



Effects of semaglutide on cardiovascular risk factors and eating behaviors in type 2 diabetes

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Abstract

Aims Aim of the present study was to evaluate the impact of once-weekly semaglutide on different end-points indicative of metabolic control, cardiovascular risk, dietary behavior, and treatment satisfaction in T2DM.

Methods This was a retrospective observational study conducted in a diabetes clinic. Changes in HbA1c, fasting blood glucose (FBG), weight, blood pressure, lipid profile, and number of antihypertensive drugs at 32 weeks (T1) after the first prescription of semaglutide (T0) were analyzed. Furthermore, at T1 patients were asked to fill-in the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Control of Eating Questionnaire (COEQ).

Results Overall, 104 patients were identified (mean age 63.6 ± 10.4 years, 58.7% men, diabetes duration 12.7 ± 8.7 years). After 32 weeks of treatment with semaglutide, HbA1c levels were reduced by 1.38%, FBG by -56.53 mg/dl, weight by 6.03 kg. Systolic and diastolic blood pressure, total, HDL-, LDL-, and non-HDL cholesterol, and triglycerides significantly improved. The number of glucose-lowering and antihypertensive drugs also decreased. At T1, DTSQ score was 32.23 ± 1.44 , whereas COEQ indicated low levels of hunger and good control of eating.

Conclusions The study documented benefits of semaglutide on metabolic control and multiple CV risk factors, simplification of therapeutic schemes and high satisfaction with diabetes treatment, and eating behaviors indicative of healthy diet and reduced food intake.

Keywords Type 2 diabetes · Semaglutide · Effectiveness · Treatment satisfaction · Eating behaviors HbA1c · Weight · Hyperglycemia · Non-HDL cholesterol

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease characterized by hyperglycemia caused by insulin resistance and deficiency of insulin secretion by the beta cells of the pancreas [1]. In the last decade, glucagon-like peptide receptor agonists (GLP1-RAs) have been approved as a new therapeutic option in T2DM. These drugs mimic the action of endogenous GLP-1, a hormone produced by enteroendocrine L cells following the ingestion of nutrients, especially carbohydrates [2]. Its main function is to increase the secretion of insulin by pancreatic β cells in a glucose-dependent manner and to inhibit the secretion of glucagon by α cells.

GLP1-RAs also preserve the function of β -cells, stimulating their proliferation and differentiation and inhibiting apoptosis [3]. GLP-1 receptors are also present in the gastrointestinal tract, in the cardiovascular system, and in the central nervous system, in particular in the nucleus of the solitary tract; these mediate a slowdown in gastric emptying, with an increase in the sense of satiety reduced hunger and lower energy intake [4, 5]. In animal models, data suggest that these effects may be due to GLP-1 acting directly on receptors in the brain, affecting perceptions of the reward value of food [6]. Due to their mechanisms of action, GLP1 RAs reduce body weight and blood pressure levels [7].

In most patients with T2DM the lipid profile is altered with hypertriglyceridemia, increased total cholesterol and low-density lipoproteins (LDL) cholesterol levels, and decreased high-density lipoproteins (HDL) cholesterol levels. All of these alterations constitute the “atherogenic dyslipidemia in diabetes” which contributes to the increase in cardiovascular risk typical of subjects with T2DM [8].

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The non-high-density lipoproteins (non-HDL) cholesterol allows a better estimate of the cardiovascular risk, because it represents the cholesterol of all atherogenic particles, such as LDL, lipoprotein A, very high-density lipoproteins low (VLDL) and intermediate density lipoproteins (IDL) [9, 10]. Non HDL cholesterol represent a prevalent CV risk factor in T2DM [11, 12], but no data are available about the impact of GLP1-RA on it.

Semaglutide is an analogue of native GLP-1 with a prolonged half-life (165 h), suitable for administration once a week (ow). Semaglutide was shown to be effective in improving metabolic control in T2DM by reducing blood glucose and glycated hemoglobin (HbA1c), body weight, and cardiovascular risk [13].

The side effects that may occur are nausea and, more rarely, vomiting and diarrhea, usually mild and limited to the first weeks of treatment [14].

Aim of the present study was to evaluate the impact of semaglutide on different end-points indicative of metabolic control, cardiovascular risk, dietary behavior, treatment satisfaction in T2DM, and a possible reduction in the use of antihypertensive drugs.

