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Effect of liraglutide administration on body mass index in adolescents with obesity: a pilot study

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ABSTRACT

Objective: To evaluate the effect of liraglutide administration on body mass index in obese adolescents 15 to 18 years of age. **Patients and methods:** A quasi-experimental study was conducted in 18 obese patients without prior drug treatment. Patients received 0.6 mg of subcutaneous liraglutide once per day during the first eight days of treatment and then 1.2 mg/day up to day 48. Body mass index, blood pressure, and metabolic profile were assessed before and after the pharmacological intervention. **Results:** There was a significant decrease in body weight (78.8 [72.8-85.1] vs. 77.7 [72.0-82.5] kg; p = 0.001), body mass index (28.7 [27.6-31.6] vs. 27.7 [26.6-30.6] kg/m^2; p = 0.001), waist circumference (96.0 [89.2-102.7] vs. 91.0 [87.5-99.5] cm; p = 0.001), and adiposity (38.2 [34.5-41.4] vs. 35.8 [30.3-39.8] %; p = 0.003) after 48 days of liraglutide administration. **Conclusions:** Liraglutide decreases body weight, body mass index, waist circumference, and adiposity in obese adolescents. (REV MEX ENDOCRINOL METAB NUTR. 2016;3:124-8)

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Key words: Adolescents. Liraglutide. Obesity.

RESUMEN

Objetivo: Evaluar el efecto de la administración de liraglutida sobre el índice de masa corporal (IMC) en adolescentes entre 15 y 18 años de edad con obesidad. **Pacientes y métodos:** Se llevó a cabo un estudio cuasiexperimental en 18 pacientes con obesidad sin tratamiento farmacológico previo. Los pacientes recibieron liraglutida a dosis de 0.6 mg vía subcutánea 1/día durante los primeros ocho días y posteriormente la dosis se incrementó a 1.2 mg/día hasta completar 48 días de tratamiento. El IMC, la presión arterial y el perfil metabólico fueron evaluados antes y después de la intervención farmacológica. **Resultados:** Después de la administración de liraglutida por 48 días, existió una disminución significativa del peso corporal (78.8 [72.8-85.1] vs. 77.7 [72.0-82.5] kg; p = 0.001), del IMC (28.7 [27.6-31.6] vs. 27.7 [26.6-30.6] kg/m^2; p = 0.001), de la circunferencia de cintura (96.0 [89.2-102.7] vs. 91.0 [87.5-99.5] cm; p = 0.001) y de la adiposidad (38.2 [34.5-41.4] vs. 35.8 [30.3-39.8]%; p = 0.003). **Conclusiones:** Liraglutida disminuye el peso corporal, el IMC, la circunferencia de cintura y la adiposidad en adolescentes con obesidad.

Palabras clave: Liraglutida. Obesidad. Adolescentes.

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INTRODUCTION

Obesity is a worldwide public health problem characterized by an excess of adipose tissue. It is generally related to an unhealthy diet and lack of physical activity. When obesity is presented during childhood, it is likely that the condition remains until adulthood[1]. Obese adolescents are more likely to develop earlier cardiovascular risk factors, bone and joint problems, sleep apnea, type 2 diabetes, and several types of cancer as well as the accompanying social and psychological problems[2-4]. This indicates the importance of timely treatment of excess weight in order to prevent the related complications.

Liraglutide is a glucagon-like peptide 1 (GLP-1) analog approved by the U.S. Food and Drug Administration (FDA) in 2010 as a complement to diet and exercise to improve glycemia control in adults with type 2 diabetes[5,6]. At the end of 2014 it was also used as adjuvant in the treatment of adult obesity. However, there are no data in regard to liraglutide during infancy and adolescence to treat only obesity. Its pharmacological characteristics in the pediatric population with obesity and type 2 diabetes have recently been published[7].

The aim of the present study was to evaluate the administration of liraglutide on body mass index (BMI) in obese adolescents.

