Original Article

Left Ventricular Size And Function In Patient With Type 2 Diabetes Mellitus Treated With Dipeptidyl Peptidase-4 Inhibitors

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Abstract

Background Patients with type 2 diabetes mellitus (T2DM) present with subclinical left ventricular systolic and/or diastolic dysfunction (LVD). Dipeptidyl peptidase-4 (DPP4) is an integral membrane glycoprotein that modulates the pathological state of diabetes mellitus (DM), and DPP4 inhibitors are a new class of anti-type-2 DM drugs. Recent preclinical studies have associated DPP4 inhibition with improved myocardial systolic and diastolic function, **Aim and objectives** to assess Effect of DPP4I on LV size and Function in type 2 DM patient, **Subjects and methods** This study was conducted on 76 patients (46 patients on random anti DM drug other than DPP4i and 30 patients not on DPP4i then they were prescribed by them) in cardiology and internal medicine departments in the faculty of medicine of Mansoura University between 2021-2022, **Result** There was statistically significant difference between the groups 1&2 and LV diameter IVSD, LV mass, LV mass index. There was statistically significant difference between the groups 1&3 and LV mass index. There was statistically significant difference between the groups 2&3 and LV diameter IVSD, LV mass and LV mass index, **Conclusion** We demonstrated significant improvements in LV diastolic function in patients treated with a dipeptidyl peptidase-4 inhibitor over 12 months. Therefore, DPP-4 inhibitor seems to have cardioprotective effects independent of glucose control and may have a role in the prevention of diabetic cardiomyopathy,

Keywords: Cardiovascular function, Dypeptidil-peptidase-4 inhibitor, Glucagon-like peptide 1, Type 2 diabetes mellitus (T2DM).

INTRODUCTION

The number of people with diabetes mellitus is increasing day by day due to population growth, aging, urbanization, increasing prevalence of obesity, stress and physical inactivity. The most common complication of Type 2 diabetes mellitus (T2DM) is the cardiovascular diseases (CVD), the leading cause of morbidity and mortality, accounting for 80% of deaths. The incidence of CVD is three to five times greater in diabetic patients than in those without diabetes **(1)**

The higher the prevalence of diabetes worldwide, the more the prescription number of antidiabetic remedy. It is projected that 366 million people will be diabetic in 2030, 290 million of whom will be living in developing countries .Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by insulin deficiency and insulin resistance. It is associated with a high risk of microvascular, cardiovascular and other complications **(2)**

Left ventricular dysfunction, increased left ventricular wall thickness, increased left ventricular mass and specific diabetic cardiomyopathy are some of the cardiovascular complications associated with diabetes. Left ventricular diastolic dysfunction has been demonstrated in diabetic patients who are normotensive and have no symptoms of cardiac disease. Increased mortality among type II diabetic patients with heart failure with normal ejection fraction also suggests a role for diastolic heart failure **(3)**

Many studies have shown that DM causes structural and functional abnormalities that are independent of the effect of atherosclerosis and these abnormalities contribute significantly to adverse cardiovascular events. Chronic hyperglycemia in DM expresses its toxicity by forming non-enzymatic glycation of tissue macromolecules, such as proteins, lipids, and deoxyribonucleic acid (DNA) to form irreversibly bound advanced glycated end products. Such products have been found to accumulate in tissues such as the heart **(4)**

Recently, the main challenges of T2DM treatment include: maintaining tight glycemic control, minimizing the risk of hypoglycemia, controlling cardiovascular risk factors (such as blood pressure and serum lipid concentrations), and reducing or controlling weight. Diabetic patients suffer from a high rate of cardiovascular events. Therefore, the

European Society of Cardiology (ESC) Guidelines on diabetes, pre-diabetes and cardiovascular disease (CVD) emphasize the need for a stringent approach in treating patients with diabetes, suggesting the importance of reducing the cardiovascular events **(5)**

