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Improved diastolic function in type 2 diabetes after a six month liraglutide treatment

Fabio Saponaro [a], *Andrea Sonaglioni* [b], *Antonio Rossi* [a], *Laura Montefusco* [a], *Michele Lombardo* [b], *Guido Adda* [a], *Maura Arosio* [a,c,*]

[a] *Unit of Endocrine Diseases and Diabetology, San Giuseppe Hospital, Multimedica IRCCS, Milan, Italy*
[b] *Unit of Cardiology, San Giuseppe Hospital, Multimedica IRCCS, Milan, Italy*
[c] *Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy*

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ABSTRACT

Aims: To investigate whether liraglutide improves diastolic function in type 2 diabetes.
Methods: Thirty-seven patients with type 2 diabetes who began liraglutide therapy between June 2013 and May 2014 were enrolled in this observational, prospective study. 26 patients received liraglutide therapy for at least 6 months. The remaining 11 patients withdrew from liraglutide therapy during the first month, were started on other hypoglycaemic therapies and formed the control group. Anthropometric, metabolic and echocardiographic parameters including pulsed wave tissue Doppler imaging were evaluated at baseline and at 6 months.
Results: In the liraglutide group the early diastolic mitral annulus velocity on the lateral (e-lat) and medial (e-med) sides of the mitral annulus increased from 9.2 ± 3.4 to 11.6 ± 4.7 cm/s ($p < 0.001$) and from 6.9 ± 1.7 to 8.4 ± 2.6 cm/s ($p < 0.003$), respectively. The ratio of early-to-late velocities on the lateral and medial sides of the mitral annulus increased from 0.7 ± 0.3 to 0.9 ± 0.4 ($p < 0.001$) and from 0.5 ± 0.1 to 0.6 ± 0.1 ($p < 0.02$), respectively. The ratio of early diastolic mitral inflow velocity to early diastolic myocardial relaxation velocity decreased from 10.7 ± 4.3 to 8.5 ± 2.5 ($p < 0.005$). No improvements in diastolic function was detected in the control group. Glucose control improved similarly in both groups: HA1bc −1.5% (−17 mmol/mol) vs −1.3% (−14 mmol/mol), $p = 0.67$.
Conclusions: In patients with type 2 diabetes, 6 months liraglutide treatment was associated with a significant improvement in diastolic function.
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1. Background

Cardiovascular complications are the main cause of diabetes-related morbidity and mortality [1]. Diabetic cardiomyopathy (DCM) increases the risk of heart failure and death regardless of coexisting coronary artery disease or concomitant risk factors [2,3]. The prevalence of DCM in patients with type 2 diabetes (T2D) may be as high as 60% [4]. DCM is characterized by a wide range of structural abnormalities, including ventricular dilation, myocardial fibrosis and steatosis, cardiomyocyte apoptosis, amyloid deposition and interstitial edema. The pathogenesis of DCM involves a multifactorial

* *Corresponding author at*: Unit of Endocrine Diseases and Diabetology, San Giuseppe Hospital, Multimedica IRCCS, and Department of Clinical Sciences and Community Health, Univ. of Milan, Via San Vittore, 12, 20123 Milan, Italy. Tel.: +39 0285994288; fax: +39 0285994033.
E-mail address: maura.arosio@unimi.it (M. Arosio).
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process that includes microvascular damage as a major contributor [5]. The pathological role of endoplasmic reticulum oxidative stress has recently been underlined [6,7].

Diastolic dysfunction (DD) is the leading element of DCM [8]. In particular, left ventricular DD (LVDD) is characterized by impaired early diastolic filling, prolonged isovolumetric relaxation and increased atrial filling. It has been described as an early sign of diabetic myocardial disease, and precedes systolic damage and heart failure [9,10]. Cardiac catheterization is the gold standard for assessing DD [11]. However, cardiac catheterization is invasive and cannot be performed in everyday clinical practice [12]. Doppler echocardiography has emerged as an important, noninvasive, diagnostic tool for DD [13].

Liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, is a new therapeutic tool for T2D. It has considerable efficacy in glycemic control and weight loss, good safety and a low risk of causing hypoglycemia [14–17]. Liraglutide has also been shown to have a beneficial effect on the cardiovascular system in both animals and humans [18]. Furthermore, it is known that the GLP-1 receptors are widely expressed in heart and vessels [19].

Preclinical and clinical trials have concentrated on the cardioprotective benefits of liraglutide by decreasing blood pressure, promoting weight loss and improving the lipid profile [20]. A randomized trial called "liraglutide effects and action in diabetes: evaluation of cardiovascular outcome results" (LEADER), is currently ongoing [21].

There is some evidence of positive effects of liraglutide in animal models [22] and humans with ischemic heart disease [23] or after reperfusion [24]. In these models, liraglutide increased regional wall motion, cellular tolerability to ischemia and the ejection fraction, and reduced infarct size [25].

Studies of the effects of liraglutide on DCM are limited and have all been performed in animals. A GLP-1 receptor agonist (GLP-1 RA) increased myocardial glucose uptake independently of its ability to enhance insulin secretion and enhanced survival of cardiac cells, improving overall cardiac function [26]. There are currently no published studies on the effects of liraglutide on DCM in humans.

Thus, the aim of this study was to evaluate the effects of 6 months treatment with liraglutide on DCM in patients with T2D.

2. Methods

2.1. Patients

Patients with T2D who began liraglutide therapy in our Diabetes Unit between June 2013 and May 2014 were enrolled in this observational, prospective study. Diagnosis of diabetes was made according to current American Diabetes Association criteria [27]. Diagnosis of DD was made according to the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE) recommendations [28]. All patients gave written informed consent for the use of personal data. Study protocol was approved by local ethic committee. Other inclusion criteria were age between 18 and 80 years, inadequate glycemic control before introducing therapy with liraglutide (glycated hemoglobin [HbA1c] >7.0% or >53 mmol/mol), and no clinical history of acute coronary syndrome, myocardial revascularization or heart failure classified as a New York Heart Association (NYHA) class III or IV. Exclusion criteria were a diagnosis of type 1 diabetes, baseline HbA1c > 12% (108 mmol/mol), active neoplasia, hepatic dysfunction (defined as alanine aminotransferase and aspartate aminotransferase more than three times the upper limit of normal values), pregnancy and severe chronic kidney disease (defined as estimated glomerular filtration rate <30 mL/min/1.73 m^2). Patients with a psychiatric disorder or history of alcohol or drug abuse were excluded. Before initiating liraglutide therapy, all patients were receiving hypoglycemic therapy, as monotherapy or in combination. Most patients were treated with lipid-lowering and anti-hypertensive drugs (Table 1). No modifications to lipid-lowering drugs or anti-hypertensive therapies were allowed during the study period.

Of 37 enrolled patients, 26 completed 6 months therapy and constituted the liraglutide group (LG).

Liraglutide was prescribed in accordance with the current clinical guidelines.

In all of patients, liraglutide was started at a dose of 0.6 mg/day, increased to 1.2 mg/day after 1 week. In patients with insufficient glycemic response, the dose was further increased during the first month, up to 1.8 mg/day.

Patients who withdrew liraglutide therapy within the first month were started on other hypoglycemic therapies that did not include GLP-1 RA or dipeptidyl peptidase-IV inhibitors (DPP-4i). These 11 patients were used as the control group (CG).

2.2. Outcome measures

Anthropometric, metabolic and echocardiographic parameters were evaluated at baseline and at 6 months from the beginning of therapy. Clinical parameters, side effects, and glycemic reports were evaluated at 2 weeks and 4 weeks after the beginning of therapy and then as needed.

2.2.1. Anthropometric and metabolic parameters

Data were collected at baseline and 6 months after the beginning of therapy for age, sex, duration of diabetes, presence of diabetes complications, height, body weight (BW), body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP) and history of previous anti-diabetic therapy. HbA1c was measured by a DCCT-aligned high-performance liquid chromatography (Tosoh Corporation, Tokyo, Japan); fasting blood glucose (FBG) by glucose hexokinase method, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides by an enzymatic method (ADVIA Chemistry Systems 1800, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA); the low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald formula.

