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Research Article

Effect of Uncontrolled Diabetic Dyslipidemia in the Prevalence of Sub-Clinic Left-Ventricular Diastolic Dysfunction in Western Region of the Republic of Macedonia -

Atila Rexhepi[1]*, Ylber Jani[2], Bekim Pocesta[3], Sotiraq Xhunga[4], Artur Serani[5], Fatmir Ferati[6], Dali Lala[7], Agim[8], Arben Mirto[9] and Ahmet Kamberi[10]

[1]Department of Internal Medicine Faculty of Medicine, Tetovo Republic of Macedonia
[2]Private Health Institute"Heart Diagnostica"Debar Republic of Macedonia
[3]Department of Cardiology Faculty of Medicine "Ss Kiril and Metodij" University Skopje Republic of Macedonia 4Department of Cardiology Medical Center Dures Republic of Albania
[7]Private Health Institute of family medicine "Florenc" Tetovo Republic of Macedonija
[8]Department of Internal Medicine-General Hospital "DR Ferit Murat" Gostivar Republic of Macedonia
[9]Private Health Institute"Rostusha" Debar Republic of Macedonia
[10]Department of Cardiology Faculty of Medicine M. Teresa Tirana Republic of Albania

***Address for Correspondence:** Atila Rexhepi, Department of Internal Medicine Faculty of Medicine, Tetovo Republic of Macedonia, Tel: +389-702-091-56; E-mail: diag@t-home.mk; E-mail: atillarexhepi@gmail.com

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ABSTRACT

Background: Data relating to the influence of uncontrolled diabetic dyslipidemia in the prevalence of sub-clinic Left Ventricular Diastolic Dysfunction (LVDD) in patients with Diabetes Mellitus type 2 (T2DM), in absence of coronary disease and high blood pressure disease, in relation to our region are scarce.

Objective: We tried to determine the influence of uncontrolled diabetic dyslipidemia in the prevalence of sub-clinic LVDD in patients with type 2 diabetes in absence of coronary disease and high blood pressure disease in Western Region of the Republic of Macedonia.

Methods: This is a multicenter, noninterventional, cross-sectional study. Prospectively tested were 400 participants. The study was conducted at outpatient in Secondary Health Care Clinics in 8 towns in the western region of the Republic of Macedonia. Study participants were selected among secondary care patient, who were receiving ongoing care for diabetes mellitus type 2 and dyslipidemia, during one year. We recorded information from all healthcare encounters during one year.

Results: Prevalence of sub-clinic LVDD grade 1, among diabetic patients with uncontrolled dyslipidemia were significantly increased in comparation with diabetic patients with controlled dyslipidemia (47.5% vs. 22.5%; p = 0.0003, respectively). The overall frequency of sub-clinic LVDD grade 1 in study population was (35%; p = 0.000). There is significant association between sub-clinic LVDD and uncontrolled diabetic dyslipidemia (OR = 2.91; 95% CI 1.89 - 4.47), females (OR = 1.92; 95% CI 1.269 - 2.921), age (OR = 1.08; 95% CI 1.002 - 1.159), BMI (OR = 1.24; 95% CI 1.109 - 1.387), LVM (OR = 2.554; 95% CI 1.289 - 5.021), duration of T2DM (OR = 2.88;95% CI 2.182 - 3.685), uncontrolled glycaemia (OR = 2.55;95% CI 1.794 - 3.675).

Conclusions: The prevalence of sub-clinic LVDD in absence of coronary disease and high blood pressure disease is higher among patients with uncontrolled diabetic dyslipidemia than among patients with controlled diabetic dyslipidemia in the western region of the Republic of Macedonia and seem to be significantly associated with demographic and clinical parameters: age, gender, BMI, LVM, duration of diabetes and glycemic control.

