Effect of Glycemic Control on Right Heart Functions in Type 2 Diabetes Mellitus Patients Free of Clinical Cardiovascular Disease

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Abstract- Diabetes mellitus (DM) is one of the most common endocrine disorders. 90% percent of all diabetics are diagnosed with type 2 DM. DM is closely associated with various vascular diseases, and successful glycemic control prevents micro and macrovascular complications. Although there is data about the relation between glycemic control and left ventricle function, there is hardly any data about the relation between the right ventricular function. We analyzed the relationship between glycemic control and right ventricle function in type 2 DM patients free of clinical cardiovascular diseases (CVD). Patients were selected from the cardiology outpatient clinic. 53 patients formed the DM group; 51 patients formed the control group. All patients' demographic data were recorded. Biochemical tests and echocardiographic examinations were performed. RA and RV diameters were significantly higher in DM group (3.36±0.32 vs 3.13±0.34, *P*=0.015; 2.80±0.32 vs 2.56±0.22 *P*=0.005 respectively). Myocardial velocity during isovolumetric contraction (RV/IVV) and myocardial acceleration during Isovolumetric contraction (RV/IVA) were significantly lower in the DM group (14.4±3.17 vs 16.04±4.13 *P*=0,019; 3.25±0.75 vs 3.95±1,25 *P*=0.015). There was an intermediate negative correlation between RV/IVV and Hemoglobin A1C (HBA1C) (r=-0.406; *P*=0.036). HBA1C level was an independent risk factor for RV IVV (β=-0.406; *P*=0.036). It is shown that RA, RV diameter were significantly higher; RV/IVV and RV/IVA were significantly lower in diabetes mellitus patients free of CVD. Furthermore, there was a significant negative correlation between RV/IVV and HBA1C levels. HBA1C level was an independent risk factor for RV/IVV.

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Keywords: Type 2 diabetes mellitus; Right heart; Isovolumetric acceleration; Glycemic control; Hemoglobin A1C (HBA1C)

Introduction

Type 2 diabetes mellitus (T2DM) is one of the major public health concerns all around the world. The estimated number of T2DM patients would be more than 400 million by the year 2030 (1). Vascular complications are responsible for all mortality and morbidity caused by T2DM (2). Especially cardiovascular diseases (CVD) are the main complications of T2DM, accounting for approximately two-thirds of deaths in T2DM patients (3). Although the exact mechanism linking T2DM with CVD is unknown, the level of blood glucose seems to be associated. Hence, numerous studies have shown the close relationship between glycemic control and CVD (4,5). Every 1% increase in glycated hemoglobin (HbA_1c) causes approximately 13% increase in cardiovascular events (3). Besides this, It is also known that successful glycemic control reduces both micro and macrovascular complication rates (6). In light of these data, glycemic control has become one of the major goals of T2DM management.

The association of glycemic control and CVD is fairly well studied. However, the effect of glycemic control on the right heart function in T2DM patients is not investigated. The aim of this prospective study was to analyze the effect of glycemic control on the right heart functions.

Materials and Methods

Study design and population

In this observational cross-sectional study, subjects were selected from the patients who were admitted to our cardiology outpatient clinic between January 1st and May

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31th 2018. Patients having; coronary artery disease (CAD), moderate to severe valve diseases, myocardial ischemia in any myocardial stress tests, any type of myocardial ischemia in electrocardiography (ECG) or transthoracic echocardiography (TTE), chronic obstructive pulmonary disease/asthma, congenital right heart disease, pulmonary hypertension (pulmonary hypertension defined as systolic pulmonary artery pressure >40 mmHg) were excluded. After exclusion, 53 patients having T2DM comprised DM group, and age-sex matched 51 patients without T2DM comprised control group. Approval was obtained from the local ethics committee.

Study protocol

The clinical and demographic features of all patients were recorded. Venous blood samples for biochemical analyses were drawn from all subjects after an overnight fasting Triglyceride (TG), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), blood urea nitrogen (BUN), creatinine, sodium, potassium, and plasma glucose level were analyzed. Standard transthoracic echocardiography (TTE) was performed. The obtained data pool of the DM and control groups were analyzed.

Evaluation of right heart functions

Right heart functions were evaluated with TTE using Toshiba Aplio 500 (Canon medical systems, USA) by an experienced blinded cardiologist. Complete 2-dimensional echocardiograms, including Doppler examination, were obtained in all standard views (parasternal long-axis, parasternal short-axis, apical four-chamber, apical two-chamber). Right heart function parameters, including right atrium (RA) and right ventricle (RV) diameters, tricuspid annular plane systolic excursion (TAPSE), right ventricular myocardial acceleration during isovolumic contraction (R-IVA), which was calculated by dividing right ventricular myocardial velocity during isovolumic contraction (R-IVV) by the time interval from the onset of this wave to the time at peak velocity (AcT) were evaluated.

