable		Patients with CAN (n= 75)	Without CAN (n=28)
Gender	**male**	41%	13.5%
	female	32%	13.5%
Family history	**yes**	52%	22%
	No	20%	6%
Smoking	**yes**	11.88%	5.94%
	No	46.55%	15.84%
	Ex	14.85%	4.95%

CAN= Cardiac autonomic neuropathy**,** ex= previous smoker

All variables were expressed in percentage. P>0.05 for all variables.

Cardiac reflex test

Of the 103 diabetic patients, only 75 (72.8%) were presented with abnormal cardiac reflex tests. From the five tests that determine CAN score, the most abnormal sympathetic response was diastolic blood pressure (BP) response to hand grip while the most abnormal parasympathetic response was heart rate (HR) response to breathing. On contrary, the lowest abnormal response was found in postural BP test (Figure 1).

Cardiac autonomic neuropathy score was classified as follows: CAN score 0 (total points 0), CAN score 1 (points 0.5-1.5), CAN score 2 (points 2-3), and CAN score 3 (points ≥ 3.5). CAN was considered absent, early, definite, or severe if the CAN scores were 0, 1, 2, or 3, respectively (jung *et al*., 2012).

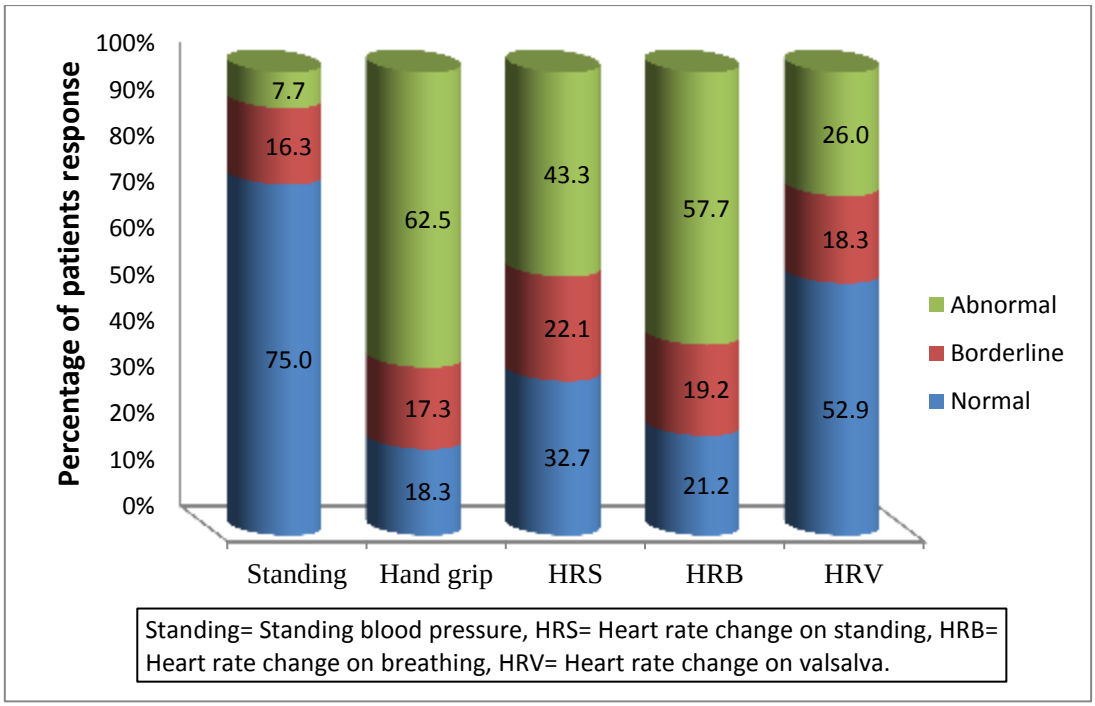

Figure 1 Prevalence of different cardiac autonomic tests.

From the whole study group, 26.2% have an early CAN (score 1), while most of the patients have definite CAN (score 3) (Figure 2).

The comparison was done between patients with CAN and those without CAN and showed a significant difference in heart rate response to breathing and heart rate response to valsalve (P< 0.01) (Table 2).

