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Exenatide once-weekly improves metabolic parameters, endothelial dysfunction and carotid intima-media thickness in patients with type-2 diabetes: An 8-month prospective study

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ABSTRACT

Aim: To evaluate the effect of exenatide long acting release (LAR) on carotid intima-media thickness (IMT) and endothelial function in patients with type 2 diabetes mellitus.

Methods: Sixty subjects with type 2 diabetes mellitus were treated with exenatide LAR as add-on to stable doses of metformin for 8 months in an open label study. Anthropometric variables, lipid profile and glycemic parameters were assessed by routine analysis. Carotid IMT by Doppler ultrasound and endothelial function by flow-mediated dilation of the brachial artery were also assessed.

Results: Exenatide significantly improved fasting glycaemia (from 8.8 ± 2.8 to 7.3 ± 2.2 mmol/L, $p < 0.0001$), HbA1c (from 8.0 ± 0.4 to 6.9 ± 1.1%, $p < 0.0001$), body mass index (from 33 ± 9 to 31 ± 6 kg/m^2, $p = 0.0348$) and waist circumference (from 109 ± 13 to 106 ± 13 cm, $p = 0.0105$). There was a significant improvement of the lipid profile, except in triglyceride level where no changes were observed. Carotid IMT and flow-mediated dilation were also improved (from 0.98 ± 0.14 to 0.87 ± 0.15 mm and from 5.8 ± 1.3 to 6.8 ± 1.7%, respectively; $p < 0.0001$ for both).

Conclusions: Treatment with exenatide LAR led to improved cardio-metabolic parameters, including carotid IMT and flow-mediated dilation, independently of glucometabolic control. These results may help to explain, at least in part, the cardiovascular safety of exenatide LAR, as recently reported in cardiovascular outcome trials.

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1. Introduction

Type 2 diabetes mellitus is a multiple etiology metabolic disorder characterized by chronic hyperglycemia in subjects with insulin resistance. This chronic hyperglycemia results in altered insulin secretion, reduced glucose utilization, and increased liver glucose production [1,2]. Persons with type 2 diabetes mellitus are usually overweight and obese [3] and they frequently have high blood pressure, dyslipidemia and, ultimately, a significantly elevated risk of cardiovascular (CV) diseases [4]. The synergism of all these cardio-metabolic risk factors makes overall a difficult barrier in the management of type 2 diabetes mellitus.

The purpose of innovative therapeutic approaches for type 2 diabetes mellitus, such as glucagon-like peptide 1 (GLP-1) receptor agonists (RA) [5], is to adjust the therapy to each patient needs, in order to intensify glucose-lowering effects without risk of hypoglycemia, less adverse events, and prevent CV events [6–10]. There have been also specific improvements in cardiac function associated with GLP-1 RAs. These agents have shown a wide range of effects on CV risk markers, such as body weight [11–13], lipid parameters [13–15], blood pressure [16] endothelial function, inflammatory markers, markers of oxidative stress [17], and subclinical atherosclerosis [18,19]. An improvement on left ventricular function in humans, rodents and dogs has also been shown [20–22]. Exenatide, administered in pigs with ischemic damage and reperfusion, not only reduced the risk of myocardial infarction, but also prevented the deterioration of systolic and diastolic heart function [23]. Local subcutaneous injections of Exenatide in rats reduced carotid IMT and protected from restenosis [24].

Exenatide twice-daily (BID) improved endothelial function of patients with type 2 diabetes mellitus *versus* glimepiride in a 16-week follow-up [25] and *versus* placebo after 7 days [26]. However, in other studies Exenatide BID has failed to show an improvement in endothelial function, which was not significant compared to insulin glargine after 6 months [27] or placebo after 4 months [28].

Exenatide once-weekly long acting release (LAR) exerts favorable effects on glycemic control [11], lipid metabolism, blood pressure [29–33] and other CV risk markers in subjects with type 2 diabetes mellitus [34], also in combination with dapagliflozin, as shown by the recent results from DURATION-8 study [35]. However, there is no evidence of the potential effect of exenatide LAR on cIMT, while its impact on endothelial function is largely unknown.

