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Relationship Between Autonomic Diabetic Neuropathy and Glycemic Control

Otonom Diyabetik Nöropati ile Glisemik Kontrol Arasındaki İlişki

Gülşah Şahin[1], Mustafa Reşat Dabak[1], Gülbüz Sezgin[2], Can Dolapçıoğlu[3], Emel Ahıshalı[3], Oya Uygur Bayramiçli[4]

[1]İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, Clinic of Family Medicine
[2]İstanbul Maltepe University, Faculty of Medicine, Department of Internal Medicine
[3]İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, Clinic of Gastroenterology
[4]Private Office

Abstract
Objectives: To assess gastrointestinal and cardiovascular diabetic autonomic neuropathy in patients with type 2 diabetes mellitus (DM).
Materials and Methods: The study group composed of DM patients examined between March and September 2012. Age, body mass index (BMI), fasting blood glucose, HbA1c, C–peptide, duration of diabetes, electrocardiogram, blood pressure, heart rate were recorded. Patients were grouped as controlled and uncontrolled diabetics. Cardiac autonomic neuropathy (CAN) tests were done. Rectoanal inhibitory reflex, resting and squeeze pressures were measured by anal manometry.
Results: A total of 50 DM patients were enrolled and the mean age of patients was 57.06±8.92 years, the mean resting anal pressure was 55.92±14.84 mmHg, and squeezing anal pressure was 83.15±31.00 mmHg. There was no significantly different resting anal pressure between mild and severe CAN groups (p=0.573), but maximum squeezing pressure was significantly different between mild and severe CAN groups (p=0.005). Anal manometric pressures were not different in patients with short or long duration of diabetes. BMI was not associated with CAN, whereas age was. Bad glycemic control was associated with a decrease in resting pressures, but no significant difference between maximum squeeze pressures and insufficient glycemic control groups. Severity of CAN was associated with a decrease in maximum squeeze pressures.
Conclusion: Cardiac and gastrointestinal autonomic dysfunction are important complications of DM. Anal manometric tests and CAN may show these complications of diabetes.
Key words: Manometry, type 2 diabetes mellitus, diabetic autonomic neuropathy

Öz
Amaç: Tip 2 diabetes mellituslu (DM) hastalarda gastrointestinal ve kardiyovasküler diyabetik otonomik nöropatinin değerlendirilmesi amaçlanmaktadır.
Materyal ve Metot: DM hastalarından oluşan çalışma grubu Mart-Eylül 2012 tarihleri arasında incelendi. Yaş, vücut kütle indeksi (VKİ), açlık kan glukozu, HbA1c, C-peptid, diyabet süresi, elektrokardiyogram, kan basıncı, kalp hızı kaydedildi. Hastalar kontrol altında olan ve olmayan diyabetikler olarak gruplandırıldı. Kardiyak otonom nöropati (KON) testleri değerlendirildi. Anal manometri ile rekto-anal inhibitör refleks, istirahat ve sıkma basınçları ölçüldü.
Bulgular: Toplam 50 DM hastası çalışmaya kaydedildi ve hastaların yaş ortalaması 57,06±8,92 yıl, istirahat anal basıncı ortalaması 55,92±14,84 mmHg ve sıkma anal basıncı ortalaması 83,15±31,00 mmHg idi. Orta ve ağır KON grupları arasında istirahat anal basıncında anlamlı fark saptanmazken (p=0,573), orta ve ağır KON grupları arasında maksimum sıkma basıncında anlamlı fark mevcuttu (p=0,005). Kısa veya uzun süreli diyabeti olan hastalarda anal manometrik basınçlarda fark saptanmadı. KON ile VKİ arasında ilişki bulunmazken yaş ile ilişki saptandı. Kötü glisemik kontrol istirahat basında azalma ile ilişkili iken, maksimum sıkma basıncı ve yetersiz glisemik kontrol grubu arasında ilişki yoktu. KON'un şiddeti maksimum sıkma basıncında azalma ile ilişkiliydi.
Sonuç: Kardiyak ve gastrointestinal otonom disfonksiyon, DM'nin önemli komplikasyonlarıdır. Anal manometri testleri ve KON diyabetin bu komplikasyonlarını gösterebilir.
Anahtar kelimeler: Manometre, tip 2 diabetes mellitus, diyabetik otonom nöropati