Keywords: Diabetic Cardiomyopathy; Uncontrolled Diabetic Dyslipidemia; Western Region of the Republic of Macedonia

ABBREVIATION

BW: Body Weight; BH: Body Height; BMI: Body Mass Index; BP: Blood Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; GLYC: Glycaemia; T2DM: Diabetes Mellitus Type 2; DCM: Diabetic Cardiomyopathy; CHD: Coronary Heart Disease; LV: Left Ventricular; LVDD: Left Ventricular Diastolic Dysfunction; HF-Nef: Heart Failure With Normal Ejection Fraction; CVHD: Cardio-Vascular Heart Disease; DD: Diastolic Dysfunction; CRE: Creatinemia; LDL-C: Low-Density Cholesterol; IVRT: Isovolumetric Relaxation Time; DCT: Deceleration Time; EAS: European Atherosclerosis Society; ESC: European Society Of Cardiology; ADA: American Diabetes Association; ACC/AHA: American College Of Cardiology; American Heart Association

INTRODUCTION

Prevalence of type 2 diabetes (T2DM) has been increasing worldwide in the last two decades and with them the incidence and prevalence of diabetes-related co-morbities [1,2]. In many experimental, pathological, epidemiological and clinical studies have shown that type 2 diabetes brings functional and structural changes in the heart, Diabetic Cardiomyopathy (DCM), regardless of coronary artery disease and high blood pressure [3]. Unfortunately, we do not yet understand the mechanism (s) responsible for causing DCM in type 2 diabetes. Excess lipid accumulation may exert direct toxic effects on cellular function with cardiac dysfunction and apoptosis, a process termed lipotoxicity [4]. Since type 2 diabetes is a significant risk factor for cardiovascular diseases, lipotoxicity may represent significant component mediating the diabetic cardiomyopathy phenotype [5]. The Left Ventricular Diastolic Dysfunction (LVDD) is a basic characteristic of diabetic heart disease (diabetic cardiomyopathy) [3]. In many epidemiological and clinical studies, the association between diabetic dyslipidemia and LVDD in patients with T2DM has been proved [6-8], while sub-clinic LVDD can be the first stage of diabetic cardiomyopathy preceding systolic abnormalities [9-11]. Presence of the sub-clinic LVDD in patients with type 2 diabetes is a risk factor for the development of heart failure with a normal ejection fraction (HF - nEF) and bring higher morbidity and mortality [10-12]. Data relating to the influence of uncontrolled diabetic dyslipidemia in the prevalence of sub-clinic LVDD in patients with T2DM in absence of coronary disease and high blood pressure disease, in relation to our region, are scarce.

Objective

In this study, we tried to determine, the influence of uncontrolled diabetic dyslipidemia in the prevalence of sub-clinic LVDD in patients with type 2 diabetes, in absence of coronary disease and high blood pressure disease, in Western Region of the Republic of Macedonia.

Methods

Study design: This is a multicenter, noninterventional, cross-sectional study. The study is in compliance with the Declaration of Helsinki. All patient that participated in this study were written informed, consent was obtained from all participating patients before they were enrolled into the study. Prospectively tested were 400 participants. The study was conducted at outpatient in Secondary Health Care Clinics in 8 towns in the western region of the Republic of Macedonia. Study participants were selected among secondary care patient, who were receiving ongoing care for diabetes mellitus type 2 and dyslipidemia, during one year. We recorded information from all healthcare encounters during one year (from June 2016 to June 2017). One group comprised of 200 diabetics patients with uncontrolled diabetic dyslipidemia and second group comprised of 200 with type 2 diabetes mellitus with controlled diabetic dyslipidemia.

Inclusion criteria: Patient was eligible for inclusion in the study if they were between 45 and 55 years of age, diagnosed and treated for diabetic dyslipidemia in accordance with validated criteria [13-15].

