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Effect of exenatide alone or in combination with metformin on adiposity, glycemic control and lipid profile in prediabetic and obese patients: A randomized clinical trial

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ABSTRACT

Objective: To evaluate the effect of exenatide alone or in combination with metformin on adiposity, glycemic control, and lipid profile in prediabetic and obese patients. **Patients and methods:** A randomized, double-blind, placebo-controlled clinical trial was carried out in 30 prediabetic obese adults. All patients received exenatide (5 µg) twice daily for a month. Afterwards and during the next two months, doses were increased to 10 µg twice daily. For three months, 15 patients received metformin (850 mg/day) and 15 patients received placebo. Fasting and 2-hour post-load (75 g anhydrous glucose) glucose levels as well as lipid profile were assessed at study initiation and again after three months. Wilcoxon signed-rank and Mann-Whitney U tests were used for statistical analyses. **Results:** After pharmacological intervention, a decrease of body weight, body mass index, waist circumference, and fasting and post-load glucose levels were observed in both groups, but significant reductions in adiposity (42.9 ± 4.4 vs. 41.0 ± 6.0%; $p < 0.01$) and total cholesterol (5.7 ± 0.9 vs. 4.5 ± 0.9 mmol/l; $p < 0.01$) and low-density

RESUMEN

Objetivo: Evaluar el efecto de exenatida sola o en combinación con metformina sobre adiposidad, control glucémico y perfil de lípidos en pacientes con prediabetes y obesidad. **Material y métodos:** Se llevó a cabo un ensayo clínico, aleatorizado, doble ciego, controlado con placebo, en 30 adultos con prediabetes y obesidad. Todos recibieron exenatida (5 µg) dos veces al día por un mes; posteriormente 10 µg dos veces al día durante dos meses. Quince pacientes recibieron metformina (850 mg/día) y 15 placebo. Al inicio y tres meses después se midió glucosa de ayuno y dos horas posterior a una carga de 75 g de glucosa anhidra, así como un perfil de lípidos. Análisis estadístico: Wilcoxon y U de Mann-Whitney. **Resultados:** Después de la intervención en ambos grupos se disminuyó peso corporal, índice de masa corporal (IMC), circunferencia de cintura y las concentraciones de glucemia de ayuno y poscarga; además de una significativa reducción con metformina de adiposidad (42.9 ± 4.4 vs. 41.0 ± 6.0%; $p < 0.01$), colesterol total (5.7 ± 0.9 vs. 4.5 ± 0.9 mmol/l; $p < 0.01$) y de las lipoproteínas de baja densidad (LDL-C)

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lipoprotein cholesterol (3.6 ± 0.8 vs. 2.7 ± 0.5 mmol/l; p < 0.01) were reached only in the metformin group. **Conclusion:** Exenatide alone or in combination with metformin decreased body weight, body mass index, waist circumference, and fasting and post-load glucose levels. The combination of drugs also decreased adiposity and total cholesterol and low-density lipoprotein cholesterol levels. (Rev Mex Endocrinol Metab Nutr. 2016;3:66-71)

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Key words: Exenatide. Metformin. Adiposity. Obesity. Prediabetes.

(3.6 ± 0.8 vs. 2.7 ± 0.5 mmol/l; p < 0.01). **Conclusión:** Exenatida sola o en combinación con metformina disminuyó peso corporal, IMC, circunferencia de cintura y las concentraciones de glucosa de ayuno y poscarga; la combinación con metformina también disminuyó adiposidad, colesterol total y LDL-C.

Palabras clave: Exenatida. Metformina. Adiposidad. Obesidad. Prediabetes.

INTRODUCTION

Overweight and obesity have reached worldwide pandemic proportions with prevalence in some countries close to 70%[1]. Obesity is related to insulin resistance and other metabolic abnormalities, becoming important risk factors for the development of type 2 diabetes mellitus and cardiovascular diseases[2].

Several pharmacological interventions have shown a decrease in body weight and improvement in the metabolic environment. One of these medications is exenatide, a glucagon-like peptide receptor agonist (GLP1 RA) which, in clinical studies, has shown increasing first- and second-phase glucose-stimulated insulin secretion, improving glucose control and lipid profile, accompanied by a reduction in body weight[3]. Another medication is metformin, a biguanide that activates the 5'-adenosine-monophosphate-activated protein kinase in several tissues, mainly liver, improving insulin sensitivity and producing significant beneficial changes in glucose control with moderate changes in body weight, li-pids, insulin levels, and diastolic blood pressure[4].

The beneficial metabolic effects of the combination of the above-mentioned drugs have been investigated in diabetic patients, showing improvement of insulin sensitivity, glucose control, lipid profile, and markers of inflammation, as well as decrease of body weight mainly in women and with a major long-term impact[5,6]. This combination has not been studied in high-risk populations without diabetes. Therefore, the aim of this study was to evaluate the effect of exenatide alone or in combination with metformin on adiposity, glycemic control, and lipid profile in prediabetic and obese patients.