Correspondence / Yazışma Adresi:
Dr. Mustafa Reşat Dabak
Kartal Dr. Lütfi Kırdar Training and Research Hospital, Clinic of Family Medicine, İstanbul
e-mail: resat_dabak@hotmail.com
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Introduction

Diabetic autonomic neuropathy (DAN) is a serious and frequent complication of diabetes mellitus which increases with diabetic age. DAN effects many organ systems like gastrointestinal, cardiovascular, genitourinary systems and can be clinical or subclinical but is a major cause of morbidity in patients with type 2 diabetes mellitus (DM).[1,2] Despite its relation to high cardiovascular death rate, its significance is still not completely understood.[2] In a study on patients with CAN, it has been found that the risk of silent myocadial infarction and mortality is increased.[1] Five year mortality rate is three times higher in patients with DAN in comparison to diabetic patients without DAN.[3] In this study, we evaluated the frequency of gastrointestinal and cardiovascular diabetic autonomic neuropathy in DM patients and their correlation with the control of glycemia and duration of diabetes.

Materials and Methods

The study group composed of type 2 DM patients, age between 45 and 75 years, who visited our clinic between March and September 2012. All participants had anal manometry performed at the department of gastroenterology.

Blood is drawn from all the patients after an 8 hour overnight fasting and looked for fasting blood glucose level, HbA1c, C–peptide. The duration of diabetes, age and BMI are recorded. Cardiac autonomic neuropathy (CAN) tests are done while being monitored on a 12-lead ECG and blood pressure is recorded. ECG recordings are done with a digital ECG device (Schiller CS-200 ECG Machine) and blood pressure is measured with a properly calibrated Blood Pressure arm device model (Omron M2). During CAN tests, the patient is kept at rest for 5 minutes in a quiet room and than blood pressure is recorded from both arms and during maneuvers, systolic and diastolic blood pressures are taken with the same device. A handgrip blood pressure device is used for necessary measurements. For the evaluation of CAN tests, a scoring system as follows is used: normal is 0, borderline is 0.5 and abnormal is 1. If the overall score of five tests is 0-0.5 points, CAN is regarded as normal; between 1-2.5 points are accepted as a moderate abnormality and a score of 3-5 is regarded as severe abnormality in CAN tests. Anal manometry is performed with MMS SOLAR GL Clinical innovations-Sandhill Model: Latitude 4 channels device (Air Charged). In this method, manometry devices with pressure sensitive catheters are used and resting, squeeze pressures and rectoanal inhibitory reflex (RAIR) is measured as decribed in the literature.

Exclusion criteria were as follows: psychiatric disease necessitating drugs, trauma to anal region (accidents, gunshot or stabwounds, falls), history of previous perianal surgery, abuse of laxatives, history of infectious colitis and inflammatory bowel disease, rectal and prostatic carcinoma, rectal prolapsus and procidentia, rectocel, multiple

sclerosis, stroke, cerebral and spinal tumors and history of radiation therapy. Informed consent is taken after detailed oral and written information.

The data were evaluated using SPSS 22.0 program. Student t-test and Spearman correlation analyses were performed for continuous variables and the results were presented as frequency, mean ± standard deviation, percentage and median. In additional, Mann Whitney U test was used for the comparison of abnormal distributed quantitative data. Comparison of quantitative data is perfomed using Chi-square test. p values <0.05 were considered statistically significant for all tests. Ethical approval was obtained from the Institutional Review Board (Dated 13 November 2012, No:93).

