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Effect of exenatide once weekly on metabolic and glycemic control in patients with prediabetes: a pilot study

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ABSTRACT

Objective: To assess the effect of exenatide once weekly on metabolic and glycemic control in patients with prediabetes. **Methods:** This was a quasi-experimental study in eight patients with prediabetes without pharmacological treatment. Exenatide (2 mg) once weekly was administered subcutaneously for 12 weeks. Measurements of metabolic and glycemic control were done before and after pharmacological intervention. Differences at baseline and final measurements were tested using Wilcoxon signed-rank test. $P \leq 0.05$ was considered significant. **Results:** After pharmacological intervention, a significant decrease in body weight (82.5 ± 9.1 vs. 80.6 ± 8.9 kg; p = 0.012), body mass index (31.5 ± 3.7 vs. 30.8 ± 3.7 kg/m^2; p = 0.012), waist circumference (101 ± 8 vs. 97 ± 7 cm; p = 0.017), and systolic blood pressure (127 ± 7 vs. 121 ± 7 mmHg; p = 0.021), as well as fasting plasma glucose (6.1 ± 0.4 vs. 5.3 ± 0.9 mmol/l; p = 0.028) and glycated hemoglobin (A1C) (5.7 ± 0.4 vs. 5.4 ± 0.4%; p = 0.046) were observed. **Conclusion:** Administration of exenatide once weekly for 12 weeks significantly decreases body weight,

RESUMEN

Objetivo: Evaluar el efecto de exenatida semanal sobre el control metabólico y glucémico en pacientes con prediabetes. **Métodos:** Estudio cuasiexperimental en ocho pacientes con prediabetes sin tratamiento farmacológico. Se les administraron 2 mg de exenatida semanal por vía subcutánea durante 12 semanas. Se hicieron mediciones del control metabólico y glucémico antes y después de la intervención. Se realizó el análisis estadístico con la prueba de rangos de Wilcoxon. Se consideró significativo un valor de $p \leq 0.05$. **Resultados:** Después de la intervención, se observó una disminución del peso corporal (82.5 ± 9.1 vs. 80.6 ± 8.9 kg; p = 0.012), del índice de masa corporal (31.5 ± 3.7 vs. 30.8 ± 3.7 kg/m^2; p = 0.012), de la circunferencia de cintura (101 ± 8 vs. 97 ± 7 cm; p = 0.008), de la presión arterial sistólica (127 ± 7 vs. 121 ± 7 mmHg; p = 0.021), de la glucosa plasmática en ayuno (6.1 ± 0.4 vs. 5.3 ± 0.9 mmol/l; p = 0.028) y de la hemoglobina glucosilada (A1C) (5.7 ± 0.4 vs. 5.4 ± 0.4%; p = 0.046). **Conclusión:** La administración de exenatida semanal durante 12 semanas redujo significativamente el peso cor-

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Key words: Exenatide. Glycemic control. Metabolic control. Prediabetes.

poral, el índice de masa corporal, la circunferencia de cintura, la presión arterial sistólica, la glucosa plasmática en ayunas y la HbA_{1c} en pacientes con prediabetes.

Palabras clave: Exenatida. Control glucémico. Control metabólico. Prediabetes.

INTRODUCTION

Prediabetes indicates milder forms of impaired glucose homoeostasis including impaired fasting glucose, impaired glucose tolerance, or both[1]. It represents a major public health problem due to its high prevalence, ranging from 26-37%[2], as well as its serious complications, including progression to type 2 diabetes mellitus (T2DM) and development of cardiovascular disease (CVD)[3].

The current treatment for prediabetes is based on lifestyle modifications, including nutrition and physical activity, that lead to body weight loss[4]. However, despite proven efficacy of these strategies, they are insufficient to delay progression for individuals at risk during the long-term because adherence can be difficult[5]. This has led to the use of pharmacological therapies for prediabetes. Certain drugs may be used in prediabetes as an adjunct to lifestyle modifications[5]. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) have been recommended by the American Association of Clinical Endocrinologists in patients at high risk of progression to T2DM and in whom lifestyle modifications and other first-line agents have failed, such as metformin or acarbose[6].