Exclusion criteria: We excluded all patients with age under 45 and over 55, arterial hypertension, ischemic heart disease (detected by anamnesis, surface electrocardiogram, exercise testing, left ventricular wall abnormalities in the echocardiographic examination), signs of

left ventricular systolic dysfunction (EF < 55 %), cardiomyopathies (primary and secondary), cardiac arrhythmias, congenital or acquired valvular heart disease, atrioventricular block of 2 - 3 degree, left/right bundle branch block, pre-excitation syndromes, patients with pacemakers, ventricular hypertrophy, dialysis patients. Patients with known a type 1 diabetes, acute and chronic cerebrovascular disease, history of malignancy, history of chronic kidney disease, dialysis patients and unexplained increased creatinine, patients with proteinuria, smokers, patients with calculated SCORE > 10% for 10 - years risk of fatal Cardiovascular Disease (CVD), uncontrolled hypothyroidism, current active liver disease or ALT, AST level > 3 times the U/L. We also excluded patients with poor echocardiographic window.

Clinical and Demographic Characteristics: The survey obtained data on: age, gender, calculated Body Mass Index (BMI), duration of diabetes, knowledge of target lipids level, cardiovascular medical history such as family history of premature CHD, the presence of known cardiovascular risk factors, Cardiovascular Heart Disease (CVHD) or CHD-risk equivalents (metabolic syndrome, smoking habits), cerebral and peripheral vascular disease, current lipid-lowering therapy. An overnight fasting blood sample was drawn from each patient to determine: blood glucose, lipid profile tests (TC, LDL-C, HDL-C, TG), urea, creatinine, ALT, AST, urine protein. The sample analysis was performed using standard biochemical analytical methods. The mean value of lipids (TC, LDL-C, HDL-C, TG), recording during the study period, were calculated. Patients with calculated LDL-C, outside the recommended targets { > 100 mg/dL (> 2.6mmol/L)} [13-15], were considered to have uncontrolled diabetic dyslipidemia.

Echocardiographic measurements: M-mode, two-dimensional and Doppler echocardiography, were performed and/or reviewed by experienced staff cardiologists, compliant with the recommendation of the American Society of Echocardiography [16] (ASE), stored in DICOM format and later reviewed by two experienced echo cardiographers. Briefly, the LV (Left Ventricular) linear dimensions were measured from a parasternal long-axis view according to the recommendations of the ASE [22]. The LV mass was calculated with a validated formula [17] and indexed both for body surface area (BSA) and height [18]. The LV relative wall thickness was calculated as follows: (2 x posterior wall thickness) divided by end-diastolic diameter [19]. The LV Ejection Fraction (EF) was calculated by biplane modified Simpson's rules. From an apical 4-chamber view, transmittal flow was sampled by pulsed-wave Doppler at the level of mitral valve leaflet tips. Peak velocities of the early phase (E) and late phase (A) of the mitral inflow were measured and their ratio (E/A) was calculated. Left ventricular myocardial velocities were evaluated by Tissue Doppler Imaging (TDI). Pulse TDI sample volume was placed at the level of the lateral and septal mitral valve annulus and peak early diastolic velocities (E') were measured and then averaged. The ration between E and E' (E/ E') was calculated.

Diastolic function: We used measurements of LA size, LV remodeling, tissue Doppler and Doppler of mitral flow as parameters of DD and the cut-offs were set according to previously published data and international guidelines [20-22]. We defined LA size as normal (< 2.2 cm/m^2), moderately enlarged (2.2 - 2.79 cm/m^2) and severely enlarged (≥ 2.8 cm/m^2). E/A ratio, the ratio of the E-wave and peak late LV filling (A-wave), was divided into low (< 1.0), normal (1.0 - 2.0) and high (> 2.0). The early myocardial peak velocity of the mitral annulus, tissue Doppler E' wave (the average of the septal e' and lateral e' measurements), was defined as decreased (< 9 cm/s) or normal (≥ 9 cm/s). E/E' the ratio of peak early LV filling (E-wave) and average tissue Doppler E' wave, was stratified into normal (< 8) and increased (≥ 8). We defined EDT, the deceleration time of early filling velocity, into low (< 140 ms), normal (140 - 220 ms) and high (> 220 ms). Isovolumetric Relaxation Time (IVRT) was either reduced (< 60 ms), normal (60 - 110 ms) or prolonged (> 110 ms). The ratio of the transmittal early and late filling phases (E:A) was calculated as a measure of diastolic function. The ratio of early filling and early myocardial velocity (E/e') was calculated as a noninvasive index of LV filling pressure.

