ORIGINAL ARTICLE

Cardiac Autonomic Neuropathy and Left Ventricular Hypertrophy in type-II diabetic patients

KRANTHI KUMAR GARIKAPATI[1], YOGESH TRIPATHI[2], RINKU GARG[3], BINDU GARG[4]
[1]*Ph.D. Scholar, Department of Physiology, Santosh deemed to be University, Ghaziabad.*
[2]*Professor & Head, Department of Physiology, School of Medical Sciences and Research, Greater Noida*
[3]*Professor & Head, Department of Physiology, Santosh deemed to be University, Ghaziabad*
[4]*Professor & Head, Department of Physiology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly.*
Corresponding author: Mr. Kranthi Kumar Garikapati, Ph.D. Scholar, Department of Physiology, Santosh deemed to be University, Ghaziabad. Email Id: kranthigarikapati86@gmail.com,

ABSTRACT

Introduction: Cardiac autonomic neuropathy (CAN) is a frequent and intractable complication of diabetes. Reduction in heart rate variability (HRV) is the first sign of CAN in its subclinical stage. Autonomic imbalance and hyperglycaemia in diabetes are associated with cardiovascular structural and functional modifications which lead to left ventricular hypertrophy (LVH). The study was undertaken to assess the changes in HRV and left ventricular mass in type 2 diabetes mellitus (T2DM) patients.

Material and methods: The case-control study was conducted on 78 T2DM subjects and 78 age & sex-matched healthy controls. CAN was assessed by frequency and time-domain parameters of HRV and LVH was measured using various ECG criteria including Cornell voltage, Cornell product, Sokolow-Lyon voltage, and Romhilt-Estes point score.

Results: All the frequency and time-domain parameters of HRV except resting heart rate, normalized LF, and LF/HF ratio were significantly reduced in T2DM patients compared to healthy controls. The prevalence of ECG-LVH was 25.7% using any single criteria and 12.2% with all the criteria. The highest prevalence (24.3%) was noted with Cornell product and Sokolow-Lyon voltage criteria followed by Romhilt-Estes point score (17.6%), and Cornell voltage criteria (16.2%).

Conclusion: Reduction in overall HRV with less high-frequency power and high LF/HF ratio are suggestive of parasympathetic dysfunction and sympathetic predominance. A significant LVH was noted with ECG-based electric criteria in T2DM patients. The study suggests that T2DM patients should be subjected to diagnostic HRV and ECG to identify the early occurrence of CAN and LVH.

Keywords: Cardiovascular autonomic neuropathy; Heart rate variability; Left ventricular hypertrophy; Type 2 diabetes mellitus.

INTRODUCTION

Cardiac autonomic neuropathy (CAN) is a frequent and insidious complication of diabetes with a poor prognosis on long-standing. The clinical manifestations associated with CAN in diabetes result in cardiovascular morbidity and mortality. CAN is an established predictor of silent myocardial ischemia and subsequent cardiovascular events in type 2 diabetes mellitus (T2DM) (1). Cardiovascular disease (CVD) is the leading cause of death in patients with DM with two to four times higher occurrence in comparison with the general population (2).

The cardiac ability to regulate beat-to-beat variation in heart rate in response to various metabolic needs is an indicator of good health and is under the control of cardiac autonomic nerves. Further, the autonomic nerves are also regulating the myocardial contractility, cardiac output, electrophysiology of heart, and vascular dynamics. CAN damages the autonomic nerves that innervate the heart and blood vessels leading to a multitude of problems. (3).

Disturbance in the control of high variability due to CAN reflects as a reduction in HRV as the first finding (3). Sympathetic predominance and parasympathetic dysfunction occur due to damage to the vagus nerve in the early stages of CAN. An increase in sympathetic tone continues until CAN progresses to the advanced stage and ensues sympathetic denervation. Parasympathetic dysfunction reflects as the reduction in high-frequency power and sympathetic predominance increases LF/HF ratio in early stages of CAN (2).

After the onset of diabetes, myocardial tissue undergoes many structural and functional modifications that lead to diabetic cardiomyopathy. Autonomic imbalance is one of the factors that accelerates atherosclerosis in T2DM. Accumulation of lipids and subsequent metabolic disbalance contribute to the ventricular dysfunction in diabetes (4). CAN also contributes to cardiomyopathy in diabetes by altering myocardial blood flow, sympathetic denervation, and change in myocardial neurotransmitters (5). Left ventricular hypertrophy (LVH) is strongly associated with T2DM independent of various covariates and also a strong predictor of cardiovascular disease (6).