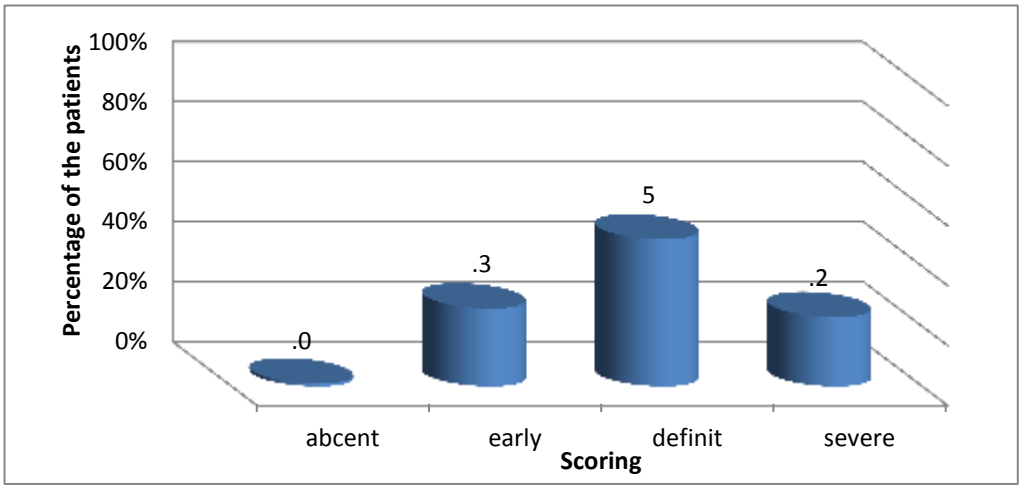

Figure 2 Scoring of cardiac autonomic neuropathy in diabetic patients.

Table 2 The results of the cardiac reflex tests in the study groups.

Parameter	Patients with CAN	Without CAN
Hand grip test	8.12 ±10.63	10.13 ±9.12
Standing BP test	7.56 ±10.68	4.8 ±7.7
30:15 ratio	0.9 ±0.15	1.02 ±0.22
E:I ratio	7.12 ±6.1	14.6 ±9.2 **
Valsalva ratio	1.16 ±0.19	1.38 ±0.18 **

CAN= cardiac autonomic neuropathy, BP= Blood pressure, 30:15 ratio= Heart rate response to standing, E:I ratio= Heart rate response to breathing,Valsalva ratio= Heart rate response to valsalva, Values are expressed in mean ± standard deviation.

** Significant difference (P value <0.01) between the study groups.

Distribution of patients and the prevalence of cardiac autonomic neuropathy according to the duration of the diabetes mellitus

The results showed that the prevalence of CAN increases in diabetic patients as the duration of DM increases (Figure 3).

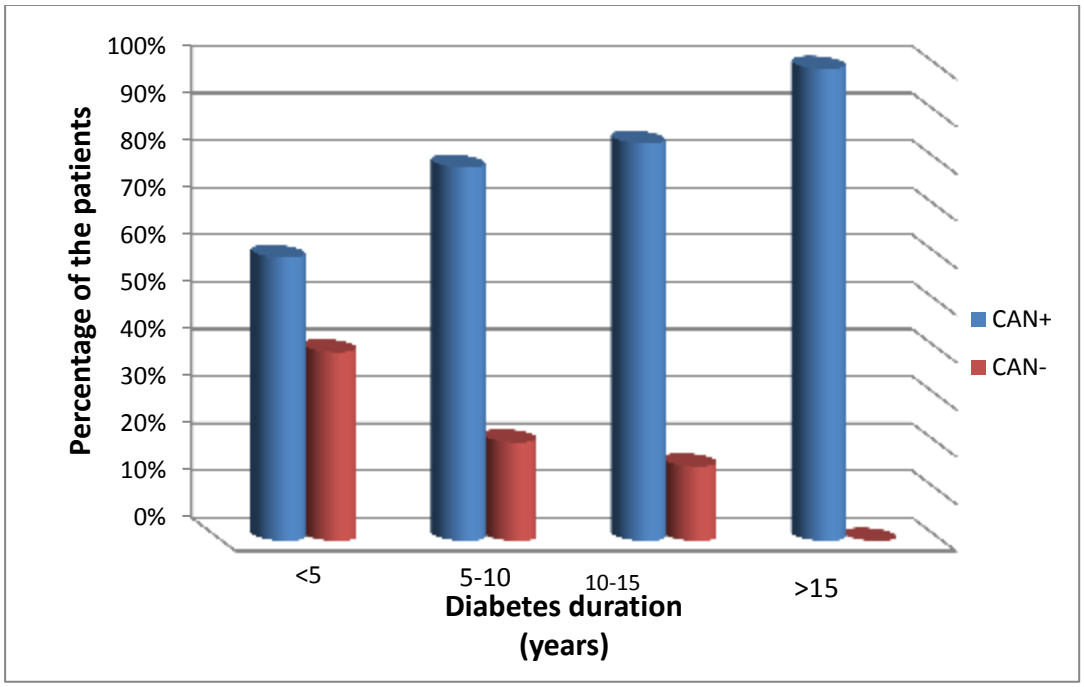

Figure 3: The prevalence of cardiac autonomic neuropathy in patients according to their diabetes duration.