PATIENTS AND METHODS

A quasi-experimental study of a single center (Institute of Experimental and Clinical Therapeutics, University of Guadalajara) was carried out in 18 nondiabetic adolescents (15-18 years of age) with obesity diagnosed according to the BMI with the World Health Organization (WHO) criteria according to age[8] and without pharmacological treatment. Subjects were selected from the same residential area and socioeconomic status. No participant was excessively sedentary (without programed physical activity) or participated in heavy physical activity (> 150 minutes/week of programed physical activity). All individuals were nonsmokers and had stable body weight for at least three months prior to the study. There was no personal history of hepatic, renal, or coronary artery disease. Subjects had not consumed any medication known to affect carbohydrate or lipid metabolism during the previous six months. All patients and their parents received general recommendations about their medical nutritional therapy and were instructed to not modify their usual forms of exercise in accordance with the Academia Nacional de Medicina of Mexico[9].

Patients were evaluated before and after the 48-day study period, a duration that was established for convenience. Tests were performed at 8:00 a.m. after a 10- to 12-hour overnight fast. Height and weight were recorded with the individuals wearing light clothing and without shoes. Height was measured and rounded off to the nearest centimeter with the subjects standing. The BMI was calculated as weight (in kg) divided by height (m^2). This measurement and adiposity (% of fat mass) was assessed by bioelectrical impedance analysis using a contact electrode foot-to-foot body fat analyzer system (TBF-300A, Tanita Corporation of America, Arlington Heights, IL, USA). The cutoffs used to determine weight status according to BMI were those proposed by the World Health Organization (WHO, 2007) sets of BMI z-score for ages 5-19 years[8].

Waist circumference (WC) was measured at the high point of the iliac crest at minimal respiration to the nearest 0.1 cm. Venous blood was obtained with the subject lying supine in a quiet room. Blood was allowed to clot for 30 minutes at room temperature and then centrifuged. The resulting serum was placed into an aliquot that was immediately used for the measurement of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and glucose levels.

Blood pressure was evaluated after a five-minute resting period with the individual sitting in a chair and determined using a digital sphygmomanometer. It was defined as the systolic and diastolic average of three consecutive measurements.

Pharmacological administration

Liraglutide (Victoza®, Novo Nordisk, Denmark) was injected once daily subcutaneously for 48 days; in the first eight days 0.6 mg was administered once a day and then titrated to 1.2 mg daily until completing the intervention period. The administration of liraglutide was done in the subject's home and assessment of compliance was calculated in accordance with self-report and analysis of the returned device.

Serum glucose was determined by the glucose-oxidase method. Lipid levels (TC, HDL-C, TG) were measured enzymatically. In particular, HDL-C was assessed after selective precipitation of non-HDL fractions. Determinations were performed with commercially available equipment (Vitros®, Ortho-Clinical Diagnostics, Johnson & Johnson Co, Rochester, NY, USA). Low-density lipoprotein cholesterol (LDL-C) was estimated using the Friedewald formula: (LDL-C = TC – HDL-C – TG/5).

Statistical analyses

Sample size was calculated using a formula for mean difference[10], with a 95% confidence level (CI), 80% power, standard deviation (SD) for BMI in an adolescent population of 2.3 kg/m^2, and an expected difference of at least 2.4 kg/m^2 of BMI due to the intervention. A sufficient change in this variable cannot be attributed to normal physiological changes or variability of the test used for their estimation after the intervention. A total of 18 patients were obtained, including 20% of probable loss. Values were converted to International Units (IU) and are presented as median and interquartile range. The BMI was considered as primary end-point and the rest of the measurements evaluated as secondary end-points, in which intra- and inter-group differences were tested by the Wilcoxon test; $p \leq 0.05$ was considered statistically significant for all comparisons.

Ethical considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee and was in accordance with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all parents and volunteers.

RESULTS

Eighteen consecutive adolescents who met the selection phase characteristics were included. Twelve subjects were female and six were male, with an age of 15.5 (14-17) years. Three subjects were eliminated during the study, two due to nausea and vomiting (Grade 2 of the CTCAE[11]); the third subject was lost to follow-up. Fifteen patients completed the study with a treatment adherence > 80%. Because the statistical analyses were done in accordance with the intention to treat, the total number of participants was included. There was a significant decrease in body weight, BMI, WC, adiposity and a tendency with fasting glucose (Table 1). The changes from baseline to the end of study were for body weight –2.5 kg (–3.1 to –1.9), BMI –0.9 kg/m^2 (–1.2 to –0.7), WC –3.0 cm (–3.5 to –2.0), and adiposity –1.4% (–2.0 to –0.6).