Glucagon-like peptide-1 is an incretin hormone with multiple glucoregulatory actions such as stimulation of insulin secretion and inhibition of the release of glucose-dependent glucagon as well as other extra-pancreatic actions, including delayed gastric emptying, inhibition of appetite, weight loss, decreased hepatic lipogenesis and beneficial cardiovascular effects[7].

Exenatide once weekly is a new formulation of exenatide, the first GLP-1 RA. Microsphere technology permits a prolonged absorption from the subcutaneous depot, which allows one injection per week instead of two injections per day with the initial formulation of exenatide[8].

These antecedents have shown favorable results in patients with T2DM[9-12]. However, due to the mechanism of action of exenatide once weekly, it is possible that it may improve metabolic and glycemic measurements such as body weight, waist circumference, and body mass index (BMI) as well as in patients with prediabetes who demonstrate initial alterations for the development of T2DM.

The aim of this study was to assess the effect of exenatide once weekly on metabolic and glycemic control in patients with prediabetes.

MATERIALS AND METHODS

A quasi-experimental study was carried out in eight consecutive patients between 30 and 60 years of age with a diagnosis of prediabetes according to the criteria of the American Diabetes Association: fasting plasma glucose of 5.6-6.9 mmol/l (100-125 mg/dl), post-load plasma glucose of 7.8-11 mmol/l (140-199 mg/dl) and A1C of 5.7-6.4%[13], without pharmacological treatment. All subjects met the diagnostic criteria.

Subjects

Study subjects were selected from the same residential area and presented a similar socioeconomic status. No participant was excessively sedentary (without programmed physical activity) or participated in heavy physical activity (> 150 min/week of programmed physical activity). All individuals were nonsmokers and their body weight remained stable for at least three months prior to the study. There was no personal history of hepatic, renal, thyroid, or heart disease. During the six months prior to the study, patients did not use any drugs that could modify body weight, blood pressure, glucose, or lipid levels.

Pharmacological administration

All patients received exenatide once weekly (2 mg) for injectable suspension (Bydureon®, AstraZeneca AB, Södertälje, Sweden), which was self-administered subcutaneously once weekly for 12 weeks. Patients were instructed on the use of the pen injection device for administration of exenatide once weekly as necessary. All patients received general recommendations about nutritional therapy and were instructed to not modify their usual exercise routine.

Procedures

Patients were evaluated before and after the intervention (3-5 days after the last injection). Tests were performed at 8:00 am after a 10- to 12-hour overnight fast.

Metabolic control (body weight, BMI, waist circumference, fat mass, blood pressure and lipid profile) and glycemic control (fasting plasma glucose, postload plasma glucose and A1C) were evaluated. Variables of glycemic control were considered as primary outcome variables.

Height and weight were recorded with the individuals wearing light clothing and without shoes. Body weight measurement was done using a bioimpedance digital scale and the measurements were reported in kilograms (kg) with two decimals. Height was determined using a stadiometer coupled to the scale with individuals standing and the measurements were rounded off to the nearest centimeter (cm). Body mass index was calculated as weight expressed in kg divided by height expressed in square meters (kg/m^2). Adiposity was evaluated as percentage (%) of fat mass through bioelectrical impedance analysis. Body weight, height, BMI, and adiposity were assessed by a contact electrode foot-to-foot body fat analyzer system. Waist circumference was measured with a flexible tape at the midline between the highest point of the iliac crest and the lowest rib in the mid-axillary line and expressed in centimeters. Blood pressure was evaluated after a resting period with the individual seated and determined using a digital sphygmomanometer. The mean of three measurements was considered as systolic blood pressure (SBP) and diastolic blood pressure (DBP) expressed in millimeters of mercury (mmHg).