Dipeptidyl peptidase-4 (DPP-4) inhibitors (DPP4i) are a pharmacological class of oral hypoglycemic drugs, which could prolong the action of the incretin peptide hormones glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP) by inhibiting their breakdown. Previous study suggested that DPP-4 inhibition might possibly have a beneficial cardiovascular effect in humans **(6)**

GLP-1 could suppress the release of glucagon from the pancreas. In addition, GLP-1 and GIP could also preserve or enhance β-cell function **(7)**

The levels of intact GLP-1 and GIP could decrease rapidly, due to enzymatic inactivation (mainly DPP-4) and renal clearance **(8)**
The aim of the study was to assess Effect of DPP4I on LV size and Function in type 2 DM patients

Subjects and Methods

This study is a case control study carried out at Mansoura University hospitals in both cardiology and internal medicine departments.

Target population 60 patients (30 patients on DPP4i and 30 patients not on DPP4i).
In this study we increased the 30 patient who are not on DPP4i "but on other random antidiabetic drug" to 46 patient and we called them "Group 1", and we devided the other sample of patients "DPP4i patients" into two groups one of them is before they take the DPP4i and the other one is after they took it by few months and we called them respectively "group 2" and "Group 3" , so we have 3 groups in this study; Group 1: 46 patients on random antidiabetic drug other than Dpp4i, Group 2: the 30 Dpp4i patients before they take the Dpp4i "Pre DPP4 inhibitors", Group 3: the 30 Dpp4i patients after they took the Dpp4i "Post DPP4 inhibitors"

Inclusion criteria Patients presented by Type 2 DM diagnosed by measuring blood glucose and by symptoms and treated with DPP4I and patients with Type 2 DM not treated by DPP4I.

Exclusion criteria Patients with Hypertension, Renal failure and Liver Cell Failure and patients with any associated CVD such as (CAD, MI, Arrhythmia, Valvular Heart diseases, Congenital Heart diseases).

Method

Clinical assessment History: complete history taking: In history taking, age, sex, residency, occupation, smoking or ex-smoker, presenting complaint, jaundice, itching, abdominal pain, presence of comorbidities, History of previous gastrointestinal bleeding, Age of diagnosis of diabetes and level of plasma glucose at time of diagnosis, duration of the disease and history of acute complication, use of oral hypoglycemics or Insulin dose (unit/kg/day) , other drug history that may affect the left ventricle "eg ACEI"
Clinical examination: General examination.
Investigations: FBG, HbA1C

ECG: 12 lead resting ECG: ECG was performed to patients as follow: Seven electrodes were positioned in a diagonal configuration, with three of them on the right side of the chest, and four on the left side. The wires and recorders were protected by one layer of elastic bandage and two layers of adhesive tape.

Echocardiography Conventional, tissue Doppler and two-dimensional speckle tracking echocardiography were performed using (GE Vivid) device.
All echocardiographic examinations were performed according to the recommendations of American society of echocardiography (ASE) and European association of cardiovascular imaging (EACVI)
Pulsed wave Doppler was used to record trans-mitral flow at the tips of the mitral leaflets in the apical four-chamber view.
Continuous wave Doppler was used to record velocity of tricuspid regurge systolic jet in apical four chamber view.
Peak velocity of early (E) and late (A) atrial diastolic filling of the Doppler Mitral flow, E/A ratio and E wave deceleration time (DT) were calculated.

Outcomes (Most important measurable outcomes)
Evaluation of Short term clinical outcome of all patients within 1 month or more for major adverse cardiac events (MACE) as regard CVS death.

Statistical analysis Analysis of data was done using Statistical Program for Social Science version 20 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described in the form of mean and standard deviation. Qualitative variables were described as number and percent. In order to compare parametric quantitative variables between two

groups, Student t test was performed. Qualitative variables were compared using chi-square (X_2) test or Fisher's exact test when frequencies were below five. Pearson correlation coefficients were used to assess the association between two normally distributed variables. When a variable was not normally distributed, A P value < 0.05 is considered significant.