2.2.2. Echocardiographic parameters

Transmitral PW Doppler analysis was used to evaluate peak early (*E*) and late (*A*) ventricular filling velocities, *E*/*A* ratio, deceleration time (DT) of early filling velocity, and isovolumic relaxation time. PW-TDI was used to evaluate early (*e′*) and late (*a′*) diastolic peak velocities on the lateral (lat.) and septal

Table 1 – Baseline characteristics.

	Liraglutide group	Control group
N (M/F)	26 (15/11)	11 (7/4)
Age (years)	61.7 ± 10*	63.5 ± 10.7
Diabetes duration (years)	11.1 ± 8.4*	13.0 ± 12.0
Hypoglycemic drugs		
Metformin (%)	84.6	60.0
Sulfonylureas/glinides (%)	23.0	20.0
Acarbose (%)	3.8	0.0
Pioglitazone (%)	15.3	0.0
Dipeptidyl peptidase-IV inhibitors (%)	30.7	6.6
Insulin (%)	30.7	33.3
Other medications		
Statins (%)	61.5	33.3
Angiotensin-converting-enzyme inhibitors (%)	30.7	26.6
Sartans (%)	23.1	40.0
Beta blockers (%)	34.6	26.6
Calcium channel blockers (%)	23.1	13.3
Diuretics (%)	19.2	53.3

Continuous data are presented as mean ± standard deviation.
* *p*: NS compared to control.

(medial or med.) sides of the mitral annulus, the e'/a' ratio, and the ratio of early diastolic mitral inflow velocity (E) to early diastolic myocardial relaxation velocity (a' average). PW Doppler analysis of pulmonary venous flow was used to evaluate peak antegrade systolic (S) and diastolic (D) velocities, the S/D ratio, and peak velocity and duration of atrial reversal (Ar) in late diastole.

Normal diastolic function was defined as e' med. $\geqslant$ 8 cm/s and e' lat. $\geqslant$ 10 cm/s [29]. DD was defined as e' med. < 8 cm/s or e' lat. < 10 cm/s, and was classified according to ASE/EAE recommendations [28] as Grade I (mild) if $E/A < 0.8$, DT > 200 ms and E/e' average $\leqslant$ 8; Grade II (moderate) if E/A 0.8–1.9, DT 160–200 ms and E/e' average 9–12; and Grade III (severe) if $E/A \geqslant 2$, DT < 160 ms and E/e' average $\geqslant$ 13 [28,29].

All echocardiograms were performed by the same cardiologist using the same ultrasound system (Philips CX 50 with 2.5–3.5 MHz probes).

2.3. Statistical analysis

Continuous data are expressed as mean ± standard deviation. Categorical data are presented as percentage. Normality of data was evaluated with the Kolmogorov–Smirnov test. Within each group, a paired Student's t test was used to compare means between baseline and 6 months. At baseline an unpaired two-tailed Student's t test was used to compare means between the liraglutide and control groups; at 6 months Student's t test was used to compare changes in metabolic parameters. Linear regression was used to quantify the relation between the change in metabolic variables (HbA1c, body weight) and the change in diastolic function (e' on the lateral side of the mitral annulus). Statistical significance was accepted at $p < 0.05$. Data were analyzed using SPSS software, version 20.

3. Results

Thirty-seven patients with T2D (22 men, 15 women) were recruited. In 11 patients (7 men, 4 women), liraglutide therapy was interrupted during the first month because of gastrointestinal side effects (such as nausea or vomiting) or inefficacy. In these patients, an improvement of glucose control was obtained using other hypoglycemic agents, such as metformin, sulfonylureas, glinides or insulin. These patients formed the CG. Patient characteristics are provided in Table 1. At baseline, there were no differences in clinical characteristics or metabolic variables between the two groups (Tables 1 and 2, respectively). Twenty-six patients received liraglutide therapy for at least 6 months. In 18 patients, the dose of liraglutide was 1.2 mg/day throughout the study period; in the remaining 8 patients, it was increased to a maximum of 1.8 mg/day over the first month.