There was significant direct correlation between standing BP with the duration of diabetes in which the orthostatic hypertension increases as the duration of diabetes increases (R= 0.23) (Figure 4). On the other hand, there was no significant correlation between hand grip test and duration of diabetes (Figure 5). Also, there were no significant correlations between heart rate variability in standing and in breathing with the duration of diabetes (Figure 6 and 7). On contrary, there was a significant indirect correlation between heart rate variability on valsalva maneuver with the duration of diabetes in which the ratio of valsalva decrease when the duration of diabetes increase (R= 0.29) (Figure 8).

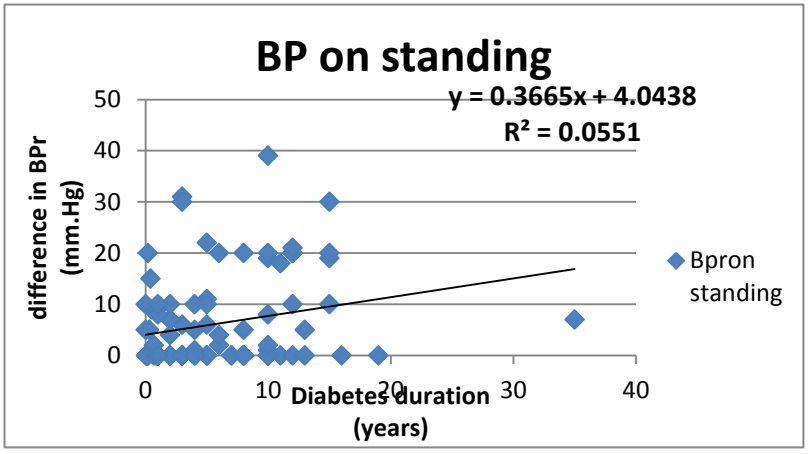

Figure 4 Correlation between orthostatic blood pressure and duration of diabetes.

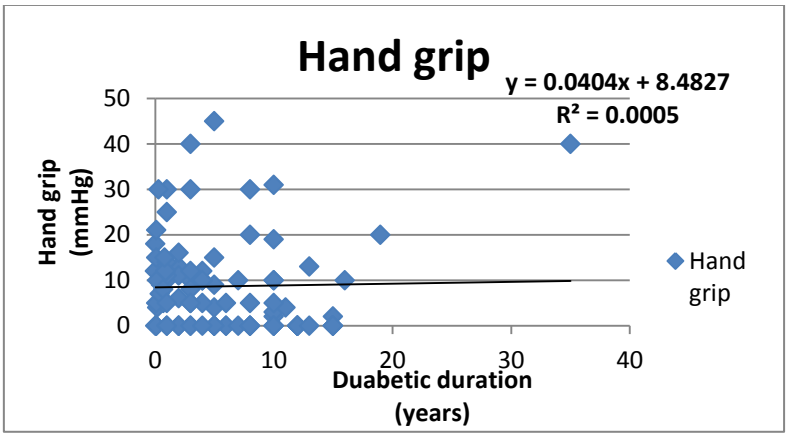

Figure 5 Correlation between hand grip blood pressure and duration of diabetes.

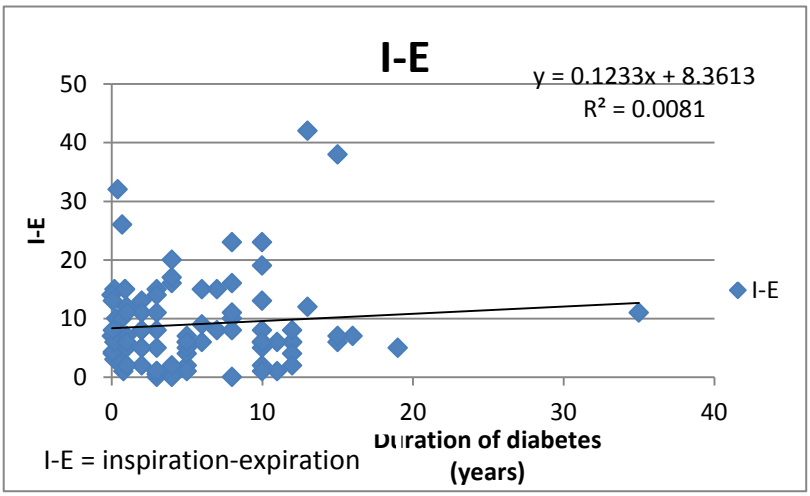

Figure 6 Correlation between heart rate on breathing and duration of diabetes**.**