In the present study we evaluated the effect of exenatide LAR on several cardio-metabolic parameters in patients with type 2 diabetes mellitus in an 8-month follow-up study, investigating for the first time the impact on carotid atherosclerosis and endothelial dysfunction.

2. Subjects, materials and methods

2.1. Patients included in the study

A cohort of 60 patients (41 men and 19 women with mean age of 60 ± 10 years) was recruited at the Unit of Diabetology and Cardiovascular Prevention, University Hospital of Palermo, Italy. All subjects involved in the study were naive to incretin-based therapies and were treated with metformin alone for at least 8 weeks at stable doses between 1500 and 3000 mg per day. Inclusion criteria of the study were the following: (1) men and women >18 years old with type 2 diabetes mellitus; (2) Body mass index (BMI) > 25 kg/m^2; (3) HbA1c ranging from 7.5% to 8.5%; (4) Primary prevention of CV disease. Exclusion criteria were the following: (1) known pregnancy or intention to become pregnant; (2) moderate to severe renal or hepatic impairment; (3) recent cerebro-cardiovascular event; (4) Previously diagnosed CV pathology (such as hypotension of severe hypertension, anemia or Takayasu arteritis); (5) known severe infections (HIV, HBV, HCV) and neoplasms; (6) triglycerides >400 mg/dl and LDL cholesterol >250 mg/dl. The procedures used were in accordance with the Helsinki Declaration of 1975, as revised in 2013. The study received the approval from the Ethics Committee and was registered in clinicaltrials.com (ref: NCT02380521). All patients gave their approval and signed written informed consent. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed for the preparation of this manuscript [36].

Exenatide LAR was prescribed at a fixed dose of 2 mg/week in addition to fixed dose of metformin as previously described for 8 months. The concomitant cardio-metabolic therapies (such as anti-hypertensive, lipid-lowering and anti-platelet agents) were maintained at stable doses throughout the study. The comorbidities presented by the subjects were not of recent onset, and they were all receiving stable treatment at the beginning of the study. All patients underwent a medical examination at baseline in order to collect clinical and biochemical data. Similar assessments for each patient were performed after 8 months of follow-up. Weight, waist circumference and height were recorded, and BMI was calculated in kg/m^2. Moreover, they were contacted monthly to improve treatment adherence and to ensure that there were not any changes in concomitant therapy. Yet, all patients underwent a routine medical examination at 6 months, due to the renewal of the therapeutic plan in accordance with local requirements.

2.2. Biochemical analyses

Serum samples were collected from each participant at baseline and after follow-up period. Plasma glucose, glycated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG) and high-density lipoprotein-cholesterol (HDL-C) were measured by routine laboratory methods while low-density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald formula.

2.3. Color Doppler ultrasound of carotid arteries

B-mode real-time ultrasound was performed at baseline and after 8 months to evaluate the carotid IMT. All the examinations were performed by a single experienced examiner (A. M.P.) in a blinded manner using the SonoAce Pico Ultrasound System (Samsung Medison Co., Korea). The examiner did not have access to previous scans when follow-up studies were

performed. The ultrasound examination was performed in a standardized manner with fixed angles of insonation, as previously reported by our group in detail [18]. The same investigation was performed at baseline and after 8 months of therapy. We calculated the coefficient of variation for repeated scans, and all coefficients of variation were below 5.0%, that is in consistent with our previous findings in studies with other GLP-1 analogue [37].

2.4. *Ultrasonic assessment of endothelial function*

Patients were asked to abstain from taking coffee or tea and to abstain from smoking for 30 min; then, each individual patient was relieved on a supine position in a bed. Measurement of FMD was performed according to well-established guidelines and following a standardized protocol [38]. Ultrasound was performed using a 7.5-MHz linear array transducer attached to a high-quality mainframe ultrasound system [39]. After being left in a room for about 10 min, the right arm brachial artery was studied in several longitudinal scans with the probe above the fold elbow. Once the longitudinal scan is more similar to a "Chinese bridge", the diameter of the vessel, defined as the distance between the upper echo margin produced by the interface between the lumen and the front wall of the vessel and the upper margin of the eco product from the interface between the lumen and the back wall of the vessel, was measured four times in the peak of the pulsed flow of the spectral curve of the ultrasound, to calculate the mean value. Next, a sphygmomanometer sleeve was placed about 3–5 cm above the elbow bend and swollen rapidly at a higher pressure of about 25–30 mmHg compared to the previously measured systolic blood pressure. This pressure was maintained for 5 min and at the end of this period rapid swelling of the sleeve was carried out, leading to reactive hyperemia and measuring the diameter of the brachial artery at intervals of about 20 s for 3 min, considering that the maximum expansion value is obtained on average between 60 and 90 s [40]. Flow-mediated dilation (FMD) value was calculated as the percentage difference between the maximum post-hyperemic diameter reached and the mean basal diameter using the formula: FMD (%) = [(post-hyperemia diameter − basal diameter)/basal diameter] × 100.