Statistical analysis

Statistical analyses were conducted with a commercially available software package (SPSS version 16.0, SPSS, Chicago, IL). In this study, data are expressed as mean±SD for continuous variables and as counts and percentages for categorical variables. Differences were considered statistically significant at $P<0,05$. Fitness to the normal distribution was analyzed with the Kolmogorov-Smirnov test. Homogeneity of variance was calculated with the Levene test and the Lilliefors significance correction test. Student`s t-test was used for comparison of continuous variables, Chi-square and Fisher's exact tests were used for comparison of categorical variables. Correlations of continuous variables were evaluated using Pearson correlation analysis. Linear logistic regression analysis was performed to explore independent factors associated with right heart functions.

Results

A total of 104 patients were enrolled. Clinical and demographical characteristics of DM and control groups are presented in table 1. There was no statistically significant difference in age and sex between DM and control groups. Mean DM duration was 3,59±1,33 years (minimum 1 year, maximum of 7 years) in the DM group. As expected, fasting blood glucose was significantly higher, and although not in therapeutic target, LDL and total cholesterol levels were significantly lower in the DM group.

Table 2 shows comparison of right heart function parameters of DM and control groups. RA and RV diameters were significantly larger in DM group. (3,36±0,32 vs. 3,13±0,32, P=0,015; 2,80±0,32 vs. 2,56±0,22, P=0,005 respectively). Furthermore R-IVV and R-IVA were significantly lower in DM group (14,44±3,17 vs. 16,04±4,30, P=0,019; 3,25±0,75 vs. 3,95±1,24, P=0,015 respectively)

To evaluate the correlation between glycemic control and right heart function, we performed a correlation analysis between HBA1C and right heart function parameters (Table 3). We showed an intermediate negative correlation between HBA1C level and R-IVV (r= -0,406; P=0,036) (Figure 1). Moreover, regression analysis revealed that the HBA1C level was an independent risk factor of R-IVV (β= -0,403; P=0,033).

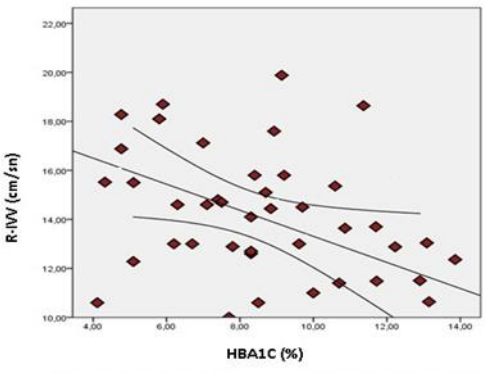

Figure 1. Graph showing the correlattion between R-IVV and HBA1C

On the other hand, there were no statistically significant correlations between DM duration and right heart function parameters (Table 4).

Table 1. Demographic, clinical and biochemical characteristics of DM and control groups (LDL: Low-density lipoprotein, HDL: High-density lipoprotein)

Variables	DM group	Control group	*P*
Age (years)	54,47±9,8	50,64±9,1	0,079
Male / Female (n)	35/18	36/15	0,086
Fasting blood glucose (mg/dl)	183,89±8,12	97,33±6,16	<0,0001
LDL (mg/dl)	121,43±38,21	156±47,12	0,008
HDL (mg/dl)	41,14±11,12	51,83±11,17	0,003
Triglyceride (mg/dl)	211,00±78,24	167,83±59,96	0,32
Total cholesterol (mg/dl)	202,43±42,19	242,22±51,79	0,007
Blood urea nitrogen (mg/dl)	30,20±14,01	25,64±10,56	0,24
Creatinine (mg/dl)	0,83±0,20	0,79±0,13	0,51
Sodium (mEq/L)	139,26±2,72	140±1,79	0,22
Potasium (mEq/L)	4,09±0,40	4,15±0,43	0,64

Table 2. Right heart parameters of DM and control groups (RV: Right ventricle, RA: Right atrium, TAPSE: tricuspid annular plane systolic excursion, AcT: Acceleration time, R-IVV: right ventricular myocardial velocity during isovolumic contraction, R-IVA: right ventricular myocardial acceleration during isovolumic contraction, EF: Ejection fraction)

Variables	Dm group	Control group	*P*
RV diameter (cm)	2,80±0,32	2,56±0,22	0,005
RA diameter(cm)	3,36±0,32	3,13±0,32	0,015
TAPSE (mm)	33,92±5,83	35,12±5,08	0,44
AcT (sn.)	0,043±0,009	0,042±0,012	0,87
R-IVV (cm/sn)	14,44±3,17	16,04±4,30	0,019
R-IVA(m/sn^2)	3,25±0,75	3,95±1,24	0,015
Left ventricular EF (%)	61,50±3,13	63,20±2,50	0,068

Table 3. Correlation analysis data of glycemic control and right heart function parameters. (RV: Right ventricle, RA: Right atrium, TAPSE: tricuspid annular plane systolic excursion, AcT: Acceleration time, R-IVV: right ventricular myocardial velocity during isovolumic contraction, R-IVA: right ventricular myocardial acceleration during isovolumic contraction)