Definition of diastolic dysfunction was as follows:

- LA volume index > 34 mL/m^2.
- E/A < 0.8; E' < 8 cm/s; mean E/e' ≤ 8: impaired relaxation (grade I).
- E/A ≤ 1.5; E' < 8 cm/s; mean E/e' ≤ 12: pseudo-normalized pattern (grade II).
- E/A > 2; E' < 8 cm/s, and mean E/e' ≥ 13: restrictive patter n (grade III).
- Elevated LV filling pressure was defined as when E/E' ratio exceeded 14.

Throughout all echocardiographic findings, a consensus reading was again applied.

STATISTICAL ANALYSIS

The collected data were entered in the software SPSS for Windows, version 19.0, which performed a statistical analysis. The distribution of variables was tested for normality using the Kolmogorov - Smirnov test, and the heterogeneity of variances was evaluated by Levene's test. A simple descriptive analysis was performed for the general characterization of the sample and distribution of variables. Continuous variables were presented as a mean ± standard deviation, and categorical variables were presented as frequency (%). Differences between groups were analyzed using the Student t-test for independent samples. Categorical data were analyzed using the chi-square (X^2) test. The association between variables were analyzed using logistic regression. A p - value < 0.05 was considered statistically significant for a confidence interval of 95%.

RESULTS

A total of 400 patients with T2DM, (46.3% females and 53.7% males: mean age 49.7 ± 3.9 years) completed the survey and provided data for a one-year medical record review. Table1, present basic demographic, clinical, echocardiographic and laboratory characteristics of the studied population. There are no differences between the studied groups in terms of age, gender, BMI, duration of T2DM, SBP, DBP, glycemic control, urea, and creatinine. No significant changes were observed in relation to a number of visits between the study group and control group (4.4 vs. 4.5. p = 0.7, respectively). No significant changes were observed in relation to electrolytes (Na^+135.2 ± 4.5 vs. 136,3 ± 5.1, p = 0.24; K^+3.9 ± 0.6 vs. 3.8 ± 0.7, p = 0.32, respectively). No significant changes were observed in relation to serum (urea, creatinine) between the study group and control group, (4.2 ± 2.2 vs. 2.1 ± 1.2, p = 0.31, respectively; 80.9 ± 7.5 vs. 80.4 ± 6.2, p = 0.7 respectively). The majority of echocardiographic data did not show significant differences among patients between two groups. As shown in table 1, there are no differences between the groups in relation to

Table1: Basic demographic, clinical, laboratory and echocardiographic characteristics of study population (N = 400).

