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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.

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