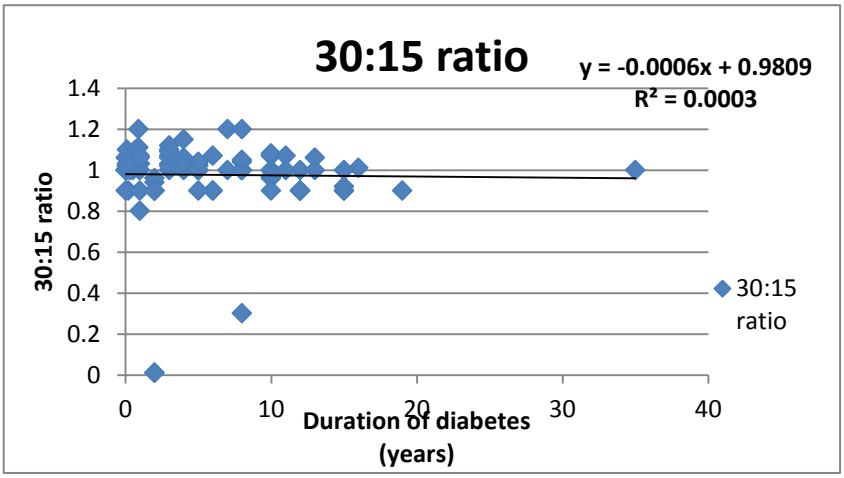

Figure7 Correlation between heart rate on standing and duration of diabetes

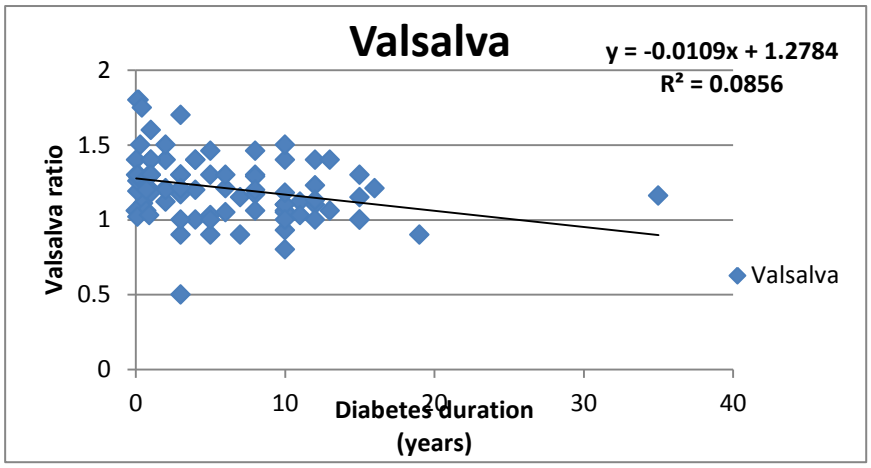

Figure 8 Correlation between valsalva ratio and duration of diabetes.

Discussion

Most of the diabetic patients in this study group (73.7%) had a positive family history with no significant changes between patients with and without cardiac autonomic neuropathy. Family history or genetic predisposition is considered as a non modifiable risk factor for type 2 diabetes mellitus (T2DM). It is likely that multiple gene variations acting on different metabolic functions leading to the development of this disease (Commonwealth Department of Health and Aged Care, 1999).

This result was agreed with Prabhakar and his co-workers in 2013 who found that most of the patients with T2DM had a positive family history of this disease independent to the presence or absence of autonomic neuropathy.

The absence of any impact of some variables as smoking on the presence or absence of cardiac autonomic neuropathy (CAN) might be attributed to the fact that most participating patients were non-smokers.

This finding was consistent with other studies that found that there are no correlations between smoking on heart rate variability (Jung *et al.*, 2012 and Falcone *et al.*, 2014). On the contrary, the results of Nan and his co-workers (2014) were inconsistent with the results of this study by finding a significant difference between BMI in patients with CAN and those without it.