Samples of venous blood were centrifuged at 2,500 rpm to obtain serum and used for chemical determinations. Glucose, triglycerides, and total cholesterol concentrations were determined by enzymatic colorimetric methods using an automated analyzer with intra- and inter-assay coefficients of variation < 1 and 2%, respectively, for all measurements. Glucose concentrations were obtained at baseline and 30, 60, 90, and 120 minutes after a 75 g oral dextrose load during an oral glucose tolerance test (OGTT) to obtain fasting plasma glucose and postload glucose concentrations. A1C was obtained by high-performance liquid chromatography with a coefficient of variation < 1%, using a method and equipment certified by the National Glycohemoglobin Standardization Program and traceable to the Diabetes Control and Complications Trial reference assay.

Treatment adherence was monitored with a self-report diary as well as recording of medication dispensed and returned by patients at every visit. The presence of adverse events was also evaluated with a self-report diary and by clinical interview and exploration at every visit throughout the study.

Table 1. Characteristics before and after pharmacological intervention

	Baseline	Final	p
Body weight (kg)	82.5 ± 9.1	80.6 ± 8.9	0.012
BMI (kg/m^2)	31.5 ± 3.7	30.8 ± 3.7	0.012
Waist circumference (cm)	101 ± 8	97 ± 7	0.017
Fat mass (%)	33.6 ± 8.3	33.6 ± 8.4	0.734
SBP (mmHg)	127 ± 7	121 ± 7	0.021
DBP (mmHg)	85 ± 8	80 ± 9	0.400
Total cholesterol (mmol/l)	5.5 ± 0.6	5.1 ± 0.9	0.271
(mg/dl)	213 ± 23	199 ± 36	
Triglycerides (mmol/l)	2.0 ± 1.3	1.9 ± 1.4	0.063
(mg/dl)	183 ± 118	168 ± 121	
Fasting plasma glucose (mmol/l)	6.1 ± 0.4	5.3 ± 0.9	0.028
(mg/dl)	110 ± 7	96 ± 16	
Post-load plasma glucose (mmol/l)	9.7 ± 1.8	7.0 ± 2.7	0.173
(mg/dl)	176 ± 32	127 ± 49	
A1C (%)	5.7 ± 0.4	5.4 ± 0.4	0.046

Data are expressed as mean and standard deviation.
*Wilcoxon rank test.
A1C: glycated hemoglobin A1c; BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Adverse events were reported to the Ethics Committee.

Statistical analysis

Convenience sampling was used for study size. Values were converted to the International System of Units (SI) and are presented as mean and standard deviation. Differences were tested using the Wilcoxon signed-rank test; $p \leq 0.05$ was considered statistically significant.

Ethical considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee and written informed consent was obtained from all volunteers.

RESULTS

Eight consecutive adults who met the selection phase characteristics were included. Three subjects were female and five were male, with an age of 44.1 ± 7.9 years. All patients completed the study with a treatment adherence > 90%.

After administration of exenatide once weekly in patients with prediabetes, we observed a significant decrease in body weight, BMI, waist circumference, and SBP as well as fasting plasma glucose and A_{1C} (Table 1).

At the end of the study, normalization of plasma glucose was observed in 75, 62.5, and 75% for fasting glucose, post-load glucose, and A1C, respectively.

The following adverse events were observed: pyrosis and pruritus, stinging and skin rash at the application site in 12.5% for each event, and subdermal nodule at the site of application in 25%. These events were related to medication but were considered mild in intensity and in no case was drug withdrawal necessary.

DISCUSSION

Opportune and effective treatment of prediabetes based on metabolic and glycemic control of

patients can translate into delaying or preventing the onset of T2DM and its complications; hence, the importance of the search for successful treatment options.

Although the effect of exenatide once weekly according to these parameters has been examined in patients with T2DM participating in clinical trials, including studies known as DURATION (Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention With Exenatide Once-Weekly)[9-12], their effects are not known in patients with prediabetes. In patients with prediabetes this measurement has been evaluated only with exenatide twice daily[14].