Methods

This was a retrospective observational study conducted in the diabetes clinic of S. Camillo Forlanini Hospital–Rome. Data on all patients treated with ow semaglutide were extracted from the electronic medical record system adopted in the hospital.

Baseline visit was represented by the first prescription of semaglutide (T0); follow-up visits were based on routine clinical practice, usually every 4 months. Values recorded after 32 weeks from baseline were used for this study (T1).

According to the summary of product characteristics, all patients were first prescribed with semaglutide 0.25 mg; semaglutide was then titrated up to 0.50 mg and successively 1.0 mg (based on patient needs).

Baseline characteristics were collected including: age, gender, diabetes duration, obesity indices (BMI, weight), smoke, HbA1c, fasting blood glucose (FBG), systolic blood pressure (SBP), diastolic blood pressure (DBP), lipid profile (total, LDL, HDL, non HDL cholesterol, and triglycerides), estimated glomerular filtration rate (eGFR), albuminuria, micro- and macro-vascular diabetes complications, comorbidities, diabetes treatment before and at initiation of semaglutide, and antihypertensive treatment.

At follow-up visit, data on changes in HbA1c, FBG, BMI, body weight, blood pressure, lipid profile, number of antihypertensive drugs were collected.

Furthermore, at T1 patients were asked to fill-in the Diabetes Treatment Satisfaction Questionnaire (DTSQ) [15, 16] and

a questionnaire on eating habits (Control Of Eating Questionnaire, COEQ) [17, 18]. Italian versions of these questionnaires were administered.

DTSQ has been specifically designed to measure satisfaction with diabetes treatment regimens [15]. It is composed of eight items, six of which are summed in a single score ranging from 0 (very dissatisfied) to 36 (very satisfied). The remaining two items are treated individually and explore the perceived frequency of hyperglycemic and hypoglycemic episodes, with higher scores indicating a higher frequency. The Italian version of the instrument has been previously translated and validated [16].

Control of eating and the degree of food cravings were measured using a modified version of the validated 16-item short form COEQ, which includes questions related to food cravings, control of eating, hunger and fullness. Based on the previous 7 days, subjects were asked to rate the first 14 questions of the original COEQ on a 10 cm visual analogue scale (VAS); 1 question with categorical response was added to investigate about type of food least liked by the patient [17, 18].

The study protocol was approved by the local ethics committee. Informed consent was obtained from all patients for being included in the study.

In Italy, GLP1-RA therapy is reimbursed by the national healthcare system in all patients with T2DM and HbA1c > 7.0% as a monotherapy (when metformin is contraindicated or not tolerated) or in combination with other antihyperglycemic agents.

Statistical analysis

Considering the preliminary, descriptive nature of this study, a formal sample size calculation was not performed. However, a minimum sample size of 47 patients allowed to detect with a statistical power of 90% a decrease in HbA1c levels of at least 0.5%, assuming an estimated standard deviation of differences of 1.0 and with a significance level (alpha) of 0.05.

Descriptive data were summarized as mean and standard deviation for continuous variables or frequency and proportion for categorical variables.

Changes in continuous study endpoints were assessed using mixed models for repeated measurements. Results are expressed as estimated mean or estimated mean difference from T0 with their 95% confidence interval (95% CI). Paired t-test derived from linear mixed models for repeated measurements were applied for within group comparisons. Statistical significance was declared if *p*-value was < 0.05.

Results

Overall, 104 patients receiving the first prescription of semaglutide between January and March 2021 were identified through electronic medical records adopted in the clinic. Baseline patient characteristics are reported in Table 1. Mean age was 64 years, 58.7% were men, diabetes duration was of 12.7 ± 8.7 years.

Metabolic control was poor (Fasting Blood Glucose 186.0 ± 60.0 mg/dl; HbA1c $8.5 \pm 1.8\%$).

At T0, patients showed poor metabolic control, high mean BMI, and poor control of cardiovascular risk factors. Furthermore, organ damage was recorded in one half of patients. Before starting semaglutide, 6 (5.8%) patients

were already treated with another GLP1-RA. Furthermore, 98 (94.2%) patients were treated with oral hypoglycemic agents (OHA), of whom 72 (69.2%) with 1 OHA and 26 (25.0%) with $\geq$ OHAs. Moreover, 11 (10.6%) patients were treated with schemes including insulin.