2.5. *Statistical analysis*

Statistical analysis was performed with SPSS for Windows V.17 (IBM Inc., Chicago, IL, USA). Differences in clinical and biochemical parameters at baseline and at the end of follow-up period were evaluated by the paired *t*-test. Correlation analysis was performed by Spearman test.

3. Results

Baseline characteristics of the study subjects are shown in Table 1. None of the subjects had to discontinue exenatide, and no significant adverse events were observed. Twenty-three patients had transient gastro-intestinal symptoms such as nausea, vomiting, diarrhea, which did not lead to a discontinuation of therapy. None of the patients quit smoking during the follow-up period.

In order to assess FMD variability and reproducibility, a subgroup of 35% of the participants were scanned twice by the ultrasounder, at each trial time-point (baseline and after 8 months). No systematic bias was found between the first and second read of the same reader.

The effect of exenatide LAR on several cardio-metabolic parameters is summarized in Table 2. We found a significant reduction in weight ($p = 0.0002$), waist circumference ($p = 0.0105$), BMI ($p = 0.0348$), fasting glycaemia ($p < 0.0001$) and HbA1c ($p < 0.0001$). Regarding plasma lipids, exenatide significantly decreased TC and LDL-C ($p = 0.0012$ and $p < 0.0001$, respectively), and significantly increased HDL-C ($p = 0.0188$). In addition, cIMT and FMD significantly improved after treatment ($p < 0.0001$ for both). Finally, no significant correlations were found between changes in cIMT and FMD and changes in all the other evaluated parameters (data not shown). As expected, systolic blood pressure also improved compared to baseline (−3.16 mm Hg; $p = 0.0001$).

4. Discussion

In this 8-month prospective study, we have seen that Exenatide LAR improves several CV risk factors. We also report for the first time that exenatide LAR significantly improved cIMT and FMD in patients with type 2 diabetes mellitus.

There is a close correlation between type 2 diabetes mellitus and the development of CV complications. The presence of altered metabolic parameters, such as central obesity, dyslipidemia, and hypertension, further increase CV risk in type 2 diabetes mellitus patients. Several studies in the literature, such as DURATION 1–6, have highlighted that exenatide LAR has positive effects on body weight and glycemic control [41]. Our study showed that exenatide LAR improved body weight decreased by about 3 kg and waist circumference reduced by about 3 cm. These results are somewhat consistent with previous studies from our group, showing similar benefit on body weight and waist circumference with the

Table 1 – Baseline characteristics of patients of the study (n = 60).

Variable	
Age (years), mean ± sd	60 ± 10
Women, n (%)	19 (32)
Smoking habit, n (%)	13 (22)
Family history of cardiovascular diseases, n (%)	34 (57)
Diabetes duration (years), mean ± sd	9 ± 8
Hypertension, n (%)	42 (70)
Dyslipidemia n (%)	36 (60)
Obesity, n (%)	31 (53)
Use of anti-hypertensive therapies	
Beta-blockers, n (%)	11 (18)
Angiotensin-converting enzyme inhibitors, n (%)	17 (28)
Calcium entry blockers, n (%)	19 (32)
Diuretics, n (%)	15 (25)
Use of lipid-lowering drugs	
Statins, n (%)	25 (42)
Omega-3 fatty acids, n (%)	7 (12)
Fibrates, n (%)	2 (3)
Aspirin use, n (%)	22 (37)

Table 2 – Changes in cardiovascular risk variables after 8 Months of Exenatide LAR treatment (n = 60).