3.1. Metabolic parameters

At baseline, the mean BMI of the LG was in the range classified as obese (32.8 ± 4.2 kg/m^2) and glycemic control was poor (HbA1c: 9.0 ± 1.6% [75 ± 18 mmol/mol]; fasting blood glucose: 190.8 ± 56.2 mg/dl). After 6 months of treatment with liraglutide, there were significant improvements in glycemic control (ΔHbA1c: −1.5% [−17 mmol/mol], $p = 0.0006$; ΔFBG: −38.9 mg/dl, $p = 0.074$) and anthropometric parameters (ΔBW: −3.7 kg, $p = 0.0005$; ΔBMI: −1.2 kg/m^2, $p = 0.0009$; ΔWC: −1.6 cm, $p = 0.019$; Table 2).

At baseline, the mean BMI of the CG group was also in the range classified as obese (35 ± 6.1 kg/m^2) and glycemic control was also poor (HbA1c: 9.0 ± 1.8% [75 ± 20 mmol/mol]; FBG: 186.2 ± 76.4 mg/dl; Table 2). After 6 months of treatment, there was a significant improvement in HbA1c (ΔHbA1c:

Table 2 – Metabolic parameters.

	Liraglutide group			Control group		
	Baseline	6 months	*p*	Baseline	6 months	*p*
HbA1c (%)°	9.0 ± 1.6*	7.5 ± 1.3	0.0006	9.0 ± 1.5	7.7 ± 1.3	0.042
FPG (mg/dl)	190.8 ± 56.2*	151.9 ± 43.2	0.074	196.2 ± 76.4	157.1 ± 68.4	0.22
BW (kg)	91.0 ± 15.4*	87.3 ± 15.3	0.0005	90.9 ± 19.6	91.3 ± 18.3	0.96
WC (cm)	112.6 ± 11.9*	111.0 ± 10.4	0.019	119.3 ± 14.0	119.7 ± 13.6	0.94
BMI (kg/m^2)	32.8 ± 4.2*	31.6 ± 4.1	0.0009	35.0 ± 6.1	35.2 ± 5.7	0.93
SBP (mmHg)	130.4 ± 17.5*	129.0 ± 13.8	0.75	137.5 ± 18.9	137.3 ± 19.2	0.98
DBP (mmHg)	76.9 ± 9.8*	77.1 ± 9.3	0.94	77.5 ± 16.7	81.1 ± 17.0	0.62
TC (mg/dl)	175.0 ± 30.5*	163.4 ± 32.4	0.19	203.3 ± 84.3	195.2 ± 81.6	0.82
HDL (mg/dl)	48.9 ± 12.0*	48.6 ± 10.6	0.92	47.5 ± 8.1	48.1 ± 7.5	0.85
TG (mg/dl)	173.2 ± 122.8*	134.7 ± 84.5	0.19	200.7 ± 104.2	187.4 ± 89.3	0.75
LDL (mg/dl)	92.4 ± 26.3*	88.3 ± 29.9	0.6	92.0 ± 26.3	91.3 ± 24.8	0.95

Abbreviations: HbA1c, glycated hemoglobin; FPG, fasting blood glucose; BW, body weight; WC, waist circumference; BMI, body mass index, SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL, high-density lipoproteins; TG, triglycerides; LDL, low-density lipoproteins.

* *p*: NS compared to baseline in control group.

° *p*: NS when compared the improvement between the two groups.

−1.3% [−14 mmol/mol], $p = 0.042$; Table 2). There were no significant changes in FBG or anthropometric parameters.

The improvement in HbA1c from baseline to 6 months was similar in the two groups ($p = 0.67$). ΔFBG was similar between the two groups (−38.9 for LG, −39.1 for CG), but was significant only for the LG; this was likely due to the different numerosity of the two groups.

Lipid profile of both groups was typical of secondary dyslipidemia at baseline and was unchanged after treatment, such as mean SBP and DBP (Table 2).

3.2. *Echocardiographic parameters*

The echocardiographic parameters reflecting diastolic function were similar in the two groups at baseline, except for

Table 3 – Echocardiographic parameters.