The prevalence of the patients with CAN in the study group is 72.8% that is consistent with the results of Gerasimos and his co-worker in 2014, who reported CAN prevalence in patients with type 2 DM to be 20-73%. A meta-analysis of 2 published articles found that CAN prevalence among diabetic patients is 32.4% and the prevalence of clinically manifested CAN is 53.5 % (Jung *et al.*, 2012). Another study found a different prevalence rate of CAN among diabetes patients (42.6%) (Abbas and Akream, 2013). This difference in CAN prevalence may be due to the differences in the exclusion criteria, sample size and the tests used for the diagnosis.

In the current study, the most abnormal parasympathetic response is the heart rate (HR) response to breathing while the most abnormal sympathetic response is the diastolic pressure response to hand grip. A finding that is consistent with what Abbas and Akream had reported in 2013. Normally and during breathing, the HR increases in inspiration due to decrease in vagal activity and decreases in expiration. In CAN, this mechanism is defected leading to deccreased HR during both breathing phases (Piyali *et al.*, 2013). Going in the same direction, Tesfaye and his co-workers in 2005 reported that CAN can be diagnosed earlier by detecting HR variability and they considered this test as a strong indicator of mortality after myocardial infarction. Furthermore, another study found that the prevalence of CAN occurs in 70% of diabetic patients. In that study, patients with abnormal HR to breathing were 90%, those with abnormal HR to standing were 81%, while patients with abnormal response to HR to valsalva were 45% (Hussein *et al.*, 2011).

The lowest abnormal response in this study was the dropping of the blood pressure on standing indicating that postural hypotension occurs only in late stages of CAN (ADA, 1988). This was in accordance with the

results of other studies stating that of the five tests used to determine the CAN score, the postural blood pressure test yielded the fewest abnormal responses (Basu *et al.,* 2010, Jung *et al.,* 2012 and Abbas and Akream, 2013).

Vinik and Ziegler (2007) reported that abnormality in both hand grip test and valsava test usually refers to a combination of sympathetic and parasympathetic problems. Furthermore, Kashara and his co-workers (2006) reported that in normal people the cause of a sharp increase in the blood pressure during hand grip test resulted from a decrease in parasympathetic activity stimulated by contracting muscle which lead to subsequant increase in HR and blood pressure. This reflex did not occur in patients with CAN.

Distribution of patients and the prevalence of cardiac autonomic neuropathy according to the duration of the diabetes mellitus

Figure 3 showed that the percentage of patients affected by CAN was increased with a longer duration of diabetes. This is clearly seen as percentage of patients with CAN increased to 100% when the duration of the diabetes prolonged to more than 15 years.

This indicates that the duration of diabetes is a strong predictor of the prognosis of diabetes. A finding that a like that obtained by David and his co-workers (2012) who reported an increase in CAN prevalence as the duration of diabetes prolonged.

This relation of CAN prevalence with diabetes duration could be explained by the prolonged exposure to the metabolic abnormalities as the duration of DM increases (Vinik *et al.,* 2003). The diagnosis of DM might be delayed even for years which could be blamed for the abnormalities in the cardiac autonomic reflex tests in the newly diagnosed diabetic patients. Furthermore, increased concentration of oxidative stress may also play a role (Schmidt *et al.,* 2005 and Hoeldtke *et al.,* 2011).

The results showed that there is a direct correlation between blood pressure in standing and the duration of DM. While, no correlation is shown between the duration of diabetes from one side and the hand grip test, HR response in breathing and HR response in standing on the other side. Furthermore, there is a perfect indirect correlation between HR variability in valsalva maneuver with the duration of diabetes.

These findings could be explained by the fact that HR changes in breathing and standing is mostly parasympathetic that usually worsen early in diabetes. On contrary, HR response in valsalva is a combined sympathetic and parasympathetic response that may need long duration to be affected. This was partially consistent with that revealed by Nazeema and his co-workers (2010) and agreed with many other research such as Vinik and his co-workers (2003) and Vinik and Ziegler (2007). Going in the same direction\, David and his co-workers (2012) reported that the R-R interval in valsalva ratio decreased as diabetes duration prolonged. Despite that, Leila and her co-worker (1997) stated that hand grip test is neither sensitive nor specific test to autonomic neuropathy.

Conclusions

This study tested patients with type 2 diabetes mellitus (T2DM) and it concluded that cardiac autonomic neuropathy (CAN) is a common complication of that affects large percentage of these patients.

DM duration and patients' age are important non modifiable risk factors for the development of CAN and heart rate variability is an important test for early detection of CAN.

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