At initiation of semaglutide, 20 (19.2%) patients were treated with semaglutide only, 79 (76.0%) patients were treated with OHAs, of whom 75 (72.1%) with 1 OHA and 4 (3.9%) with 2 OHAs, and 8 (7.7%) patients were treated with schemes including insulin.

After 32 weeks of treatment with semaglutide, HbA1c levels were reduced by 1.38% and all continuous endpoints showed statistically significant and clinically relevant improvements (Table 2).

At the end of the observation, 100% of patients were treated with 0.5 mg.

The COEQ items at T1 indicated low levels of hunger, good control of eating and meal portion size, and low levels of food cravings, with most of items reaching a median VAS value between 0 and 1. Intermediate levels of pleasantness and fullness after meals were registered, with items reaching a median VAS value of around 5 (Fig. 1). The last item indicated the lowest liking for high-fat foods in 58.7% of patients (Fig. 2).

DTSQ score at T1 was close to the maximum value (median value 33, interquartile range 32–34).

As for the use of antihypertensive drugs, at T0, 40 patients (38.8%) were not treated with antihypertensive drugs, while 34 (33.0%), 24 (23.3%), and 5 (4.9%) were treated with 1, 2, 3 antihypertensive drugs, respectively. At T1, 39 patients (37.5%) were not treated with antihypertensive drugs, while 38 (36.5%), 23 (22.1%), and 4 (3.8%) were treated with 1, 2, 3 antihypertensive drugs, respectively.

Overall, 17 out of 104 (16.3%) patients reported side effects, of whom 13 (12.5%) nausea and 4 (3.8%) abdominal bloating. These symptoms were generally mild and decreased over time. Two patients discontinued the treatment with semaglutide during 32-week follow-up. No episode of severe (requiring third part assistance) or clinically relevant (blood glucose < 54 mg/dl) hypoglycemia occurred.

Discussion

Main findings

This study documented the effectiveness and tolerability of semaglutide in patients with uncontrolled T2DM.

After 32 weeks of treatment, HbA1c levels and body weight significantly decreased (-1.38% and -6.03 kg, respectively) and the entity of the reduction was in line with results obtained in the SUSTAIN program [13, 19, 20], where HbA1c was reduced from 1.1 to 1.5% with

Table 1 Baseline patient characteristics

	Mean and standard deviation or proportion
N	104
Age (years)	63.6 ± 10.4
Men (%)	58.7
Diabetes duration (years)	12.7 ± 8.7
BMI (Kg/m ²)	32.9 ± 5.9
Smokers (%):	
No	66.3
Yes	26.9
Ex	6.7
HbA1c (%)	8.5 ± 1.8
Fasting blood glucose (mg/dl)	186.0 ± 60.0
Systolic blood pressure (mmHg)	135.8 ± 12.8
Diastolic blood pressure (mmHg)	79.6 ± 8.3
Total cholesterol (mg/dl)	190.3 ± 46.1
LDL cholesterol (mg/dl)	105.5 ± 39.5
HDL cholesterol (mg/dl)	44.8 ± 12.3
Non HDL cholesterol (mg/dl)	145.5 ± 44.7
Triglycerides (mg/dl)	200.0 ± 118.4
Hypertension (%)	61.2
Dyslipidemia (%)	100.0
Retinopathy (%)	9.6
Organ damage (%)*	51.0
Myocardial infarction (%)	10.6
Stroke (%)	2.9
Coronary rivascularization (%)	9.6
Heart failure (%)	2.9
eGFR < 60 ml/min*1.73 m2	5.8
Albuminuria > 300 mg/dl	1.0

*Myocardial infarction, stroke, limb/feet amputation, coronary or peripheral revascularization, heart failure, carotid or peripheral vessels plaques, retinopathy, kidney damage markers (eGFR < 60 , albuminuria > 300 mg/die, haemodialysis, kidney transplantation

Table 2 Changes in estimated mean levels of continuous clinical endpoints over time