Results

The study is carried out on 50 patients with DM. The mean age was 57.06±8.92 years, the mean BMI was 31.46±5.16 kg/m², and the median duration of diabetes was 11.00 (1.00-32.00) years. Thirty-six (72.00%) of the patients were female and the median number of birth 3.00 (0.00-6.00) in the female diabetic patients. Patients were also classified by diabetic status, 25 (50.00%) patients had HbA1c below 7%, 20 (40.00%) patients had HbA1c 7-9%, and 5 (10.00%) patients had HbA1c above 9%. In addition, the mean resting pressure was 55.92±14.84 mmHg, squeeze pressure was 83.15±31.00 mmHg, and the median RAIR was 45.00 (0.00-77.00) mmHg. The relation between cardiac autonomic neuropathy and age, BMI, fasting blood glucose, HbA1c, C-Peptid, duration of diabetes are summarized on Table 1.

Table 1.The relation between cardiac autonomic neuropathy and age, BMI, fasting blood glucose, HbA1c, C-Peptid, duration of diabetes

	Mild CAN (n=36)	**Severe CAN(n=14)**	
	n (%)	**n (%)**	**p***
Gender Female Male	26 (72.20) 10 (27.80)	10 (71.40) 4 (28.60)	0.607
	Mean (SD)	**Mean (SD)**	**p†**
Age (years)	56.19±9.43	59.29±7.31	0.227
BMI (kg/m²)	31.41±5.52	31.60±4.26	0.901
Fasting blood glucose (mg/dl)	136.36±44.70	142.93±58.80	0.710
Hb1Ac (%)	7.27±1.39	7.30±1.34	0.959
	Median (min-max)	**Median (min-max)**	**p‡**
C-Peptid (ng/ml)	1.74 (0.10-15.17)	1.80 (0.34-3.81)	0.991
Duration of diabetes (years)	10.50 (1.00-32.00)	12.00 (6.00-28.00)	0.204

*Fisher's Exact Test, †Student's t-test ‡Mann Whitney U Test, BMI: Body Mass Index, CAN: Cardiac Autonomic Neuropathy

Thirty-six (72.00%) of the patients had mild CAN and 14 (28.00%) had severe CAN. There was no statistically significant difference in age, BMI, fasting blood glucose, HbA1c, treatment modality in regard of CAN results (p>0.05). The relation between cardiac autonomic neuropathy tests and in subgroups of glycemic control is shown on Table 2.

Table 2. The relation between cardiac autonomic neuropathytests and in subgroups of glycemic control

		Glycemic control		p
		Good control (n=25)	Insufficient control (n=25)	
Test – 1; Mean±SD		1.22±0.16	1.17±0.11	0.234*
	Normal; n(%)	11 (44.00)	11 (44.00)	
	Borderline; n(%)	8 (32.00)	7 (28.00)	
	Abnormal; n (%)	6 (24.00)	7 (28.00)	
Test- 2; Mean±SD		12.46±5.25	11.69±6.78	0.658*
	Normal; n (%)	9 (36.00)	8 (32.00)	
	Borderline; n (%)	5 (20.00)	3 (12.00)	
	Abnormal; n(%)	11 (44.00)	14 (56.00)	
Test- 3; Mean±SD		1.03±0.05	1.06±0.11	0.262*
	Normal; n (%)	14 (56.00)	15 (60.00)	
	Anormal; n(%)	11 (44.00)	10 (40.00)	
Test- 4; Median(min-max)		4.00 (-37.00-18.00)	2.00 (-23.00-56.00)	0.838†
	Normal; n (%)	18 (72.0)	19 (76.00)	
	Bordeline; n (%)	7 (28.0)	4 (16.00)	
	Abnormal; n (%)	0 (0)	2 (8.00)	
Test- 5; Median(min-max)		13.00 (-17.0-75.0)	13.00 (-5.0-38.0)	0.566†
	Normal; n (%)	9 (36.0)	9 (36.00)	
	Borderline; n (%)	8 (32.0)	5 (20.00)	
	Abnormal; (%)	8 (32.0)	11 (44.00)	

*Student's t Test, †Mann Whitney U Test

There was no statistically significant difference between the groups in regard of diabetes duration (p>0.05). Regarding the duration of diabetes there was no statistically significant difference in CAN tests between the groups (p>0.05). Cardiac autonomic neuropathy tests in subgroups according to the duration of diabetes are summarized on Table 3.