LVH diagnosis can be made using electrocardiography, echocardiography, and cardiac MRI Electrocardiography being a very simple, easily available, and affordable investigation has been extensively used for the LVH diagnosis. Cornell voltage criteria, Sokolow-Lyon voltage criteria, and Romhilt-Estes point score system are the most common ECG-based criteria used to assess LVH (7). Increased voltage criteria are diagnostic of LVH and can be observed in the early course of diabetes. Early detection of ANS dysfunction and cardiac changes with timely intervention can revert the natural course of progression of CAN and delay the adverse cardiac events (8). Hence, the present study was undertaken to assess the HRV and ECG-LVH in type-2 diabetic patients.

MATERIAL & METHODS

The present case-control study was carried out in the diabetic clinic of the General Medicine department in a tertiary care hospital, Uttar Pradesh, India. The study subjects consisted of 74 type-II diabetic patients of both sexes, aged between 30 to 65 years. Seventy-four age and sex-matched healthy subjects were taken as a control group. Institutional ethics committee approval was obtained and written informed consent was taken from all the study subjects in accordance with the Helsinki Declaration of 1975 (revised in 2013).

Inclusion criteria: Type-II diabetes patients diagnosed in accordance with the criteria of the World Health Organization (WHO), under the treatment (9).

Exclusion criteria: Patients with hypertension, electrocardiographic evidence or history of any cardiovascular diseases, electrolyte imbalance, history of renal failure, endocrine abnormalities, neurological disorders, history of asthma, patients on any medication known to affect the heart rate variability, smokers, alcohol abusers, menstruating, pregnant and lactating women were excluded from the study.

Subjects were recruited based on the selection criteria and were instructed to refrain from vigorous physical activity or heavy exercise for at least 24 hours preceding and avoid coffee, tea, or heavy meal at least 2 hours prior to the reporting in the autonomic function test lab on their subsequent visit in the forenoon. The test procedure was conducted between 8:30 AM and 12 Noon in a well-controlled ambient temperature.

Biochemical parameters including fasting blood sugar (FBS) and glycated hemoglobin (HbA1c) values were recorded from the patients record file. Anthropometric parameters like height, weight, waist circumference, and hip circumference were measured while the subjects wore light clothing, and emptied urinary bladder prior to the measurement. Body mass index (BMI), body surface area (BSA), and waist-hip ratio (WHR) were calculated from the above measurements.

Analysis of HRV: After a rest of 15 minutes, a continuous 20 minutes Lead-II ECG was recorded and stored for later analysis using Lab Chart ECG analyser of data acquisition software, Power lab 26T-ML4856, AD Instruments (Australia) at a sampling frequency of 1KHz. The last 5 minutes artifact-free ECG recording was used to analyse short-term frequency-domain and time-domain variables using the HRV module of the LabChart Pro analyzer (v 8.1.16).

The frequency-domain variables of the power spectrum were obtained using Lomb-Scargle Periodogram. The frequency-domain parameters consisted of total power (TP: 0-0.40 Hz): it represents the overall autonomic activity; very low frequency (VLF: below 0.04Hz): denotes the parasympathetic activity; low frequency (LF: 0.04–0.15Hz) reflects sympathetic control with parasympathetic modulation and high frequency (HF: 0.15–0.40Hz) power in absolute values (ms^2), LF & HF components were also obtained in normalized units and as a ratio (LF/HF ratio): which is an indicator of the balance between sympathetic and parasympathetic activity.

The time-domain parameters of HRV include mean R-R interval, the standard deviation of all normal R-R intervals (SDNN), the square root of the mean squared differences between consecutive R-R intervals (RMSSD), the standard deviation of successive differences (SDSD), and percentage of consecutive normal R-R intervals that differ by >50 ms (pNN50); in which, mean R-R interval & SDNN denotes overall HRV which represents both sympathetic and parasympathetic activity, and RMSSD & pNN50 correlates the HF component hence represents the parasympathetic activity (10).

Recording of electrocardiography: Resting 12 Lead ECG was recorded in lying position using Clarity Med ECG 100D- 3 channel electrocardiograph. The recording was done at a paper speed of 25 mm/second with a voltage gain setting at 10mm/mV.