Change in	Visit	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	p-value
HbA1c (%)	T0	8.55(8.27;8.83)		
	T1	7.16(6.88;7.44)	− 1.38 (− 1.68; − 1.09)	< 0.0001
FBG (mg/dl)	T0	186.03 (177.05;195.01)		
	T1	129.5 (120.52;138.48)	− 56.53 (− 67.17; − 45.89)	< 0.0001
BMI (Kg/m ²)	T0	32.9 (31.81;33.99)		
	T1	30.73 (29.63;31.82)	− 2.18 (− 2.56; − 1.79)	< 0.0001
Weight (Kg)	T0	94.23 (90.75;97.72)		
	T1	88.2 (84.72;91.69)	− 6.03 (− 7.13; − 4.93)	< 0.0001
SBP (mmHg)	T0	135.82 (133.63;138.01)		
	T1	133.06 (130.87;135.25)	− 2.76 (− 4.08; − 1.44)	< 0.0001
DBP (mmHg)	T0	79.57 (78.05;81.08)		
	T1	75.72 (74.21;77.23)	− 3.85 (− 5.02; − 2.67)	< 0.0001
Total chol (mg/dl)	T0	190.33 (181.44;199.22)		
	T1	172.18 (163.29;181.07)	− 18.14 (− 23.99; − 12.3)	< 0.0001
HDL-chol (mg/dl)	T0	44.84 (42.49;47.18)		
	T1	47.44 (45.1;49.79)	2.61 (1.14;4.07)	0.0006
LDL-chol (mg/dl)	T0	105.49 (97.87;113.12)		
	T1	94.56 (86.94;102.19)	− 10.93 (− 16.47; − 5.39)	0.0002
TG (mg/dl)	T0	199.99 (181.44;218.54)		
	T1	150.89 (132.35;169.44)	− 49.1 (− 65.47; − 32.72)	< 0.0001
Non HDL-chol (mg/dl)	T0	145.49 (137.11;153.87)		
	T1	124.74 (116.36;133.12)	− 20.75 (− 26.71; − 14.79)	< 0.0001

HbA1c Glycated haemoglobin, *FBG* Fasting blood glucose, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *chol* Cholesterol, *HDL* High-density lipoprotein, *LDL* Low-density lipoprotein, *TG* Triglycerides, 95% CI=95% confidence intervals

*Values in bold are statistically significant

semaglutide 0.5 mg and from 1.4 to 1.8% with semaglutide 1 mg; weight was reduced from 3.5 to 4.6 kg with semaglutide 0.5 mg and from 4.5 to 6.5 kg with semaglutide 1 mg. In addition, real-world studies conducted in US and Europe confirmed the effectiveness and safety of semaglutide when administered under routine clinical practice conditions, although the magnitude of benefits varied based on patient profiles and settings [21–27].

In addition to the effect on HbA1c and weight, in our study we documented improvements in lipid profile and blood pressure.

Finally, our population presented multiple associated risk factors (dyslipidemia, hypertension, obesity), 50% had organ damage and 23.1% had history of cardiovascular event.

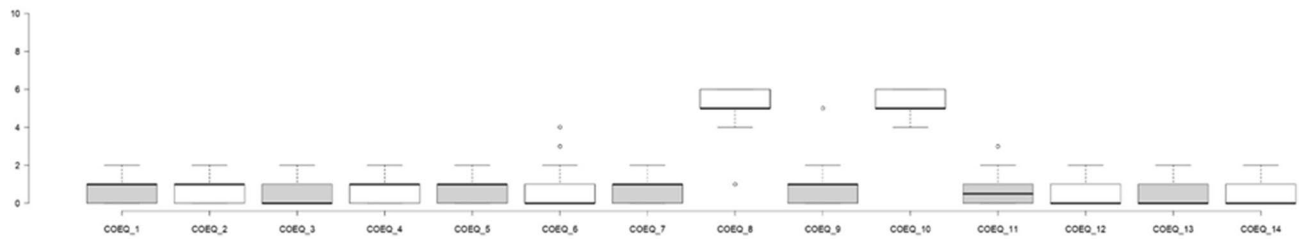
Comparison with existing knowledge

The recent documentation of the positive CV effects of semaglutide in reducing the MACE risk [13] is extremely encouraging in relation to the clinical use of this drug. Furthermore, a post-hoc analysis of the LEADER and SUSTAIN 6 CV outcome trials confirmed the importance of addressing multiple risk markers in T2DM to reduce CV and

renal risk, therefore stressing the importance of multifactorial interventions targeting all risk markers [28].

Following these findings, in July 2021 new AMD-SID (Associazione Medici Diabetologi; Societa' Italiana di Diabetologia) Italian Guidelines stated that GLP1-RA can be prescribed as a first line therapy in T2DM with a previous cardiovascular event. ADA Guidelines (ADA 2022) also suggested to consider GLP1-RA as a first choice therapy in high cardiovascular risk patients [29, 30].