Variables		Gr. of Diabetics with Controlled dyslipidemia. (n - 200)			Gr. of Diabetics with Uncontrolled Dyslipidemia. (n - 200)			
		N. (%)	Mean	SD	N. (%)	Mean	SD	*P* - value
Gender	Females	95 (47.5)			93 (45.8)			0.90
	Males	105 (52.5)			107 (54.2)			0.91
Age (y)		200 (100)	49.3	±3.8	200 (100)	50.1	± 3.9	0.92
BMI (kg/m²)		200 (100)	25.1	± 2.7	200 (100)	26.8	± 3.1	0.79
N.of Measures		200 (100)	4.05	± 0.6	200 (100)	4.05	± 0.6	1.00
SCORE (> 5 < 10)		200 (100)	6.8	± 1.4	200 (100)	7.1	± 1.2	0.85
SBP (mmHg)		200 (100)	125.6	± 5.7	200 (100)	134.5	± 4.3	0.66
DBP (mmHg)		200 (100)	80.7	± 8.2	200 (100)	82.1	± 8.8	0.89
DM - d (y)		200 (100)	4.5	± 1.8	200 (100)	4.2	± 1.9	0.18
LDL - C (mmol/l)		200 (100)	2.4	± 0.2	200 (100)	3.9	± 0.7	**0.04**
Glyc. (mmol/l)		200 (100)	6.1	± 5	200 (100)	6.5	± 7	0.78
Urea (mmol/l)		200 (100)	6.9	± 6	200 (100)	7.5	± 4	0.78
Creatinin (mmol/l)		200 (100)	81.5	± 6	200 (100)	80.3	± 5	0.94
LAVI (ml/m²)		200 (100)	30.0	± 5.6	200 (100)	34.4	± 0.6	**0.0015**
E (cm)		200 (100)	0.71	± 0.13	200 (100)	0.67	± 0.14	**0.002**
A (cm)		200 (100)	0.58	± 0.17	200 (100)	0.66	± 0.17	**0.001**
E/A ratio < 0.8		45(22.5)		± 0.03	95 (47.5)			**0.0003**
E/E'ratio ≥ 8		45 (22.5)		± 0.03	95 (47.5)			**0.0003**
DT (m/s)		200 (100)	190.6	± 15.8	200 (100)	203.4	± 30.7	**0.0001**
IVRT (m/s		200 (100)	95.7	± 14.3	200 (100)	103.3	± 20.3	**0.0001**
LVM (gr)		200 (100)	100.5	± 17.5	200 (100)	103.4	± 23.1	0.065

Values are mean ± SD; y = year; BMI: Body Mass Index; N: Number of Laboratory Measures During the Study Period; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; DMD: Diabetes Mellitus Duration; Glyc: Glycemia; serum LDL-C: Low Density Cholesterol; LAVI: Left Atrial Volume Index by Biplane Simpson Method; Mitral E: Peak Wave; A: Mitral Peak Wave; E/A ratio: early to late transmitral flow velocity; E/E'-ratio: Aearly transmitral flow to average mitral tissue doppler; DT: Deceleration Time; IVRT: Isovolumetric Relaxation Time; LVM: Left Ventricular Mass.

left ventricular dimensions, the thickness of left ventricular septum and posterior wall, ejection fraction, fractional shortening, and LVM. However, significant difference between the studied groups, were observed in relation to: Diabetics with uncontrolled dyslipidemia have significantly increased LA volume index in comparation with LA volume index among diabetics with controlled dyslipidemia (33.26 ± 3.7 vs. 31.65 ± 3.5; p = 0.0001,respectively), significant lower peak velocity of E-wave (0.67 ± 0.14 vs. 0.71 ± 0.13; p = 0.003, respectively), significant higher peak velocity of A-wave (0.66 ± 