Operational design The researcher introduced himself to all participants included in this study and asked them to participate after illustrating the goal of the study. All selected all participants received comprehensive information regarding objective and the expected benefit of the study. All ethical considerations were taken throughout the whole work.

Ethical Considerations The study was approved by Institutional Review Board (IRB)of faculty of medicine Mansoura University, the study is not funded, the candidate and all supervisor have no conflict of interest. The patients are treated according to the principles of declaration of Helsinki.

Results

In this study we reprotocolized the number of the Patient and we tried to increase the studied groups to get more accurate statistics; Group 1: 46 patients on random antidiabetic drug other than Dpp4i, Group 2: 30 Dpp4i patients Pre Dpp4i, Group 3: 30 Dpp4i patients Post DPP4i

Table (1) demographic characteristics of the studied groups

	Group 1 (n=46)	**Group2 (n=30)**	**Group3 (n=30)**	**test of significance**	**Paired significance**
Age/years mean±SD	47.48±8.78	48.83±10.22	48.83±10.22	F=0.258 P=0.773	P1=0.550 P2=0.550 P3=1.0
Sex Male Female	N(%) 25(54.3) 21(45.7)	N(%) 13(43.3) 17(56.7)	N(%) 13(43.3) 17(56.7)	 MC P=0.531	P1=0.34 P2=0.34 P3=1.0
Residence Dakahlia Sharkia	 30(100) 0	 30(100) 0	 30(100) 0	 MC P=1.0	P1=1.0 P2=1.0 P3=1.0
Smoking history non smokers smokers	 30(100) 0	 30(100) 0	 30(100) 0	 MC P=1.0	P1=1.0 P2=1.0 P3=1.0
Occupation Housewife Manual Office worker Retired	 10(33.3) 4(13.3) 10)(33.3) 6(20.0)	 12(40) 3(10) 7(23.3) 8(26.7)	 12(40) 3(10) 7(23.3) 8(26.7)	 MC P=0.117	 P1=0.09 P2=0.09 P3=1.0

F: One Way ANOVA test, MC: Monte Carlo test , P1:difference between group1 &2, P2:difference between group1 & 3, P3: difference between group2& group3

This table shows that there was statistically insignificant difference between the groups (1&2) and (1&3) and sex, residence, smoking history and occupation. There was statistically insignificant difference between the groups (2&3) and sex, residence, smoking history and occupation. There was statistically insignificant difference between the studied groups and Age

And as regard the drug history there were no history of non-diabetic drugs that may affect the left ventricle "eg ACEI" About 13 patients of the group 1 were using insulin as a part of their anti-diabetic medics for less than 10 years

Table (2) ECG findings of the studied groups

ECG	**Group 1 (n=46)**	**Group2 (n=30)**	**Group3 (n=30)**
LT BBB	1(2.2)	0	0
Normal	37(80.4)	30(100)	30(100)
RT BBB	1(2.2)	0	0
Sinus bradycardia	2(4.4)	0	0
TWI in III	1(2.2)	0	0
TWI in AVL	3(6.5)	0	0
TWI in VI	1(2.2)	0	0

This table shows that according to ECG findings, there were 37 (80.4%) of the group 1 had Normal ECG , 1 (2.2%) had LT BBB, 1 (2.2%) had RT BBB, 2 (4.4%) had Sinus bradycardia, 1 (2.2%) had TWI in III, 3 (6.5%) had TWI in AVL and 1 (2.2%) had TWI in VI**.** There were 30 (100%) of the group 2 had normal ECG and 30 (100%) of the group 3 had Normal ECG