LVH diagnosis: It was done using the following criteria:

1. Cornell voltage criteria: SV3 + RaVL is ≥ 2.8 mV in men and ≥ 2.0 mV in women.
2. Sokolow–Lyon voltage criteria: SV1 + RV5 or RV6 ≥ 3.5 mV or RaVL ≥ 1.1 mV.
3. Cornell product: SV3 + RaVL (+ 6 mm in women) x QRS duration ≥ 2,440 mm × msec
4. Romhilt-Estes point score system:

ECG features for Romhilt-Estes point score system	Points
1. Voltage criteria (presence of any of the following): S wave or R wave in any limb lead ≥ 20 mm; S wave in V1 or V2 ≥ 30 mm; R wave in V5 or V6 ≥ 30 mm	3
2. ST-T wave changes (LV strain): ST-segment and T wave in opposite direction to QRS in V5 or V6 (without digitalis)	3
3. Left atrial abnormality (P terminal force): Terminal negative deflection of the P wave in V1 ≥ 1 mm (0.1mV) and ≥ 40 ms in duration	3
4. Left axis deviation: Mean electrical axis (QRS axis) ≤ −30°	2
5. Prolonged QRS duration ≥ 0.09 sec	1
6. Delayed intrinsicoid deflection time in V5 or V6 ≥ 50 msec	1
a score of ≥5 is positive for LVH (11).	

Statistical analysis: Data analysis was done using the Statistical Package of Social Science (SPSS) version 20.0. The qualitative data were expressed as frequency and percentages. Normally distributed quantitative data comparison between groups was done using student t-test (independent), and Mann–Whitney U-test was performed for comparison between groups of non-normally distributed data. Statistically significant was considered when the p-value was <0.05.

RESULTS

Seventy-four T2DM subjects and 74 healthy controls were studied for the assessment of HRV and LVH. Table 1 shows the comparison of demographic and glycemic parameters between the two study groups. Observations showed a statistically significant difference in weight (p= 0.000), BMI (p< 0.001), BSA (p< 0.001), WC (p< 0.001), WHR (p< 0.001), FBS (p< 0.001) and HBA1c (p< 0.001) with higher values in the T2DM subjects as compared to the controls. The mean duration of diabetes was noted as 6.75 (± 4.02) years.

Table 2 shows the comparison of short-term recording of frequency and time-domain HRV parameters between

the two study groups. A statistically significant higher value of heart rate (p< 0.001) was noted in the T2DM subjects. Further, a statistically significant difference (p< 0.001) was noted in frequency-domain parameters with lower values of total power, VLF, HF, LF in absolute units, normalized HF, and higher values of normalized LF & LF/HF ratio in T2DM subjects compared with healthy controls. All time-domain parameters (SDNN, SDSD, RMSSD & pNN50) showed a statistically significant difference (p< 0.001) with lower values in the diabetic group compared to the control group.

The prevalence of LVH with different ECG criteria between the two study groups was shown in Table 3. The highest prevalence of LVH was noted with Cornell product & Sokolow-Lyon voltage criteria (24.3% each) followed by Romhilt-Estes point score criterion (17.6%) and Cornell voltage criteria (16.2%). All measured criteria for LVH were noted positive in 12.2% of the diabetic subjects and any single criterion was positive in 25.7% of T2DM patients. LVH was observed in 4.1% of the healthy controls with both Cornell product & Sokolow-Lyon voltage criteria.

Table 1: Comparison of demographic and glycemic parameters between controls and T2DM subjects

Parameters	Controls (N=74)	T2DM subjects (N=74)	p-value
Age (years)	51.93 ± 5.43	51.97 ± 5.21	0.963
Weight (Kg)	63.89 ± 5.96	73.06 ± 7.76	< 0.001*
BMI (Kg/m²)	23.05 ± 1.88	26.50 ± 2.15	< 0.001*
BSA (m²)	1.71 ± 0.11	1.81 ± 0.13	< 0.001*
WC (cm)	86.64 ± 6.72	99.22 ± 10.50	< 0.001*
HC (cm)	96.04 ± 5.86	94.55 ± 4.62	0.089
WHR	0.90 ± 0.06	1.05 ± 0.10	< 0.001*
Duration of T2DM (yrs)	---	6.75 ± 4.02	---
FBS (mg/dl)	90.31 ± 6.78	131.41 ± 24.99	< 0.001*
HBA1c (%)	5.81 ± 0.41	8.10 ± 1.04	< 0.001*

*Statistically Significant. Data expressed as mean ± SD. BMI: Body mass index, BSA: Body surface area, WC: Waist circumference, HC: Hip circumference, WHR: Waist hip ratio, FBS: Fasting blood sugar; HBA1c: Glycosylated haemoglobin.