Variable	Baseline	8 months	*p*-value[a]
Weight (kg)	89 ± 18	86 ± 17	0.0002
BMI (kg/m^2)	33 ± 9	31 ± 6	0.0348
Waist circumference (cm)	109 ± 13	106 ± 13	0.0105
Fasting glycaemia (mmol/l)	8.8 ± 2.8	7.3 ± 2.2	<0.0001
HbA1c (%)	8.0 ± 0.4	6.9 ± 1.1	<0.0001
HbA1c (mmol/mol)	64 ± 4	52 ± 12	<0.0001
Total cholesterol (mmol/l)	4.4 ± 0.9	4.2 ± 1.0	0.0012
Triglycerides (mmol/l)	1.5 ± 0.7	1.5 ± 0.6	0.9189
HDL-cholesterol (mmol/l)	1.2 ± 0.3	1.3 ± 0.3	0.0188
LDL-cholesterol (mmol/l)	2.5 ± 0.8	2.2 ± 0.9	<0.0001
Endothelial Function (%)	5.8 ± 1.3	6.8 ± 1.7	<0.0001
Carotid IMT (mm)	0.98 ± 0.14	0.87 ± 0.15	<0.0001

All values expressed in mean ± standard deviation.
[a] Paired T-test.

use of another GLP-1RA, liraglutide, in type 2 diabetes mellitus patients [13,42].

In the Liraglutide Effect and Action in Diabetes (LEAD)-6, no significant differences were observed in type 2 diabetes mellitus patients between liraglutide vs. exenatide *bis in die* (BID) treatment on body weight (−3.24 vs. −2.87 kg, respectively) after 26 weeks while, in the DURATION-6, type 2 diabetes mellitus under liraglutide had a greater weight loss than those in the exenatide LAR group (−3.6 kg vs. −2.68 kg, respectively) after 26 weeks of therapy [32].

However, it should be considered that clinical trials have shown that with the continuation of therapy, exenatide may exert a beneficial effect on body weight up to 3 years [34] and 7 years [43], suggesting that exenatide does not induce tolerance on the effect on weight reduction in the medium and long term.

In the present study we also found a significant reduction in plasma lipids consistent with previous observations, reporting ameliorated lipid profile by exenatide and independently of glucose balance and weight loss [34]. Another study, with a 52-week follow up, showed that exenatide LAR increased HDL-C and reduced LDL-C and TG [44]. This is consistent with the data we found in the present study. Regarding plasma glycemia and HbA1c, the glycemic control achieved in our study is consistent with what reported in the exenatide LAR studies DURATION 1–6 [32], since our subjects reduced HbA1c by 1.1% after 8 months of exenatide LAR therapy.

In this study we also found improved cIMT and FMD, two early surrogate atherosclerotic markers, after exenatide LAR treatment. Our results are in agreement with the ones reported by Irace et al., who reported for the first time an improvement in FMD in a small sample of subjects with type 2 diabetes mellitus treated with exenatide [25]. Several mechanisms may be potentially involved in such beneficial effect. Exenatide LAR may improve insulin secretion and sensitivity, leading to improved glycemic control and reduced oxidative stress. Exenatide improved the antioxidant potential and reduced oxidative stress in human *in vitro* monocytes/-macrophages cells by decreasing reactive oxygen species and malondialdehyde levels [45]. It has also been reported that exenatide increases the expression and activity of superoxide dismutase and glutathione reductase, two antioxidant enzymes [45]. Other mechanism proposed for this effect is an opening of the ATP-sensitive potassium channels [26]. Another study also showed that exenatide improves diastolic function and reduces arterial wall stiffness in patients with type 2 diabetes mellitus [28]. However, it should be highlighted that duration and severity of type 2 diabetes mellitus, as well as the presence of comorbidities, may influence the treatment's impact on the endothelium [46]. The patients in the present study were without both moderate and severe liver and renal disorders, as well as without having suffered a major CV event, that might be a reason that a longer duration of exenatide LAR treatment was not necessary to achieve significant impacts on endothelial function and wall thickness.