Table (3) Comparison between echocardiographic parameters of the 3 groups

	Group 1 (n=46)	Group2 (n=30)	Group3 (n=30)	test of significance	Paired significance
LV diameter LVIDd	50.566±6.52	49.33±3.89	50.33±3.75	F=0.541 P=0.584	P1=0.313 P2=0.849 P3=0.456
LV diameter IVSD	10.61±2.28	9.17±1.23	10.20±1.47	F=5.77 P=0.004*	P1=0.001* P2=0.341 P3=0.03*
LV mass	270.50±64.13	159.47±31.98	190.53±38.24	F=8.41 P<0.001*	P1<0.001* P2=0.151 P3=0.018*
LV mass index	96.28±27.49	71.50±14.21	85.33±17.27	F=11.87 P<0.001*	P1<0.001* P2=0.034* P3=0.015*
LV systolic function "M-Mode"	61.30±10.32	61.53±5.35	61.67±5.42	F=0.02 P=0.980	P1=0.902 P2=0.846 P3=0.948
LV systolic function Simpson	64.67±10.17	61.70±5.17	61.57±5.22	F=0.003 P=0.997	P1=0.989 P2=0.953 P3=0.947
LV diastolic function Normal Grade I Grade II	 20(43.5) 24(52.2) 2(4.3)	 30(100) 0 0	 30(100) 0 0	 χ2MC=44.93 P<0.001*	 P1<0.001* P2<0.001* P3=1.0

Parameters described as mean±SD

F:One Way ANOVA test , MC:Monte Carlo test , P1:difference between group1 &2 , P2:difference between group1 & 3, P3: difference between group2& group3

This table shows that there was statistically significant difference between the groups 1&2 as regard LV thickness IVSd, LV mass, LV mass index and Diastolic function. There was statistically significant difference between the groups 1&3 as regard LV mass index and diastolic dysfunction. There was statistically significant difference between the groups 2&3 as regard LV thickness IVSd, LV mass and LV mass index.

Table (4) Comparison between HBA1C and glucose assessment of the studied groups

	Group 1 (n=46)	Group2(n=30)	Group3(n=30)	test of significance	Paired significance
HbA1c	8.76±1.27	12.67±1.83	6.97±1.35	F=119.82 P<0.001*	P1<0.001* P2<0.001* P3<0.001*
FBG	122.67±38.43	170.80±33.56	130.13±30.98	F=18.17 P<0.001*	P1<0.001* P2=0.373 P3<0.001*
2H PPG	263.89±51.74	274.60±42.79	218.13±37.89	F=13.36 P<0.001*	P1=0.320 P2<0.001* P3<0.001*

F:One Way ANOVA test , MC:Monte Carlo test , P1:difference between group1 &2 , P2:difference between group1 & 3, P3: difference between group2& group3

Parameters described as mean±SD

This table shows that there was statistically significant difference between the groups (1&2) as regard HbA1c and FBG. There was statistically significant difference between the groups (1&3) as regard HbA1c and 2H PPG. There was statistically significant difference between the groups (2&3) as regard HbA1c, FBG and 2H PPG. There was statistically insignificant difference between the groups (1&3) as regard FBG. There was statistically insignificant difference between the groups (1&2) as regard 2H PPG.

Table (5) correlation between laboratory findings and echocardiographic findings among group 1