Table 2: Comparison of short-term HRV parameters between groups

HRV Parameters	Controls (N=74)	T2DM subjects (N=74)	Mann-Whitney U	p-value
Heart rate (b/min)	75.13 ± 8.87	91.80 ± 11.41	674.5	< 0.001*
Frequency-domain parameters				
Total power (ms^2)	1605.46 ± 989.95	433.35 ± 425.65	629	< 0.001*
VLF (ms^2)	491.48 ± 382.98	209.72 ± 188.68	1227	< 0.001*
LF (ms^2)	428.70 ± 323.71	141.88 ± 151.97	931	< 0.001*
HF (ms^2)	651.51 ± 515.39	80.79 ± 129.70	389	< 0.001*
LF (nu)	41.12 ± 12.46	70.21 ± 11.46	258	< 0.001*
HF (nu)	55.93 ± 12.00	29.63 ± 10.96	323	< 0.001*
LF/HF ratio	0.81 ± 0.43	2.87 ± 1.47	254	< 0.001*
Time-domain parameters				
SDNN (ms)	38.49 ± 12.23	19.16 ± 9.26	575.5	< 0.001*
SDSD (ms)	34.86 ± 13.89	10.67 ± 7.59	348	< 0.001*
RMSSD (ms)	34.95 ± 13.96	10.66 ± 7.58	348	< 0.001*
pNN50 (%)	15.07 ± 13.66	0.64 ± 1.77	403.5	< 0.001*

*Statistically Significant. Values expressed as mean ± SD. VLF: Very low-frequency power; LF: Low-frequency power; HF: High-frequency power; nu: normalized units; ms^2: square milliseconds; SDNN: Standard deviation of all R-R intervals; SDSD: Standard deviation of successive differences; RMSSD: Square root of the mean squared differences between consecutive R-R intervals; pNN50: percentage of consecutive RR intervals that differ by >50 ms.

Table 3: Prevalence of left ventricular hypertrophy (LVH) between the study groups.

ECG Criteria	Controls (N=74)		T2DM subjects (N=74)	
	No. of cases	Percentage (%)	No. of cases	Percentage (%)
Cornell voltage	0	0	12	16.2
Cornell product	3	4.1	18	24.3
Sokolow-Lyon voltage	3	4.1	18	24.3
Romhilt-Estes point score	0	0	13	17.6
All criteria positive for LVH	0	0	9	12.2
Anyone criterion positive for LVH	3	4.1	19	25.7

DISCUSSION

The present study was aimed to assess the HRV and LVH in diabetic subjects to identify CAN and LVH, which are strong and independent predictors of adverse cardiac events. Recruitment of the healthy controls was matched with the age of the study group to avoid any age-related changes which could affect the results. The study noted higher weight, BMI, BSA, WC, and WHR in T2DM subjects when compared to healthy controls. Vasanthakumar J et al., in their community-based cross-sectional study, noted a

high prevalence of generalized obesity (measured by BMI), central obesity (measured by WC), and combined obesity in T2DM patients. Higher BMI has been noted as an important risk factor for the development of CAN along with the duration of diabetes and degree of hyperglycemia. (13).

Further, the study noted that all the frequency and time-domain parameters of HRV including absolute units of TP, VLF, HF, LF, normalized HF, SDNN, RMMSD, SDSD & pNN50 were significantly reduced, and resting heart rate, normalized LF & LF/HF ratio were significantly increased in diabetic subjects compared with controls. Pramodh V et al., and Mirza M et al., also observed similar results of heart rate and HRV parameters in their respective studies. Kudat H et al., reported lower values of both frequency and time-domain HRV parameters but, no significant difference was noted in LF/HF ratio between diabetic subjects and controls. This could be due to comparable changes in both LF & HF parameters. In frequency-domain parameters of HRV, decrease in HF power and increase in LF/HF ratio are the indicators of parasympathetic dysfunction and sympathetic predominance respectively; whereas in time-domain parameters, reduction in RMSSD & pNN50 is the sign of parasympathetic impairment and decrease in SDNN is indicative of a reduction in total power. Reduction in HRV is the earliest clinical indicator of CAN and a strong & independent predictor of increased mortality after acute myocardial ischemia. A rise in resting heart rate is another independent predictor of all-cause mortality (10). The decreasing trend of frequency-domain parameters of HRV has been noted right from the diagnosis of T2DM (17).