0.17 vs. 0.58 ± 0.18; p = 0.0000, respectively), significant longer IVR-time (103.4 ± 20.3m/s vs. 95.7 ± 14.3m/s; p = 0.0001, respectively), significant longer DC-time (203 ± 30.9m/s vs. 190 ± 15.8m/s; p = 0.000, respectively), significant higher E/E' ratio (8.0 ± 0.79 vs. 7.5 ± 0.83; p = 0.000, respectively). As shown in table 2, figure 1 and figure 2, the prevalence of sub-clinic LVDD grade 1, among diabetics patients with uncontrolled dyslipidemia were significantly increased in comparison with diabetics patients with controlled dyslipidemia (47.5% vs. 22.5%; p = 0.0003, respectively). The overall frequency of sub-clinic LVDD grade 1, in the study population, was (35%; p = 0.000). Logistic Regression model was used to identify the association of sub-clinic LVDD with demographic, clinical and echocardiographic characteristics. As shown in table 3, there is a significant association between sub-clinic LVDD and uncontrolled diabetic dyslipidemia. (Wald = 22.9; p = 0.000). Patients with uncontrolled diabetic dyslipidemia for (OR = 2.86; 95% CI 1.86 - 4.40), have 1.05 times higher risk for sub-clinic LVDD in comparison with patients with controlled diabetic dyslipidemia. There was observed a significant association between sub-clinic LVDD and females among patient with uncontrolled diabetic dyslipidemia. (Wald = 8.24; p = 0.004). Females (OR = 1.92; 95% CI 1.303 - 4.070), have 2.303 times higher risk for sub-clinic LVDD in comparison with males. A significant association between sub-clinic LVDD and BMI were observed among patients with uncontrolled diabetic dyslipidemia (Wald = 25.2; p = 0.000). Patients with increased BMI among patients with uncontrolled diabetic dyslipidemia for (OR = 1.15; 95% CI 1.089-1.215) have 1.15 times higher risk for sub-clinic LVDD in comparison with the patients with normal BMI. A significant association between sub-clinic LVDD and LVM were observed among patient with uncontrolled diabetic dyslipidemia (Wald = 9.076; p = 0.003). Patient with increase LVM, for (OR = 10.096; 95% CI 2.243 - 4.543) have 10.09 times higher risk for sub-clinic LVDD in comparison with the patient and normal LVM. Age of patient with uncontrolled diabetic dyslipidemia was significantly associated with sub-clinic LVDD (Wald = 8.242; p = 0.004; OR = 1.082; 95% CI 1.026-1.141). There was observed significant association sub-clinic LVDD and duration of T2DM among patient with uncontrolled diabetic dyslipidemia (Wald = 55.815; p = 0.000; OR = 2.88; 95% CI2.18 - 3.80). Uncontrolled glycemia in patients with uncontrolled diabetic dyslipidemia was