Glycemic and metabolic controls were improved for exenatide once weekly in our study according to some aspects. This correlates with all DURATION studies for 24-30 weeks of intervention[9,10] and with the study of exenatide twice daily in prediabetes[14].

A decrease in body weight and BMI was observed in our study, which is the main recommendation for the treatment of prediabetes[4,6]. A decrease in waist circumference was also observed, decreasing cardiovascular risk as a large waist circumference has been related to CVD[3]. We did not observe a significant change in fat mass despite decreased body weight and waist circumference. This can be explained by a decrease in other elements of body composition that were not evaluated in this study or possibly due to fat redistribution. A previous study describes a short course of treatment with GLP-1 RA that induces a redistribution of adipose tissue deposits[15]. However there are antecedents of decreases in fat mass (–11%)[16], subcutaneous fat (–4.4%)[17], and visceral fat deposition (–38%)[18]. Further studies would be interesting to assess the effect on body composition, including the amount of subcutaneous and visceral fat.

In our study, only SBP was modified, without changes in DBP. This is similar to what was reported in the DURATION studies where a greater decrease was seen in SBP (–2.8 mmHg) than DBP (–0.8 mmHg)[9,10]. This effect on blood pressure can be explained by its action via GLP-1 RA activation on blood vessels and kidney, including improvement of endothelial function, vasodilatation, and natriuresis[12].

In our study, serum lipid concentrations were not modified by treatment. In this regard, a pooled analysis of data from all patients who received exenatide once weekly in the DURATION studies demonstrated modestly significant reductions in total cholesterol (–0.17 mmol/l) and triglycerides (–0.09 mmol/l)[9,10]. Modulating key enzymes of lipid metabolism in liver and impairing hepatocyte *de novo* lipogenesis and β-oxidation are actions related to GLP-1 AR[12]. Significant decreases of serum lipids in studies of longer duration may be observed.

In our study, glycemic control was improved by exenatide once weekly. We observed a decrease in fasting glucose and A1C without significant changes in post-load glucose. The pharmacological effects of GLP-1 AR are related to pancreatic actions mainly as insulin secretion, inhibition of the release of glucose-dependent glucagon and other extra-pancreatic effects[7,8]. In DURATION-1, the absolute reduction in postprandial glucose excursion was greater with exenatide administered twice daily than once weekly (–6.9 vs. –5.3 mmol/l)[9,10]. In another study, impaired fasting glycemia and impaired glucose tolerance were improved by exenatide twice daily[14]. These observations suggest that repeated acute exposure to GLP-1 AR might produce greater inhibition of gastric emptying and pancreatic actions than seen with continuous GLP-1 AR activation.

Exenatide once weekly was well tolerated by patients in our study. Reports of pyrosis and injection site reactions were in general rare and mild in intensity and were less than reported in other studies[10].

Several limitations of the present investigation should be taken into account. These include sample size, lack of control group, limited age range, and duration of the intervention. However, this approach is being considered as a pilot for planning and designing an improved study.

The abovementioned findings may be the basis for proposing the administration of exenatide once weekly as a treatment option for patients with prediabetes. Long-term studies with larger sample sizes will be necessary to confirm our results.

In conclusion, administration of exenatide once weekly for injectable suspension for 12 weeks improves metabolic control, including a significant decrease in body weight, BMI, waist circumference, and SBP as well as an improvement in glycemic control. Fasting plasma glucose and A1C decreased in patients with prediabetes.

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DECLARATION OF INTEREST

No conflict of interest is reported with regard to this manuscript. The authors declare no competing interests with the mentioned pharmaceutical company. Financial support for the entire study including the medications used was obtained from a grant of the University of Guadalajara to the principal investigator as a benefit of his position as a Level 3 Investigator of the Sistema Nacional de Investigadores.

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