In the present study, the prevalence of LVH in T2DM patients with standard ECG criteria used in the study was 25.7% with anyone of the criteria and 12.2% with all the criteria. Jobe M et al., noted 35.2% of LVH with combined ECG criteria. In individual criteria, they recorded 24.6% with Cornell voltage and 12.8% with Sokolow-Lyon voltage. Lutale JJK et al., in their study on diabetic patients of Tanzania, noted an overall 16% prevalence of ECG-LVH. Further, they observed a prevalence of 12.2% with Sokolow-Lyon voltage criteria and 5.1% with Cornell product criteria.

A retrospective cohort study conducted by Haxha S et al., noted Cornell Voltage criteria identified LVH in 8% diabetic individuals compared to 5.6% in non-diabetic individuals; whereas Sokolow-Lyon voltage criteria identified an almost similar prevalence of LVH between diabetic and non-diabetic individuals (8.5% vs 8.1%). The study also stated that Cornell Voltage detected LVH is the strong predictor of mortality in both diabetic and non-diabetic subjects compared to Sokolow-Lyon voltage criteria. Vijay S. Nagaonkar., reported a low correlation of ECG-LVH with echocardiography. The study stated 4% of LVH prevalence with ECG correlated with LVH detected with echocardiography. However, the study noted that the sensitivity can be increased for detection of LVH with Sokolow-Lyon voltage criteria and Romhilt-Estes point score system. The difference in the prevalence of ECG-LVH in various studies could be due to the patients' age, gender, race, subcutaneous fat, glycemic control, duration of diabetes, presence of additional confounding factors, and the measuring techniques used.

LVH is one of the common and well-established left ventricular abnormalities that strongly promotes adverse cardiac events (22). The underlying pathophysiology of diabetic cardiomyopathy (DCP) is complex and multifactorial and involves several mechanisms for myocyte hypertrophy like hyperglycemia, insulin resistance, oxidative stress, abnormal fatty acid metabolism, accumulation of advanced glycation end products (AGEs), and overactivation of the renin-angiotensin-aldosterone system (RAAS). At the early stages, screening of DCP becomes important as with appropriate management and strict glycemic control, the pathological changes can be reversed before they progress to an irreversible stage (23). Hence, early screening of diabetic cardiac changes using HRV and LVH become important for prognostic purpose and prevention of further adverse cardiovascular events.

CONCLUSION

Frequency and time-domain parameters of HRV were reduced in T2DM patients. Parasympathetic dysfunction and higher sympathetic activity were indicated by the decrease in normalized HF and an increase in resting heart rate & LF/HF ratio in T2DM patients. The decreased HRV is an early sign of CAN in diabetes. The ECG-LVH was evident in T2DM patients with higher positivity noted in Cornell product and Sokolow-Lyon voltage criteria followed by Romhilt-Estes point score and Cornell voltage criteria. The early detection of CAN, regular assessment of cardiac function with timely management can revert the early CAN and prevent future adverse cardiac events.

Limitations: Sample size of the study was small to conclude the evidences to apply for population and presence of LVH with ECG criteria was not compared with Echocardiography.