		LV diameter LVIDd	LV diameter LVSD	LV mass	LV mass INDEX	LV systolic function"M-Mode"	LV systolic function Simpson	LV diameter LVIDd	LV diastolic function
HbA1c	R	.061	-.068	.073	.077	.021	.002	.164	.164
	P	.687	.653	.628	.611	.891	.990	.275	.275
FBG	R	-.069	.040	-.078	-.046	-.107	-.034	-.036	-.036
	P	.647	.790	.608	.763	.478	.822	.811	.811
PP2H	R	.041	-.121	-.075	-.117	.023	.017	-.015	-.015
	P	.786	.422	.620	.439	.879	.911	.922	.922
HB	R	-.167	-.030	-.113	-.123	.187	.313*	.023	.023
	P	.266	.842	.453	.416	.213	.034	.878	.878
PLT	R	.158	-.107	-.074	-.099	.064	.026	-.052	-.052
	P	.296	.481	.625	.514	.671	.862	.732	.732
TLC	R	-.154	.043	-.034	-.008	.022	-.045	.031	.031
	P	.307	.778	.821	.956	.887	.765	.836	.836
ALT	R	-.074	-.051	-.185	-.186	.138	.150	-.059	-.059
	P	.627	.739	.219	.215	.361	.321	.696	.696
AST	R	.165	.021	.117	.088	-.007	.003	.207	.207
	P	.273	.890	.439	.563	.961	.986	.168	.168
ALB	R	.258	-.094	-.035	.037	-.327*	-.251	.240	.240
	P	.084	.533	.815	.806	.027	.092	.109	.109
UREA	R	.249	-.085	.136	.175	-.090	-.123	.057	.057
	P	.095	.572	.369	.245	.553	.415	.708	.708
S.CR	R	.026	.212	.258	.286	-.178	-.185	.301*	.301*
	P	.863	.157	.083	.054	.238	.219	.042	.042
FT3	R	.139	.076	.110	.123	-.141	-.216	.206	.206
	P	.358	.618	.467	.417	.350	.150	.170	.170
FT4	R	.364*	-.089	.168	.113	-.167	-.187	-.098	-.098
	P	.013	.557	.266	.455	.266	.214	.516	.516
TSH	R	-.046	.028	.094	.114	-.008	-.062	.085	.085
	P	.760	.854	.534	.449	.959	.681	.572	.572

r:Spearman correlation co-efficient

This table shows that there was statistically significant positive correlation between HB and LV systolic function by Simpson method. There was statistically significant positive correlation between FT4 and LVIDd. There was statistically significant difference with positive correlation between S.CR and LVIDd.

Table (6) correlation between laboratory findings and echocardiographic findings among group3

		LV diameter LVIDd	LV diameter IVSD	LV mass	LV mass INDEX	LV systolic function"M-Mode"	LV systolic function Simpson
HbA1c	R	.048	.208	.171	.178	.034	.035
	P	.801	.269	.365	.348	.858	.856
FBG	R	.323	-.156	-.054	-.062	-.229	-.224
	P	.082	.410	.778	.746	.223	.234
PP2H	R	.139	-.057	-.056	-.067	-.131	-.199
	P	.463	.763	.767	.724	.489	.291
HB	R	-.054	.300	.188	.194	.029	.171
	P	.778	.107	.319	.305	.880	.365
PLT	R	-.231	.033	-.077	-.088	-.183	-.061
	P	.219	.864	.687	.644	.334	.747
TLC	R	-.031	.200	.152	.153	-.156	-.229
	P	.871	.289	.424	.419	.410	.223
ALT	R	-.277	.021	-.043	-.045	.049	-.047
	P	.139	.914	.820	.813	.798	.805
AST	R	-.117	.065	.075	.082	.410*	.230
	P	.538	.735	.696	.667	.025	.221
ALB	R	-.139	.317	.222	.224	.245	.290
	P	.463	.088	.239	.234	.192	.120
UREA	R	-.128	.062	-.033	-.031	-.102	-.004
	P	.501	.745	.861	.871	.591	.983
S.CR	R	-.154	.032	-.082	-.076	.001	.210
	P	.416	.866	.667	.689	.996	.265
FT3	R	-.235	-.064	-.082	-.080	-.141	-.051
	P	.211	.738	.668	.675	.458	.791
FT4	R	-.385*	.080	-.065	-.069	.011	.123
	P	.036	.674	.735	.718	.953	.518
TSH	R	-.053	-.272	-.218	-.213	.075	.122
	P	.783	.145	.247	.259	.693	.521

r: Spearman correlation co-efficient

This table shows that there was statistically significant positive correlation between AST and LV systolic function "M-mode". There was statistically significant negative correlation between FT4 and LVIDd.