Exenatide LAR CV effects were assessed in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) CV outcome trial [10], where the primary composite CV outcome (CV death, non-fatal myocardial infarction and non-fatal stroke) occurred in 839 out of 7356 patients in the exenatide group compared to 905 out of 7396 patients in the placebo group (HR 0.91, IC 95% 0.83–1.00). Therefore, exenatide LAR showed CV safety ($p < 0.001$ for non-inferiority), although the CV benefit could not be demonstrated since the analysis approached the statistical significance ($p = 0.06$ for superiority [10]). The results found in the present study may help to explain, at least in part, the CV safety of exenatide LAR, as recently reported in the EXSCEL. Although, we did not find any significant correlations between changes in cIMT and FMD and changes in all the other evaluated parameters, we cannot exclude possibility that exenatide LAR's effect on these two early surrogate atherosclerotic markers might have been mediated by the improved glycemic and metabolic parameters, and that such significant reduction in cIMT and improvement in FMD may be result of a favorable pleiotropic, non-glycemic exenatide LAR's effects, such as those on oxidative stress, cytokines and other inflammatory markers as well as adhesion molecules, hence preventing the atherosclerotic plaque formation [47].

Our findings are consistent with several published data in the last years with the use of GLP-1 receptor agonists, including exenatide LAR [47], as well as our previous studies where other drug from the same class was used [13,18] and a meta-analysis that included 31 studies supporting the use of incretin-based therapies for the treatment of atherosclerosis

[48]. Such pleiotropic effects seem to be independent of changes in body weight, glycaemia or LDL-C, although we cannot exclude the fact that the magnitude of improvement may increase with increasing weight loss [49].

A limitation of our study is the absence of a control arm, with patients under metformin only. However, the data already present in the literature indicate that metformin does not significantly affect cIMT [50,51] or FMD [52], but at best metformin only has an effect on waist circumference and body weight [53,54].

Also, most of our patients at the time of enrollment were under antihypertensive, anti-hypercholesterolemic and anti-platelet drug therapy. Although these drugs may have had an impact on the parameters assessed, all these therapies remained mainly unchanged throughout the study period, to avoid possible bias.

On the other hand, strengths of the study include the real-world setting, blinded measurements of cIMT and FMD as well as a high compliance rate with exenatide LAR therapy. This is the first study showing reduced cIMT after 8 months of exenatide LAR treatment. In addition, exenatide has been shown to augment endothelial function, however, only few studies have examined the effects of exenatide LAR on endothelial function. To the best of our knowledge the present study is with the largest follow-up and the largest sample size to the date evaluating such effects of exenatide LAR.

Exenatide LAR treatment resulted in an improvement in cardio-metabolic parameters, including cIMT and endothelial dysfunction, and the effect on cIMT and endothelial dysfunction seemed to be independent of glucometabolic control. These results may help to explain, at least in part, the CV safety of exenatide LAR, as recently reported in the CV outcome trial EXSCEL. In addition, our findings indicate that exenatide LAR might have a positive effect on subclinical atherosclerosis and endothelial function as similarly as other agents from the same class, and may prevent both development and progression of atherosclerosis and consequently delay the development of cardiovascular diseases. Although further basic and clinical studies are needed to elucidate the exact mechanisms involved, a huge preclinical data indicate on direct beneficial effects on endothelial cell, smooth muscle cell, and immune cell function through the GLP-1 receptor dependent, but also GLP-1 receptor independent pathways [47].

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Conflict of interest and funding

MR has given lectures and participated in conferences, advisory boards and clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, Kowa, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Novartis, Roche Diagnostics and Servier. GM, AMP, DN, AMF, RVG, GC and RC have participated in clinical trials sponsored by AstraZeneca, Eli Lilly and Novo Nordisk. This study was partially funded by AstraZeneca as an external sponsored research. The project is registered in clinicaltrials.gov (Reference: NCT02380521). The authors declare that they have no competing interests. MR is currently Chief Medical and Scientific Advisor, Diabetes, Novo Nordisk Europe East and South. The authors did not receive financial or professional help with the preparation of the present manuscript, such as from pharmaceutical companies, including Novo Nordisk. The present article was written independently, and it reflects the sole opinion of the authors.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.02.006.

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