	Liraglutide group			Control group		
	Baseline	6 months	*p*	Baseline	6 months	*p*
Transmitral PW Doppler imaging						
E-wave (cm/s)	79.9 ± 17.1*	82.4 ± 14.9	0.46	90.2 ± 24.3	113.0 ± 35.4	0.09
DT (m/s)	181.3 ± 32.6*	184.5 ± 23.9	0.66	189.3 ± 37	163.3 ± 31.6	0.33
A-wave (cm/s)	97.0 ± 18.5°	99.1 ± 18.8	0.47	110.5 ± 8.4	119.7 ± 29.8	0.38
E/A ratio	0.8 ± 0.2*	0.8 ± 0.2	0.44	0.8 ± 0.3	1.0 ± 0.4	0.09
IVRT (ms)	79.9 ± 13.3*	78 ± 12.7	0.66	85.0 ± 17.6	79.5 ± 18.4	0.44
PW tissue Doppler imaging						
e′ lat.-wave (cm/s)	9.2 ± 3.4*	11.6 ± 4.7	0.0006	9.2 ± 2.5	8.1 ± 2.0	0.31
a′ lat.-wave (cm/s)	13.8 ± 3.3*	14.5 ± 4.0	0.30	16.3 ± 6.1	15.7 ± 4.3	0.85
e′/*a′* lat. ratio	0.7 ± 0.3*	0.9 ± 0.4	0.0001	0.6 ± 0.2	0.5 ± 0.1	0.47
e′ med.-wave (cm/s)	6.9 ± 1.7*	8.4 ± 2.6	0.0031	7.3 ± 2.4	7.7 ± 2.2	0.78
a′ med.-wave (cm/s)	12.6 ± 3.0*	13.1 ± 3.5	0.51	12.3 ± 3.7	13.7 ± 5.5	0.46
e′/*a′* med. ratio	0.5 ± 0.1*	0.6 ± 0.1	0.0139	0.6 ± 0.1	0.6 ± 0.2	0.76
E/*e′* average ratio	10.7 ± 4.3*	8.5 ± 2.5	0.005	11.6 ± 4.3	15.5 ± 8.7	0.19
PW Doppler imaging of pulmonary venous flow						
S-wave (cm/s)	64.0 ± 14.7*	60.9 ± 11.8	0.21	63.4 ± 6.5	73.5 ± 14.3	0.17
D-wave (cm/s)	46.2 ± 6.5*	47.6 ± 7.1	0.66	43.0 ± 6.8	56.8 ± 25.0	0.14
S/D ratio	1.4 ± 0.2*	1.2 ± 0.2	0.0255	1.5 ± 0.2	1.4 ± 0.3	0.42
Ar-wave (cm/s)	36.8 ± 6.8*	33.6 ± 6.3	0.0143	35.8 ± 6.3	35.5 ± 6.1	0.95
Ar-wave duration (ms)	119.7 ± 19.3*	107.1 ± 17.7	0.0097	127.3 ± 18.3	120.5 ± 19.9	0.65

* *p*: NS and ° $p = 0.0112$ compared to baseline in control group. Abbreviations: E-wave, peak early ventricular filling velocity; DT, deceleration time of early filling velocity; A-wave, peak late ventricular filling velocity; IVRT, isovolumic relaxation time; *e′* lat.-wave, early diastolic peak velocity on the lateral side of the mitral annulus; *a′* lat.-wave, late diastolic peak velocity on the lateral side of the mitral annulus; *e′* med.-wave, early diastolic peak velocity on the medial side of the mitral annulus; *a′* med.-wave, late diastolic peak velocity on the medial side of the mitral annulus; S-wave, peak antegrade systolic velocity; D-wave, peak antegrade diastolic velocity; Ar-wave, peak velocity of atrial reversal in late diastole; Ar-wave duration, duration of atrial reversal in late diastole.