Table 2: Frequency of sub-clinic Left Ventricular Diastolic Disfunction in T2DM with uncontrolled and controlled LDL-C (N = 400).

Chi-square: 13.34; p = 0.0003 Diabetic group with uncontrolled LDL - C (N - 200)			
	Patients with Sub-clinic (LVDD)	Patients with Normal (LV) Diastolic function	Totals
Count (No)	95	105	200
Percent (%)	47.5	52.5	100
Chi-square: 13.34; p = 0.0003 Diabetic group with controlled LDL-C (N - 200)			
	Patients with Sub-clinic (LVDD)	Patients with Normal (LV) Diastolic function	Totals
Count (No)	45	155	200
Percent (%)	22.5	77.5	100

LDL-C: Low Density Cholesterol; sub-clinic (LVDD); Left Ventricular Diastolic Dysfunction; LV: Left Ventricular.

significantly associated with subclinical sub-clinic LVDD (Wald = 27.078; p = 0.000; OR = 2.55; 95% CI 1.794 - 1.363).

DISCUSSION

In this study, we observed that the frequencies of sub-clinic LVDD among diabetic patients with uncontrolled dyslipidemia were significantly increased in comparison with diabetic patients with controlled dyslipidemia (47.5% vs. 22.5%; p = 0.0003, respectively). In animal and clinical studies, the correlation between LVDD and the level of fat in the blood is proven regardless of age, BMI, BP and heart rate frequency [6]. Luuk J et al [6], demonstrated that lipid oversupply to cardiomyocytes may lead to lipotoxic injury, plays a role in the development of diabetic cardiomyopathy. Since a diastolic relaxation is an energy-dependent process, it may be impaired by conditions decreasing energy availability such as dyslipidemia [23]. In fact, as shown in our study, the frequency of sub-clinic LVDD among diabetic patient with uncontrolled dyslipidemia was significantly increased. These data are in line with earlier observations [24-26]. The influence of gender in the prevalence of LVDD is proved in some but not in all reports. Suis BE et al [27], proved that changes in the diastolic function in women with T2 diabetes were more significant. Jani Y et al [26], report that women with T2 diabetes in relation to men have a greater risk for development of sub-clinic LVDD. In the present study, we observed that the frequency of sub-clinic LVDD among diabetic female with uncontrolled dyslipidemia was significantly higher in comparison with diabetic men with uncontrolled dyslipidemia. In the Fang ZY *et al* [28] study, the influence of gender in the distribution of sub-clinic LVDD, at the ones with T2DM, was not proved. Also, Bajraktari G et al [29] study, does not prove the influence of gender in the distribution of sub-clinic LVDD, at the ones with T2DM. In both studies, it is mentioned as a limitation of the studies was the small number of women included in the studies. In the present study, in a group of diabetics with uncontrolled dyslipidemia, sub-clinic LVDD was significantly associated with age. As the reduced ventricular compliance is secondary to the aging process since the ventricular stiffness increases with age and impairs diastolic function altering LV filling pressure [30]. Nevertheless, nature of some Doppler-echocardiographic changes with aging is partially unclear and precise discrimination between pathologic or physiologic changes remain difficult. In the Luuk J et al [6] study, LVDD was associated with diabetic dyslipidemia independently of age, BMI, blood pressure and heart rate. In the present study, in the group of diabetics with uncontrolled dyslipidemia, sub-clinic LVDD was significantly associated with BMI. Patients with uncontrolled dyslipidemia and sub-clinic LVDD have significantly increased BMI. Others have found similar results [31-33]. Studies have demonstrated increased LVM, among diabetic patient with LVDD without cardiovascular disease [26,35,37]. In the present study, in the group of diabetics with uncontrolled dyslipidemia, sub-clinic LVDD was significantly associated with LVM. Patients with uncontrolled dyslipidemia and sub-clinic LVDD have significantly increased LVM. Others have found similar results [26,35,37]. In the present study, in the group of diabetics with uncontrolled dyslipidemia, sub-clinic LVDD was significantly associated with duration of T2DM. This result is in accordance with results of other studies [34,35]. In the present study, we observed that uncontrolled glycemia in the group of diabetics with uncontrolled dyslipidemia was significantly associated with sub-clinic LVDD. The association between glycemic control and diastolic function is not a universal finding [29-31]. The diastolic function may be unchanged despite improved glycemic control [32]. These data suggest that factors in addition to advanced glycation end-products are likely to contribute to diastolic dysfunction [28,36,38]. In our study, statin therapy was a pharmacological treatment for lowering LDL-C levels in patients with type 2 diabetes, but it is clear that statins are not the universal solution to the problem of high cholesterol levels and the optimization of lipid-lowering therapy remains a therapeutic challenge. Although there are no clinical trials investigating the role of lipid-lowering therapy in individuals with established DCM, the benefits of dyslipidemia treatment can be anticipated in these patients, along with a role in primary disease prevention [39].

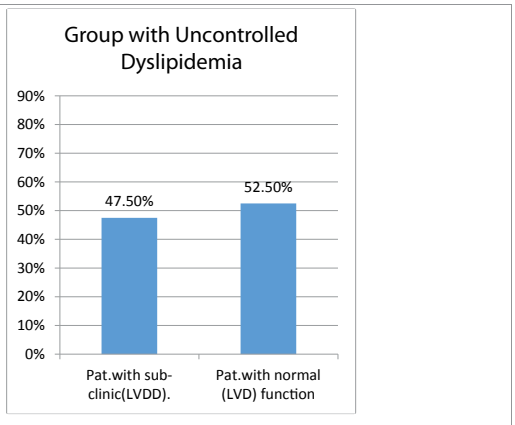

Figure 1: Frequency of sub-clinic LVDD in T2DM with uncontrolled LDL-C.

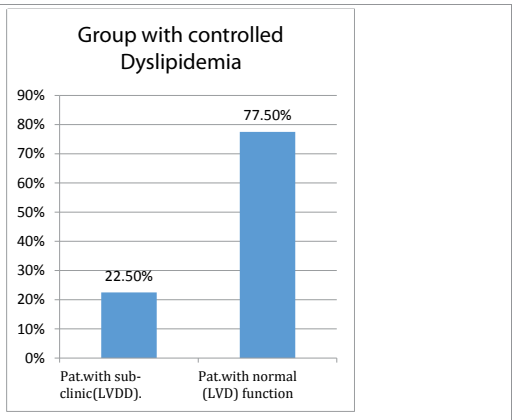

Figure 2: Frequency of sub-clinic LVDD in T2DM with controlled LDL-C.