In our study population and in general T2DM population, obesity is present in the majority of patients and its role as main driver of the disease is well known [31]. Weight loss is one of the most important therapeutic goals and is associated with an improvement of all the cardiovascular risk factors – cholesterol, tryglicerides, blood pressure—and with an improvement of cardiac function and overall prognosis (ESC 2021) [32]. GLP1-RAs were the first glucose-lowering drugs that induce weight loss [33–35] due to their pleiotropic actions including a central nervous system interaction with reward circuits and food intake. Semaglutide effect was demonstrated to be superior to that of dulaglutide (SUSTAIN 7) and liraglutide (SUSTAIN 10) in T2DM at therapeutic doses [36, 37].

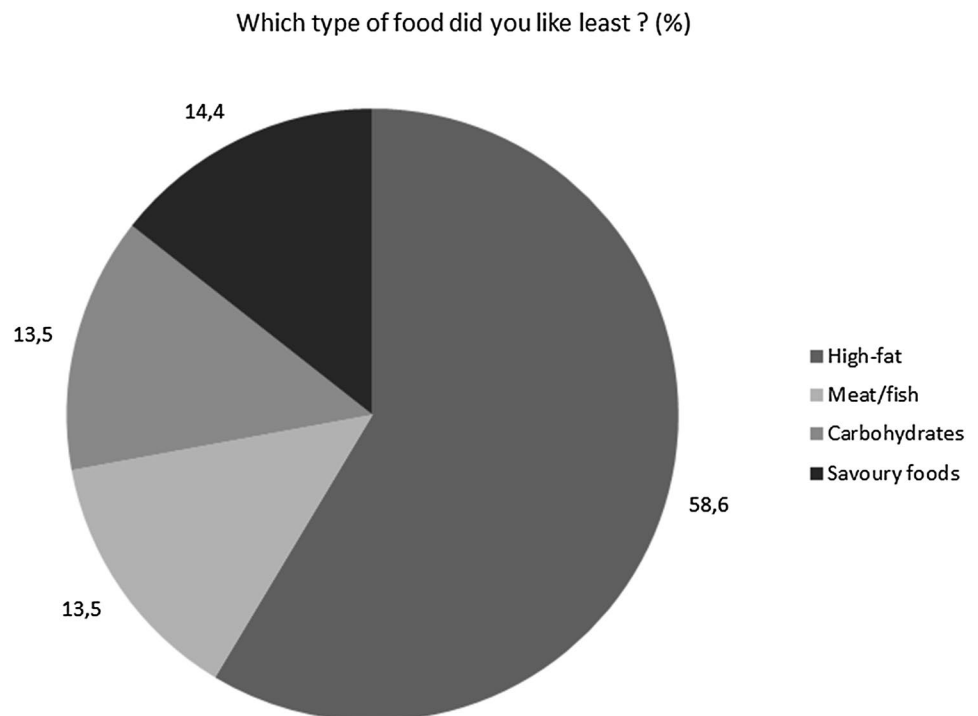


Based on the previous 7 days, patients were asked to rate the following questions on a 10 cm visual analogue scale (VAS):

COEQ_1	How often have you had food cravings? (never/very often).
COEQ_2	How strong have any food cravings been on average? (not at all strong/extremely strong).
COEQ_3	Overall, how difficult has it been to control your eating? (not at all difficult/extremely difficult).
COEQ_4	How difficult has it been to resist any food cravings? (not at all difficult/extremely difficult).
COEQ_5	How often have you eaten in response to food cravings? (never/after every food craving).
COEQ_6	How difficult has it been to control your meal portion sizes? (not at all difficult/extremely difficult).
COEQ_7	How hungry have you felt? (not at all hungry/extremely hungry).
COEQ_8	How full have you felt after meals? (not at all full/as full as I have ever felt).
COEQ_9	How often have you had thoughts of food? (rarely/very often).
COEQ_10	How pleasant have your meals been? (not at all pleasant/extremely pleasant).
COEQ_11	How often have you had food cravings for chocolate or chocolate flavoured foods? (never/very often)
COEQ_12	How often have you had food cravings for other sweet foods? (never/very often).
COEQ_13	How often have you had food cravings for fruit or fruit juice? (never/very often).
COEQ_14	How often have you had food cravings for savoury foods? (never/very often).