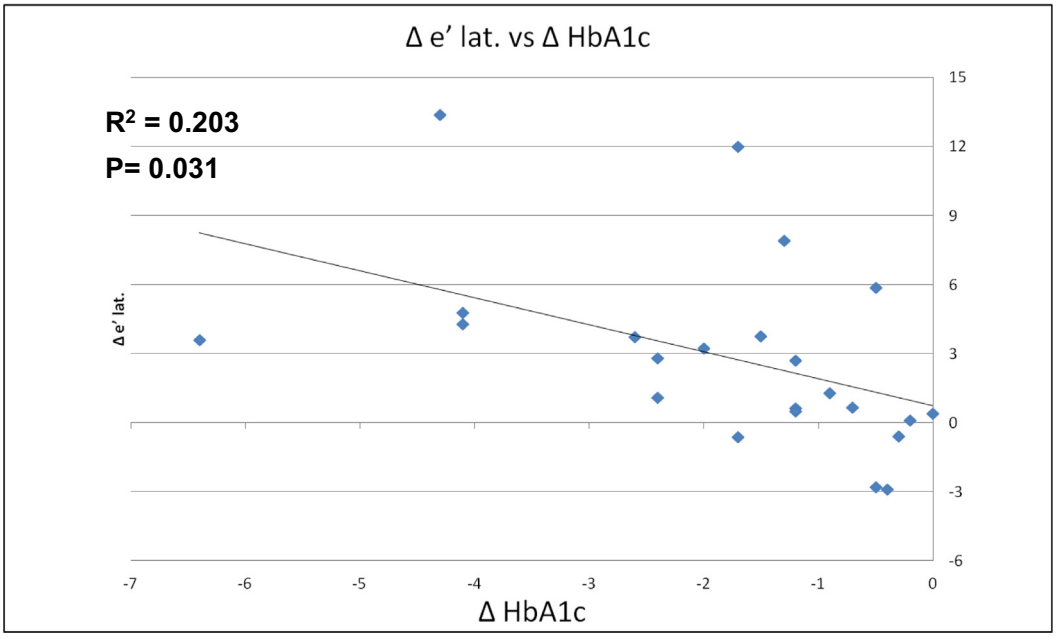

Fig. 1 – Correlation between the improvement in diastolic function and the decrease of HbA1c in LG. LG, liraglutide group. Δe′ lat, early diastolic peak velocities on the lateral side of the mitral annulus. HbA1c, glycated hemoglobin.

A-wave velocity (Table 3). In the LG at baseline, 11 patients (42%) had Grade I (mild) DD and 15 patients (58%) had Grade II (moderate) DD. In the CG at baseline, four patients (36%) had Grade I DD and seven patients (64%) had Grade II DD. No patient had NYHA class II-IV.

After 6 months of liraglutide therapy, the following differences with respect to baseline were observed in the LG (Table 3): an increase in e′ on both sides of the mitral annulus (e′ lat. and e′ med.); an increase in the e′/a′ lat. and e′/a′ med. ratios; a reduction in the E/e′ ratio; a reduction in the S/D ratio on the right superior pulmonary vein; a reduction in the peak Ar velocity on the right superior pulmonary vein; and a reduction in the Ar-wave duration on the right superior pulmonary vein. Seventeen patients (65%) in the LG exhibited an improvement in diastolic function, 10 of them (38%) achieved normal diastolic function on the last control.

In the LG, there was a significant correlation between the improvement in diastolic function (expressed as Δe′ lat.) and the decrease in HbA1c ($R^2 = 0.203$, $p = 0.031$; Fig. 1). There was no correlation between the improvement in diastolic function and the decrease in BW ($R^2 = 0.048$, $p = 0.302$; Fig. 2).

By contrast, in the CG, no echocardiographic parameters changed significantly from baseline to 6 months.

In addition, no patient in the CG exhibited normal diastolic function, no patient exhibited an improvement in DD grade and two patients exhibited a worsening of DD grade.

Systolic function did not change from baseline to 6 months in either group.

4. Discussion

Previous studies have demonstrated that liraglutide has positive effects not only on glycemic and weight control in humans [14], but also on left ventricular diastolic function in animals [6,7]. In this study, we have shown for the first time that liraglutide significantly improved diastolic function in human patients with T2D treated for 6 months. Our results showed a significant improvement in several diastolic function parameters measured using PW-TDI and PW Doppler of pulmonary venous flow. These techniques are not routinely used in clinical practice, but are more sensitive than transmitral Doppler technique [30].