Discussion

a number of experimental evidences suggest that DPP4I may provide cardioprotective actions beyond their glucose lowering effect. For instance, it has been reported that DPP4 inhibition prevents LV dilatation and myocardial remodeling in diabetic and non-diabetic animals exhibiting elevated DPP4 cardiac activity. Interestingly, increased plasma DPP4 activity (DPP4a) has been found to be associated with LVD in animals and patients with HF **(9).**

The study was done on 76 patients (46 patients on random anti diabetic drug other than DPP4i and 30 recently discovered type 2 diabetes mellitus patients on DPP4i therapy only and followed up using transthoracic Echocardiographic data , ECG and other labs), we divided these patients into 3 groups : Group 1 which include T2DM on random antidiabetic drug other than DPP4i , Group 2 which include naïve recently discovered type 2 DM before they take the DPP4i , Group 3 the same group 2 after DPP4i for 12 months.
In this study we compared group 1 with group 3, then compared group 2 with group 3 to assess the effect of DPP4i on LV size and function in T2DM

In this study we tried to choose the type patients who have a similar risk profile so that we can study the effect of the drug on the myocardium without any other factor that may affect the myocardium and we found that there were statistically insignificant difference between the groups without DPP4i therapy & those with DPP4i.

Our attitude is similar to **Fujiwara et al. (10)** whose baseline characteristics including age, sex, residence, smoking history and occupation did not significantly differ between the DPP4-I and non-DPP4-I groups
Although we tried to match the clinical characteristics of patients on DPP4i with those in the control group, and the decision to put DPP4i as an anti-hyperglycemic therapy in the clinic was made by clinicians but it was small group of patients for short duration due to limited financial resources and thus subjected to various biases.

In this study we demonstrated that according to ECG findings, there were 37 (80.4%) of the group 1 had normal ECG, 1 (2.2%) had Lt BBB, 1 (2.2%) had Rt BBB, 2 (4.4%) had Sinus bradycardia, 1 (2.2%) had T wave inversion in lead III, 3 (6.5%) had T wave inversion in lead aVL and 1 (2.2%) had T wave inversion in lead VI**.** All patients of group 2&3 were in sinus rhythm.

In this study we also illustrated that there was statistically significant difference between the groups 1&2 as regard LV thickness IVSd, LV mass, LV mass index and Diastolic function ; thus we can see that the IVSd , LV mass and LV mass index were smaller in group 2 than group 1 while Diastolic dysfunction was more common in group 1. We noticed a statistically significant difference between the groups 1&3 as regard LV mass index and diastolic dysfunction which is decrease in mass index in group 3 than group 1, but the Diastolic function showed improvement in DPP4i than other antidiabetic drugs; this means that DPP4i has cardio protective effect on the myocardium in comparison to patients on other anti-diabetic drugs. We also noticed statistically significant difference between the groups 2&3 as regard left ventricular thickness "IVSd" , LV mass and LV mass index in that we can notice that all the three are increased in group 3 than group 2 but this difference is too small and didn't induce a pathological state like dilated or hypertrophied myocardium. There was statistically insignificant difference between all groups as regard LV systolic function either by "Simpson method" or by "M-Mode".

Our thesis was similar to several preclinical studies which found that DPP4 inhibition improves diastolic function. **Shigeta et al. (11)** reported that DHF improves without coronary artery disease. The ratio of matrix metalloproteinase-2 (MMP-2) to tissue inhibitor of MMP-2 increases in a DPP4-dependent fashion in patients with DM, which causes DHF with enhanced interstitial fibrosis. Pharmacological DPP4 inhibition reverses DM-induced fibrosis via the MMP-2 axis and DHF via the m-DPP4/SDF-1α axis of angiogenesis. Inhibiting DPP4 also reverses DHF induced by pressure overload via a GLP-1/cAMP-dependent mechanism distinct from that in the diabetic heart. **Connelly et al. (12)** reported that DPP4 inhibition results in increased SDF-1α and an improved end-diastolic pressure–volume relationship.