Table 3. Cardiac autonomic neuropathytests in subgroups according to the duration of diabetes

		Duration of diabetes		p
		5-10 years (n=16)	> 10 years (n=34)	
Test – 1; Mean (SD)		1.18±0.08	1.20±0.16	0.567*
	Normal; n (%)	6 (37.50)	16 (47.10)	
	Borderline; n (%)	8 (50.0)	7 (20.60)	
	Abnormal; n (%)	2 (12.50)	11 (32.40)	
Test- 2; Mean (SD)		13.38±5.51	11.50±6.23	0.299*
	Normal; n (%)	9 (56.25)	8 (23.50)	
	Borderline; n (%)	1 (6.25)	7 (20.60)	
	Abnormal; n (%)	6 (37.50)	19 (55.90)	
Test- 3; Mean (SD)		1.06±0.11	1.03±0.07	0.353*
	Normal; n (%)	11 (68.8)	18 (52.90)	
	Abnormal; n (%)	5 (31.3)	16 (47.10)	
Test- 4; Median(min-max)		-1.50 (-37.00-18.00)	5.00 (-23.00-56.00)	0.134†
	Normal; n (%)	12 (75.00)	25 (73.50)	
	Borderline; n (%)	4 (25.00)	7 (20.60)	
	Abnormal; n (%)	0 (0.00)	2 (5.90)	
Test- 5; Median (min-max)		12.00 (-17.00-37.00)	13.00 (-5.0-75.0)	0.708†
	Normal; n (%)	5 (31.30)	13 (38.20)	
	Borderline; n (%)	4 (25.00)	9 (26.50)	
	Abnormal; n (%)	7 (43.80)	12 (35.30)	

*Student's t Test, †Mann Whitney U Test

The mean resting pressure was 56.60±15.95 mmHg and the mean maximum squeeze pressure was 89.65±33.01 mmHg in mild CAN. In addition, the mean resting pressure was 54.21±11.99 mmHg and the mean maximum squeeze pressure was 67.36±18.16 mmHg in severe CAN. There was no significantly different resting anal pressure between mild and severe CAN groups (p=0.573). On the other hand, there was significantly different maximum squeeze pressure between mild and severe CAN groups (p=0.005).

The mean resting pressure was 59.16±14.58 mmHg in the good glycemic control group and 52.54±14.65 mmHg in the insufficient glycemic control group (p=0.041). In addition, the mean maximum squeeze pressure was 86.74±25.63 mmHg in the good glycemic control group and 79.84±34.45 mmHg in the insufficient glycemic control group (p=0.441). The median RAIR was 47.00 (0.00-74.00) mmHg in the good glycemic control group and 38.00 (0.00-77.00) in the insufficient glycemic control group (p=0.698). When patients were evaluated according to the duration of diabetes, there was no statistically significant difference in resting and squeeze pressures and RAIR in patients with short or long duration of diabetes but pressures were lower in patients with a longer history of diabetes (p=0.134, p=0.371 and p=0.625, respectively).

Discussion

Cardiovascular diseases are seen three times more frequent in DM.[4] The presence of DAN is associated with cardivascular mortality and other mortality causes.[1,5] This study aimed to evaluate the frequency of gastrointestinal and cardiovascular diabetic autonomic neuropathy in DM and their correlation with the control of glycemia and duration of diabetes.