Although preliminary, these results are supported by the complete lack of improvement in diastolic function in the CG, in whom glycemic control was achieved with hypoglycemic drugs other than GLP-1 RA and DPP-4i. No significant echocardiographic changes were observed in the CG, despite a decrease in HbA1c similar to that observed in the LG.

However, the finding in the LG that the increase in e′ lat. (a marker of overall diastolic function) was significantly and inversely related to the decrease in HbA1c suggests that the metabolic changes may have been involved in the improvement in cardiac function.

It is well known that a reduction in body weight and insulin resistance may independently improve diastolic function in patients with T2D [31]. In the current study, a significant weight reduction was observed in the LG, but not in the CG, as expected. Surprisingly, there was no significant relation between weight loss and the improvement in diastolic function in the LG group.

The mechanism underlying these improvements can be only speculative and both direct and indirect effects can have a role. Many experimental data in animals have demonstrated direct cardiovascular effects of GLP-1 receptor stimulation [32,33]. Observed responses include increased cardiac glucose uptake, modifications in free fatty acid and lipid

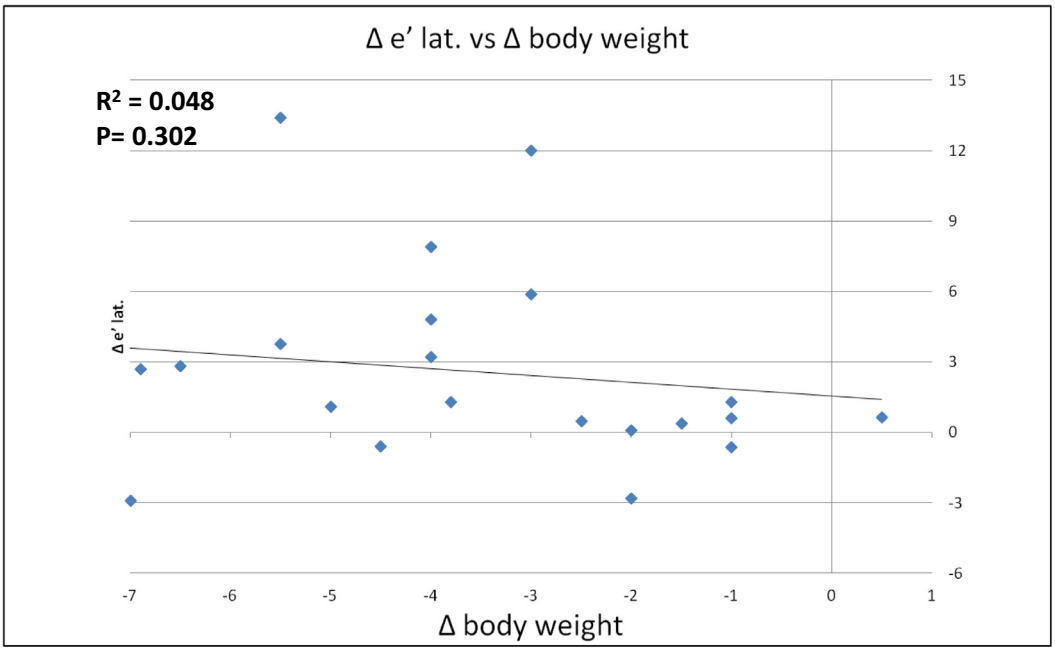

Fig. 2 – Correlation between the improvement in diastolic function and the decrease in body weight. Δ*e*′ lat, early diastolic peak velocities on the lateral side of the mitral annulus.

metabolism and increased nitric oxide production with a consequent rise in vascular relaxation and thus afterload decrease [34,35,22,26]. In patients with ischemic-reperfusion damage and heart failure (both diabetic and non diabetic) the effects comprehend improvement in LV ejection fraction, regional wall motion and overall cardiac performance [36,23–25]. The described effects have a notably rapid onset, few weeks in the large majority of the studies.