However, we were dissimilar to **Nogueira et al. (13)** who found that no significant differences in the echocardiographic evaluation of the diastole were detected between groups at baseline. Left ventricular diastolic dysfunction (LVDD) was diagnosed in 53% (8/15) of patients in the SITA group and in 64% (9/14) of patients in the NPH group ($p = 0.710$).
Our study was similar to **Nogueira et al. (13)** found that sitagliptin treatments resulted in significant decrease in HbA1c values from baseline ($p < 0.001$).

Also we were similar to **Leung et al. (14)** who found that patients in both groups had better glycaemic control compared to that at baseline, but we were dissimilar to him because he found that there was no difference in the degree of reduction in HbA_{1c} between the two groups (1.8% vs 1.3%, p = 0.260).

We were dissimilar to **Fujiwara et al. (10)** who found that HbA1c did not significantly differ between the DPP4-I and non-DPP4-I groups (−1.3 ± 1.1 vs. −1.3 ± 1.9 %, p = 0.37).

This dissimilarity between our study and some studies may be because it was small pilot study and for shorter duration of follow up of the anti-hyperglycemic drugs. Netherless to say that even if the groups were not completely equal as regard diabetes duration and therapy we demonstrated that subjects on DPP4i had improvement in glucose control in comparison to other group of non DPP4i.

In this study we found that among group 2, there was statistically significant difference with positive correlation between FBG and LV diameter "LVIDd". There was statistically significant difference with negative correlation between ALB and LV diameter "LVIDd". There was statistically significant difference with positive correlation between AST and LV systolic function "by Simpson method".

We were similar to **Hashikata et al. (15)** who found that improvement in LV diastolic dysfunction ,but did not show correlation with glucose-lowering effects but showed a significant negative correlation with endothelial function. He demonstrated that improvement in diastolic function was accompanied by a decrease in the HbA1c levels, which suggests that improvement in diabetes metabolism may lead to amelioration of cardiac function. However, 71 % (10/14) of the patients improved diastolic function in patients with <1 % decrease or increase in the HbA1c levels after teneligliptin treatment.

We were dissimilar to **Ravassa et al. (16)** found that plasma DPP4a was inversely associated with LVSWi (β = -0.210, p = 0.025), LVEF (β = -0.291, p = 0.040) and MFS (β = -0.365, p = 0.008) independently of all the considered potential confounding factors (HbA1c, SBP, presence of CKD, anti-hypertensive treatment and anti-diabetic treatment).

Among group 3, we found that there was statistically significant difference with positive correlation between AST and LV systolic function. There was statistically significant difference with negative correlation between FT4 and LV diameter LVIDd.
We were similar to **Ewid et al. (17)** found a mild significant correlation between AST/ALT ratio and and LVEF ($r = -0.24$; $P < 0.05$).

We concluded that addition of DPP-4 inhibitor therapy with sitagliptin to the treatment protocol of patients with T2DM and CAD is associated with a sustained improvement in myocardial performance, DPP-4 inhibitor may have had cardioprotective effects, seemingly beyond and independent of glucose control, with positive effects on left ventricular diastolic function. Therefore, the DPP-4 inhibitor may be a promising drug for the prevention of diabetic cardiomyopathy.

Conclusion

We demonstrated significant improvements in LV diastolic function in patients treated with a dipeptidyl peptidase-4 inhibitor over 12 months. Therefore, DPP-4 inhibitor seems to have cardioprotective effects independent of glucose control and may have a role in the prevention of diabetic cardiomyopathy as regard the left ventricular size we found minimal increase in size of the left ventricle but didn't progress to a pathological condition during the period of follow up.

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