Fig. 1 Control of eating questionnaire (COEQ)

Fig. 2 Control of eating questionnaire (COEQ)



Semaglutide produces significant benefits on cardiovascular risk, as demonstrated in SUSTAIN 6, where a significant lower rate vs. placebo of 3 points MACE was

documented [13]. The reduction of CV risk is mediated by improvements in risk factors. In our study, total cholesterol level significantly decreased by 18.14 mg/

dl, LDL-cholesterol by 10.93 mg/dl and triglycerides by 49.1 mg/dl at T1. However, it is noteworthy that in spite of the significant LDL-cholesterol reduction – from 105 to 95 mg/dl – many patients did not reach the recommended targets for T2DM (ESC 2021) [32]. Furthermore, non-HDL cholesterol is an established but seldom investigated cardiovascular risk factor [9–12]. Its therapeutic goal is stringent (< 100 mg/dL) in high risk population [6, 7]. In our study, it decreased by 20.75 mg/dl, but at T1 mean level was 125 mg/dL [12]. These findings reinforce the urgent need to intensify lipid-lowering therapy and dietary education, with semaglutide contributing to the achievement of the target.

Important information comes also from the analysis of treatment schemes. The present study substantially involved T2DM patients treated with 1 or 2 OHAs with elevated baseline levels of HbA1c. A small minority of patients were already treated with GLP1-RA and 1 out of 10 patients were treated with insulin before starting semaglutide. This picture underlines the existence of a certain clinical inertia, due, as known, to multifactorial reasons, such as COVID-19 pandemics, long waiting lists, transfer of new patients from other hospitals, low patient adherence, etc.... However, at semaglutide initiation, the proportion of patients treated with insulin and with more than 1 OHA decreased. Even the use of antihypertensive drugs slightly diminished. These data support the most recent evidence on simplification of therapy as a key strategy to overcome clinical inertia [29].

Finally, DTSQ average values documented high levels of satisfaction with treatment (median score was 33 against a maximum score of 36) [15, 16]. Satisfaction with treatment is an important mediator of patient adherence and achievement of targets [38].

Reduced appetite and energy intake, with less preference for energy-rich foods, were investigated in previous studies and were identified as a possible mechanism to explain the weight loss observed with once-weekly and oral semaglutide [14, 39, 40].

In our setting, we administered a translated and modified version of COEQ adapted for Italian T2DM patients: after 32 weeks of therapy a lower fatty food preference was declared (61%) with a relatively preserved proteic (fish, meat) and carbohydrate rich food (grains, bread, pasta) intake. In another study on 3685 obese subjects, semaglutide induced specific fat mass loss, and energy intake reduction; COEQ questionnaire documented food habits changes with lower craving [18].

In our study, semaglutide significantly improved glucose control and reduced body weight (HbA1c decrease: -1.38% ; weight loss: -6.03 kg with 0.5 mg of semaglutide) confirming or even surpassing results of SUSTAIN studies [36, 37, 41]. In addition to drug effect, in our

real-world setting, even the attention to the individual dietetic plan, based on Mediterranean Diet model, and dietary/lifestyle education played a role [42]. In the future, it will be interesting to investigate the hepatological impact of this treatment approach in T2DM patients with Nonalcoholic Fatty Liver Disease.

Strengths and limitations

The major strength was the inclusion of clinically important but seldom investigated endpoints: non-HDL cholesterol, reduction of antihypertensive drugs prescribed, treatment satisfaction, and eating behaviors. Among limitations, it should be underlined the lack of administration of DTSQ and COEQ at T0 to assess changes over time in the scores and the lack of information about mild hypoglycemia and glycemic variability.

Conclusion

The study documented benefits of treatment with once-weekly semaglutide on metabolic control and CV risk factors, simplification of therapeutic schemes and high satisfaction with diabetes treatment, and eating behaviors indicative of healthy diet and reduced food intake. GLP1-RAs represent a pivotal drug class that can change favorably the natural history of diabetes.

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Declarations

Conflict of interest The author(s) declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was approved by the ethics committee of the “S. Camillo-Forlanini” Hospital, Rome, Italy (Prot. 840 CE Lazio 1 – June 12th, 2021). Informed consent was obtained from all patients for being included in the study.

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