Clinical Implications: These data provide further evidence that increased frequency of sub-clinic LVDD among diabetic patients with uncontrolled dyslipidemia is common and that patients at particular risk of sub-clinic LVDD can be identified. Targeted interventions to improve management of diabetic dyslipidemia in such patients the early discovery of sub-clinic LVDD as well as the early inclusion of medical treatment with b-blockers and ACE-inhibitors, we can successfully do a primary prevention of a clinical manifestation of heart failure. This study provides a framework identifying diabetic patients who are at high risk for development of myocardial systolic dysfunction and many of the factors identified may be amenable to improvement Older patients, females, diabetics with increased BMI, increased LVM, uncontrolled glycemia and longstanding DM, can be targeted for greater attention to diabetic dyslipidemia control, particularly in light of the evidence for improvement in clinical outcomes with antilipemic therapy in this population.

This study was not without limitations: A larger sample would certainly increase the statistical power of the study, and probably

Table 3: Logistic Regression Model: Association of sub-clinic (LVDD) in T2DM with uncontrolled dyslipidaemia and (Age, Gender, BMI, glycaemic control, Duration of D.M).

		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I. for EXP(B)	
								Lower	Upper
Step 1[a]	**Uncontr. LDL-C**	1.052	.220	22.931	1	**.000**	2.864	1.862	4.406
	Constant	- 2.254	.365	38.169	1	.000	.105		
Age Step 1[a] Constant		 .079 - 4.555	 .027 1.369	 8.323 11.065	 1	 **.004** .001	 1.082 .011	1.026	1.141
Gender Step 1[a] Constant		 0.834 -.521	 .291 .197	 8.242 6.968	 1 1	 **.004** .008	 2.303 .594	1.303	4.070
Step 1[a]	**BMI**	.140	.028	25.200	1	**.000**	1.151	1.089	1.215
	Constant	- 4.365	.750	33.895	1	.000	.000		
Step 1[a]	**LVM** Constant	2.312 - 2.609	.767 .810	9.076 10.379	1 1	**.003** .001	10.096 .074	2.243	4.543
Step 1[a]	**Uncontrol Glycem.** Constant	.937 -6.434	.180 1.219	27.078 27.873	1 1	**.000** .000	2.554 .002	1.794	3.635
Step 1[a]	**D. Durat.** Constant	1.058 -4.919	.142 .663	55.815 55.091	1 1	**.000** .000	2.880 .007	2.182	3.635

Uncontr. LDL-C: Uncontrolled LDL-C; Glycem: glycaemia; D. Durat: Duration of T2DM.

same differences would, therefore, become more expressive. It was impossible to rule out coronary heart disease, as a reason for sub-clinic LVDD, by coronary angiography because it is difficult to influence asymptomatically patients for an invasive procedure and also from an ethical standpoint. This limitation is unavoidable. We do not believe that subtle coronary arteriosclerosis would have an influence in the received results at a significant degree, also will not reduce the values of the basic conclusions of the study.

CONCLUSIONS

The prevalence of sub-clinic LVDD in absence of coronary disease and high blood pressure disease is higher among patient with uncontrolled diabetic dyslipidemia than among patient with controlled diabetic dyslipidemia in the western region of the Republic of Macedonia and seem to be significantly associated with demographic and clinical parameters: Age, Gender, BMI, LVM, duration of diabetes and glycemic control. Increased prevalence of sub-clinic LVDD, in absence of coronary disease and high blood pressure disease, seems to be influenced significantly by uncontrolled diabetic dyslipidemia. This calls for the awareness and intervention controlling dyslipidemia in these patients.

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