Adverse events during the study were reported to the Ethics Committee. The following were observed: decrease in appetite (83%), nausea (50%), dizziness (39%), vomiting (33%), dyspepsia (17%), diarrhea (11%), nonspecific abdominal pain (11%), and headache (6%).

DISCUSSION

The incidence of childhood obesity is increasing together with a substantial rise in cases of type 2 diabetes[12,13]. Liraglutide was originally indicated for glycemia control purposes in adult patients with type 2 diabetes. The safety of liraglutide, tolerability, pharmacokinetics, and pharmacodynamics characteristics have previously been reported in a clinical trial in adolescents with obesity and type 2 diabetes[7]. Recently, liraglutide commercialization was authorized for treatment of adult obesity. However,

Table 1. Clinical and laboratory characteristics of the study group

	Liraglutide				
	Baseline		Final		p
Weight (kg)	78.8	72.8-85.1	77.7	72.0-82.5	0.001
BMI (kg/m^2)	28.7	27.6-31.6	27.7	26.6-30.6	0.001
WC (cm)	96.0	89.2-102.7	91.0	87.5-99.5	0.001
Adiposity (%)	38.2	34.5-41.4	35.8	30.3-39.8	0.003
Systolic BP (mmHg)	114	108-119	111	108-118	0.450
Diastolic BP (mmHg)	70	70-79	75	69-76	0.864
Fasting glucose, mmol/l (mg/dl)	5.0 (90.5)	4.6-5.3 (83.0-95.5)	4.7 (85.0)	4.4-48 (81.0-87.0)	0.073
Total cholesterol, mmo/l (mg/dl)	3.7 (145)	3.2-4.4 (126-174)	3.7 (145)	3.4-4.1 (133-162)	0.959
LDL-C, mmol/l (mg/dl)	2.2 (87)	1.8-2.9 (73-114)	2.2 (86)	1.7-2.7 (67-105)	0.287
HDL-C, mmol/l (mg/dl)	0.9 (35)	0.8-1.1 (32-44)	1.0 (41)	0.9-1.1 (36-45)	0.276
Triglycerides, mmol/l (mg/dl)	1.1 (103)	1.0-1.4 (90-126)	1.0 (97)	0.9-1.3 (84-116)	0.523

BMI: body mass index; BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; WC: waist circumference.

there is scant literature demonstrating effectiveness in body weight control during other life stages. The results of this clinical trial extend the previous findings of studies with another GLP-1 receptor agonist, exenatide[14,15]. Findings in the present study are consistent with those reported in the literature. Liraglutide decreased body weight, BMI, WC, and adiposity. A reduction of 3 cm in WC and 2.5 kg of weight in adolescents included in the present study could be an important clinical consideration because it is well known that its increment is related to cardiovascular risk. In addition, the tendency to decrease fasting glucose may contribute in delaying the onset of diabetes, which should be proven with specific studies. Therefore, liraglutide could be considered as a pharmacological option for the treatment of childhood obesity along with permanent medical evaluation of the known adverse effects.

With exenatide administration, a significant decrease of 4.4% in subcutaneous fat and improvement in the metabolic profile of patients with metabolic syndrome has been shown[15], although liraglutide has proven to have superior efficiency. Data are consistent with our results[16].

Several limitations of the present investigation should be taken into account because they may interfere with the results obtained. These include lack of a control group, lack of follow-up after the intervention, postprandial glucose level evaluation, and for safety reasons, limited range of age, and titration of liraglutide to higher dose (1.8 mg) and over a long term. However, this approach is being considered as a pilot for planning and designing of an improved study.

Liraglutide was well tolerated by patients. Reports of nausea, abdominal pain, diarrhea, headache, and vomiting were in general transient and of mild-to-moderate intensity and consistent with that reported in an adult population[17]. These results reflect a favorable scenario for obesity treatment. Liraglutide was recently considered, after the beginning the present study, as an option in the handling of obesity in adults and as a new horizon for the treatment of eligible pediatric patients with type 2 diabetes[7,18].

In conclusion, liraglutide administration for 48 days achieved a significant decrease in BMI, body weight,

WC, and adiposity among obese adolescents aged 15 to 18 years.

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DISCLOSURE OF INTEREST

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