Parameters	r value	*P*
RV diameter (cm)	-0.890	0.65
RA diameter (cm)	-0.138	0.49
TAPSE (mm)	0.76	0.70
AcT (sn)	-0.460	0.81
R-IVV (cm/sn)	-0.406	0.036
R-IVA (cm/sn^2)	-0.47	0.081

Table 4. Correlation analysis data of DM duration and right heart function parameters. (RV: Right ventricle, RA: Right atrium, TAPSE: tricuspid annular plane systolic excursion, AcT: Acceleration time, R-IVV: right ventricular myocardial velocity during isovolumic contraction, R-IVA: right ventricular myocardial acceleration during isovolumic contraction)

Parameter	r value	*P*
RV diameter (cm)	0.05	0.77
RA diameter (cm)	0.112	0.52
TAPSE (mm)	- 0.039	0.57
AcT (sn)	0.06	0.72
R-IVV (cm/sn)	- 0.281	0.39
R-IVA (cm/sn^2)	- 0.182	0.080

Discussion

In this study, we revealed that RA and RV diameters were significantly larger, R-IVV and R-IVA were significantly lower in T2DM patients free of clinical CVD. Although there was a significant negative correlation between glycemic control and R-IVV, we could not find any correlation between DM duration and right heart function. Moreover, HBA1C was an independent risk factor for R-IVV.

T2DM is a chronic metabolic disorder characterized by insulin resistance and hyperglycemia (7). Although the exact mechanism is unclear, diabetes mellitus (DM) causes pathological remodeling of the heart (8). Perivascular and interstitial fibrosis, left ventricular hypertrophy are pathognomonic signs of the diabetic heart (9). Extracellular matrix turnover abnormalities, induced by hyperglycemia, seems to be the possible starting point (8). ventricular hypertrophy and increased ventricular mass remain major morphological changes caused by hyperglycemia (10).

Most of the previous studies regarding diabetic changes were dedicated to the left ventricle. In a very recent study, Jorgensen *et al.*, showed that the increasing burden of uncontrolled metabolic risk factors was associated with structural and functional left ventricular dysfunction in T2DM patients (11). In a different study, DM duration was found to be associated with left ventricular structural and functional alterations (12). Furthermore, Wu *et al*., investigated chronic renal failure patients and postulated that patients also having T2DM have larger left ventricle mass (13). Besides, Aepfelbacher *et al*., postulated that improved glycemic control is associated with regression of septal thickness and left ventricular mass in type 1 DM patients (14).

Despite the most recent improvements in the era, RV remains the cardiac chamber for which scientific data regarding function, morphology, adaptation to loading is still behind what we know for the left ventricle. There is limited data analyzing the relationship between right heart function parameters and glycemic control. In a previous study, Morgan *et al.,* revealed that T2DM could influence the right ventricular function in the absence of coronary artery disease (15). In a histopathological study, Nunoda *et al*., concluded that RV cardiac myocyte diameter was significantly larger in DM patients (16). In our study, we showed that RA, RV diameters, although in normal limits, were significantly larger in DM patients, possibly because of the extracellular changes caused by hyperglycemia.

The amount of myocardial tissue in RV is significantly lesser than the left ventricle. Hence, the compensation capability of RV is limited. In our opinion, this makes RV more susceptible to any condition affecting RV even at the cellular level. That's why possible RV functional deterioration, even at the subclinical period, could be detected by using relevant echocardiographic techniques. Because of relative volume independence, IVA considered being a reliable index of global contractility used to analyze the systolic function of both ventricles (17). It has been successfully tested in various patient populations, including valvular heart diseases, heart failure, endocrine disorders (18,19). In a previous study, Suran *et al.*, showed that IVA might be used to assess early systolic alterations in both ventricles in type 1 DM patients (20). Our data showed that R-IVV and R-IVA were significantly lower in the DM group. There is hardly any data analyzing the relationship between glycemic control in T2DM and R-IVA in literature. In our study, although there was a significant negative correlation between R-IVV and glycemic control, the correlation between R-IVA and glycemic control was not statistically significant in T2DM. Possible toxic effect of hyperglycemia on RV myocytes seems to decrease the peak velocity reached. As a result, R-IVV decreases. Because the acceleration time also decreases, we could not find a significant decrease in R-IVA. Furthermore, we did not find a significant relationship between DM duration and right heart function parameters. According to the current knowledge, the risk of microvascular complications is directly related to the duration in which the vascular tree is exposed to the hyperglycemic state. The risk increases with a longer duration of hyperglycemia and decreases with intensive hyperglycemic treatment (21,22). In other words, good glycemic control overwhelms DM duration.

This study has limitations that warrant consideration. First, due to financial reasons, we couldn't evaluate volumes of the right heart. Second, it was a single-center study, and a certain number of patients were included. A study involving more patients could have more significant results and data.

In this study, we concluded that T2DM deteriorates RV functions, and there is a correlation between glycemic control and RV functions in patients free of clinical CVD. Furthermore, the effect of glycemic control on RV functions overwhelms DM duration. Finally, HBA1C might be an independent risk factor for the right heart

functions.

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