Among the indirect effects, besides the reduction in BW and insulin resistance, the decrease in SBP could also have a role in the cardiac function improvement. However, at variance with other wider studies [37,38], the reduction of SBP that we observed was not statistically significant (−1.4 mmHg) and therefore probably of little influence in our patients. Only studies specifically designed to study this effects such as the LEADER trial, that is currently underway, (21) could give a definite answer.

Parameters used to evaluate diastolic function in the current study deserve further explanation. DCM is characterized by reduced longitudinal distensibility of the left ventricle, with decreased filling ability and increased left atrial pressure. Quantification of ventricular function in the longitudinal axis is clinically relevant, as contraction and relaxation in this direction occur mainly due to the activity of subendocardial fibers [39], which exhibit the primary myocardial effects in many cardiac diseases, including DCM. PW-TDI is highly suited for measurement of left ventricle longitudinal motility, because it has higher temporal resolution than other ultrasound techniques, and thus allows measurement of myocardial contraction and relaxation speed. Furthermore, the PW-TDI profile of mitral annulus velocity can be considered a marker of the overall function of the left ventricle [40].

Most studies have shown the importance of sampling *e*′ lat. with PW-TDI for its relative independence from the preload [41], compared to the transmitral Doppler technique [32]. This variable is rarely affected by ischemic processes and its measurement is easier and reproducible [42]. In this study, we evaluated *e*′ peak velocities on the medial and lateral sides, and found a significant increase in both *e*′ med. and *e*′ lat. from baseline to 6 months. Moreover, *e*′ med. reached the threshold of normality for healthy adults (>8 cm/s) [28]. These findings describe an improvement in longitudinal motility, which is reflective of a gain in global left ventricle diastolic performance. Moreover *e*′ velocity, considered singularly, has been shown to be an independent prognostic factor [43] and the main predictor of ventricular remodeling, acute heart failure hospitalization and post-infarction mortality [44].

The *E*/*e*′ ratio acts as a useful and reliable noninvasive estimate of left ventricle filling pressure. A decrease in the *E*/*e*′ ratio accurately reflects the downward trend in left ventricle filling pressure as well as the improvement in left ventricle relaxation. An *E*/*e*′ ratio <8 is considered normal [28]. In the current study, *E*/*e*′ decreased from 10.7 to 8.5 after 6 months of treatment with liraglutide. The importance of this result is stressed by the relation between *E*/*e*′ and pulmonary capillary pressure [32]. An *E*/*e*′ ratio >10 identifies a mean pulmonary capillary pressure >12 mmHg, which defines pulmonary hypertension, a severe complication of DD [28], with sensitivity of 78% and specificity of 95%.

PW Doppler analysis of pulmonary venous flow showed an improvement in left ventricle compliance and resistance against blood flow, as shown by the reductions in the *S*/*D* ratio and Ar-wave duration. The Ar-wave reflects the flow of blood wrongly directed to the pulmonary veins due to decreased ventricular compliance. In this study, after 6 months of treatment with liraglutide, the Ar-wave peak velocity was below the limit considered normal (<35 cm/s) [28].

Larger, prospective and randomized trials are required to confirm these results and better explain the overall mechanisms through which liraglutide may improve diastolic function.

The limitations of this study include the reduced size of analyzed population, the lack of an adequate CG, the difference in size between the two groups and the consequent lack of a statistical analysis that included a correction for the therapies taken by the patients.

In addition, echocardiography is a highly operator-dependent procedure, no single criterion has been identified to diagnose DD and the cut-off values of the various criteria may have slight variations in different populations.

5. Conclusions

In this preliminary, independent study, liraglutide had a beneficial effect on DD in patients with T2D. This is an important finding, because DD is a known additive risk of mortality [45].

Larger, prospective clinical trials are needed to fully evaluate the long-term effectiveness of liraglutide on DD and on real cardiovascular morbidity and mortality, to better understand its exact mechanisms of action, to confirm the independence of these effects and to determine if there is a class effect.

Conflict of interest statement

No actual or potential conflicts of interest exist.

Authors' contributions

AR, FS and AS were equally involved in the conception of the study. AS performed all echocardiograms. FS performed all data collection, analysis and interpretation, and drafted the first version of the manuscript. All authors contributed to the revision of the manuscript and have read and approved the final manuscript.

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