In previous studies due to insufficient standartization of CAN tests, the prevalence of CAN was found to be between 1% and 90%.[5] Veglio et al reported a prevalence of 66.5% for CAN, Murray et al 60%.[6,7] Ewing et al followed up 534 diabetic patients for 10 years and found out a CAN prevalence of 60%.[8] Diabetes Control and Complication Trial (DCCT) showed a prevalence of 6.2 % for CAN, and another study reported it as 6.2 % but in diabetics who had a pancreas transplantation, the prevalence of CAN was 90%.[7,9,10] The prevalence of CAN is reported as 34 % by Ziegler, as 60 % by Pappachan, as 57.5 % by Mehta, as 62 % by Tentolouris and 67.6 % by Thi.[11,12] In our study 46 (92%) of the diabetic patients had mild and severe CAN.

BMI wasn't reported as a risk factor for CAN, but in some studies, obesity was a risk factor for CAN.[6,9,13,14] In our study, BMI was not associated with CAN. In most of the studies age is a risk factor for CAN but there was no correlation between age and CAN.[6] Another factor which is strongly associated with CAN is the duration of diabetes. Chen HS et al showed in 2001 that CAN prevalence was 46.1% in patients with a disease duration less than 5 years, but 69.4% in patients with a disease duration over 20 years.[15] Another study also found a correlation with the duration of diabetes and CAN.[1] Disease duration of 10 years and more in type 1 and 2 diabetes increases the risk of CAN.[11,16] Another study reported that with the duration of diabetes the frequency of neuropathy increases.[2] In patients with DM for less than five years, the prevalence of neuropathy is 20.8%, but in patients with DM for more than ten years it is 36.8%.[17] Longterm hyperglycemia is the main culprit of the development of diabetic neuropathy.[1,2] There was no relation between duration of diabetes and levels of CAN.

Besides, in the study group there is no statistically significant correlation between the duration of diabetes and the presence of neuropathy ($p>0.05$), but the duration of diabetes was longer in patients with severe CAN in comparison to patients with mild diabetes anyway. These findings confirm the necessity of performing CAN tests in diabetic clinics routinely. Studying larger number of patients can possibly show the effect of diabetes duration on CAN. On the other hand, it is well known that higher Ewing scores mean an increase in the severity of neuropathy.[11] According to longterm data of Rochester Diabetic Neuropathy Cohort Study, the exposure time and severity of hyperglycemia is only accociated with the severity of neuropathy.[18]

Gastrointestinal problems of diabetic patients are quite frequent and are probably caused by peripheric neuropathy.[2] They are mostly seen in patients with longer disease duration and bad glycemic control.[1,2] Constipation alternating with diarrhea and megacolon is seen.[19] Schiller et al found fecal incontinence in 20 % of patients with DM.[20]

Deen et al found RAIR dysfunction in all the diabetic patients with fecal incontinence but there was no significant change in comparison to control groups.[21] In a study by Rogers et al in diabetic patients with fecal incontinence, the resting and squeeze pressures were significantly decreased in comparison to control group.[22] Russo et al said that; with an increase in blood glucose level, there is a statistically significant decrease in resting and maximum squeeze pressures.[23] In our study, resting pressure was significantly higher in the good glycemic control group than in the bad glycemic control group. However, even if not statistically significant, maximum squeeze pressure and RAIR were lower in the bad glycemic control group.

When we compare resting pressure, maximum squeeze pressure, RAIR and disease duration, pressures decreased in the long-term disease group, but these decreases were not statistically significant.

Our limitation was that female patients have possible secondary anal problems after childbirth.

In conclusion, we can say that CAN tests are sensitive, noninvasive and easily appliable to diabetic patients. Anal manometric tests can also give clues of the gastrointestinal neuropathic complication of DM. Earlier detection of cardiac and gastrointestinal autonomous dysfunction could lead to better glycemic control. Further randomised and prospective studies on larger patient groups are needed.

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