REFERENCES

1. Refaie W. Assessment of cardiac autonomic neuropathy in long standing type 2 diabetic women. The Egyptian Heart Journal. 2014 Mar 1;66(1):63-9.
2. Bissinger A. Cardiac autonomic neuropathy: why should cardiologists care about that? Journal of diabetes research. 2017 Oct 29;2017.
3. Balcıoğlu AS, Müderrisoğlu H. Diabetes and cardiac autonomic neuropathy: clinical manifestations, cardiovascular consequences, diagnosis and treatment. World journal of diabetes. 2015 Feb 15;6(1):80-91.
4. Lorenzo-Almorós A, Tuñón J, Orejas M, Cortés M, Egido J, Lorenzo Ó. Diagnostic approaches for diabetic cardiomyopathy. Cardiovascular diabetology. 2017 Dec;16(1):1-4.
5. Ghonem M, Wafa AA, Al Biomy A. Effect of cardiovascular autonomic neuropathy (CAN) on left ventricular function in normotensive type 1 diabetic patients: A study by pulsed wave tissue Doppler echocardiography. The Egyptian Heart Journal. 2012 Mar 1;64(1):7-13.
6. Eguchi K, Boden-Albala B, Jin Z, Rundek T, Sacco RL, Homma S, et al. Association between diabetes mellitus and left ventricular hypertrophy in a multiethnic population. The American journal of cardiology. 2008 Jun 15;101(12):1787-91.
7. Al Hadad HS, Edankadhum B, Al Naffi K. Correlation between diabetes mellitus and left ventricular hypertrophy. American Journal of BioMedicine. 2018 Jan;7 (1): 1-12.

8. Voulgari C, Tentolouris N, Stefanadis C. The ECG vertigo in diabetes and cardiac autonomic neuropathy. Experimental diabetes research. 2011 Mar;2011.
9. Classification of diabetes mellitus. Geneva: World Health Organization. 2019.
10. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Frontiers in public health. 2017 Sep 28;5:258.
11. Bauml MA, Underwood DA. Left ventricular hypertrophy: an overlooked cardiovascular risk factor. Cleve Clin J Med. 2010 Jun 1;77(6):381-7.
12. Vasanthakumar J, Kambar S. Prevalence of obesity among type 2 diabetes mellitus patients in urban areas of Belagavi. Indian Journal of Health Sciences and Biomedical Research (KLEU). 2020;13(1):21.
13. Rolim LC, Sá JR, Chacra AR, Dib SA. Diabetic cardiovascular autonomic neuropathy: risk factors, clinical impact and early diagnosis. Arq Bras Cardiol. 2008 Apr 1;90(4):e24-31.
14. Pramodh V, Kumar MP, Prasad BA. Heart rate variability in type 2 diabetics. International Journal of Biomedical Research. 2014;5(5):364-7.
15. Mirza M, Lakshmi AN. A comparative study of heart rate variability in diabetic subjects and normal subjects. Int J Biomed Adv Res. 2012 Sep 1;3(8):640-4.
16. Kudat H, Akkaya V, Sozen AB, Salman S, Demirel S, Ozcan M, Atilgan D, Yilmaz MT, Guven O. Heart rate variability in diabetes patients. Journal of international medical research. 2006 May;34(3):291-6.
17. Benichou T, Pereira B, Mermillod M, Tauveron I, Pfabigan D, Maqdasy S, et al. Heart rate variability in type 2 diabetes mellitus: A systematic review and meta–analysis. PloS one. 2018 Apr 2;13(4):e0195166.
18. Jobe M, Kane A, Jones JC, Pessinaba S, Nkum BC, Ba SA et al. Electrocardiographic left ventricular hypertrophy among Gambian diabetes mellitus patients. Ghana medical journal. 2015;49(1):19-24.
19. Lutale JJK, Thordarson H, Gulam-Abbas Z, Vetvik K, Gerdts E. Prevalence and covariates of electrocardiographic left ventricular hypertrophy in diabetic patients in Tanzania. Cardiovasc J Afr. 2008 Feb;19(1):8-14.
20. Haxha S, Pedersen-Bjergaard U, Nielsen JB, Pallisgaard J, Devereux RB, Okin PM, et al. Cornell voltage left ventricular hypertrophy predicts all-cause mortality better than Sokolow-Lyon voltage in patients with and without diabetes–data from 183,749 primary care ECGs. European Heart Journal. 2020 Nov;41(Supplement_2):ehaa946-3042.
21. Vijay S Nagaonkar. Study of correlation between ECG findings and echocardiographically detected left ventricular diastolic dysfunction. MedPulse International Journal of Medicine. September 2017; 3(3): 103-107.
22. Dawson A, Morris AD, Struthers AD. The epidemiology of left ventricular hypertrophy in type 2 diabetes mellitus. Diabetologia. 2005 Oct;48(10):1971-9.
23. Acar E, Ural D, Bildirici U, Şahin T, Yılmaz İ. Diabetic cardiomyopathy. Anatolian Journal of Cardiology/Anadolu Kardiyoloji Dergisi. 2011; 11: 732-7.