Patients and methods

A randomized, double-blind, placebo-controlled clinical trial was carried out in 30 adults (30-50 years of age) with prediabetes (American Diabetes Association criteria)[7] and obesity (body mass index [BMI] 30-39.9 kg/m^2). Subjects were selected from the same geographic area and socioeconomic status. All individuals were nonsmokers. Their body weight had been stable for at least three months prior to the study. No patient was excessively sedentary or participated in excessive physical activity. Subjects were instructed to continue with their normal physical activity. Blood pressure was < 140/90 mmHg. Subjects had not taken any medications known to affect metabolism.

During the course of the study, all patients received medical nutritional therapy as well as subcutaneously injected exenatide (5 µg, Baietta®, Eli Lilly Co., Mexico City, Mexico) twice daily for one month. Afterwards and during the next two months, doses were increased to 10 µg twice daily. After simple random allocation using a random number list, 15 patients received metformin (850 mg/day) (Laboratorios Silanes, S.A., Mexico) and 15 patients received

placebo, with the same pharmacological presentation for three months.

Prior to testing, an isocaloric diet of at least 250 g of carbohydrates/day was followed for three days. Tests were performed at 8:00 a.m. after a 10- to 12-hour overnight fast. Body weight and height were recorded with the subjects wearing light clothing and without shoes. Height was measured and rounded off to the nearest centimeter with the subjects standing. Waist circumference was taken at the midline between the highest point of the iliac crest and the lowest rib in the mid-axillary line. The BMI was calculated as body weight (kg) divided by height squared (m^2). Adiposity (% of fat mass) was assessed by bioelectrical impedance analysis using a contact electrode foot-foot body fat analyzer system (TBF-300-A, Tanita Corporation of America, Inc., Arlington Heights, IL, USA). Blood pressure was measured three times at the left arm with a digital sphygmomanometer (Omron Hem-907 XL®) with the subject seated in a chair after a 5-minute rest. The mean of the three measurements was considered as the value of systolic blood pressure (SBP) and diastolic blood pressure (DBP) expressed in mmHg. 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, which was immediately used for measurement of serum glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides. Two-hour post-load (75 g anhydrous glucose) glucose level was measured.

Serum glucose was determined by the glucose-oxidase technique (Beckman Instruments, Inc., Brea, CA, USA) with an intra- and inter-assay coefficient of variation of < 1%. Serum lipid levels (total cholesterol, HDL-C and triglycerides) were measured enzymatically. In particular, HDL-C was assessed after selective precipitation of non-HDL fractions. Determinations were performed with commercially available equipment (Ortho-Clinical Diagnostics, Inc., Rochester, NY, USA) with an intra- and inter-assay coefficient of variation of < 3%. Low-density lipoprotein cholesterol (LDL-C) was estimated by the Friedewald formula:

LDL-C = total cholesterol – HDL-C – triglycerides/5.

Statistical analyses

Sample size was calculated with a formula for clinical trials[8] with a statistical confidence of 95% (95% CI), statistical power of 80%, standard deviation for adiposity of 7.5% and 0.70 mmol/l for glucose concentration, and expected between-group differences of at least 8.6% for adiposity and 0.85 mmol/l for glucose level, obtaining a total of 15 patients per group including 20% of expected loss. Values are presented as mean ± standard deviation. Intra-group differences were tested using the Wilcoxon signed-rank test and inter-group differences with Mann-Whitney U-test; $p \leq 0.05$ was considered statistically significant.

Ethical considerations

The study protocol was reviewed and approved by an Institutional Ethics Committee (DF/CB029/10). Written informed consent was obtained from all volunteers.

RESULTS

Both groups were comprised of seven females and eight males. There were no significant differences in age between groups (41.9 ± 7.3 and 42.3 ± 7.5 years in placebo and metformin groups, respectively; p = 0.788). Clinical and laboratory baseline characteristics were similar between groups (Table 1).

After the pharmacological intervention, a decrease of body weight, BMI, waist circumference, and fasting and post-load glucose levels were observed in both groups, with a significant reduction in adiposity, total cholesterol, and LDL-C levels only in the metformin group (Table 1).

Written informed consent was withdrawn immediately after the first month of treatment in one patient from the metformin group. One patient from the placebo group presented venous thromboembolic disease during the second month of treatment and was excluded from the study. Adverse events

Table 1. Baseline and post-intervention characteristics of the studied groups

	Exenatide + Placebo		Exenatide + Metformin	
	n = 15	n = 14	n = 15	n = 14
	Before	After	Before	After
Body weight, kg	91.6 ± 11.4	86.8 ± 11.2¶	91.3 ± 15.8	84.9 ± 15.7†
BMI, kg/m^2	34.3 ± 3.3	32.7 ± 3.5¶	34.7 ± 3.6	32.6 ± 4.9†
Fat mass, %	40.6 ± 5.3	40.1 ± 5.9	42.9 ± 4.4	41.0 ± 6.0‡
Waist, cm	108 ± 10	104 ± 11‡	109 ± 12	103 ± 10‡
Systolic BP, mmHg	118 ± 8	118 ± 6	126 ± 4	124 ± 15
Diastolic BP, mmHg	78 ± 4	80 ± 8	80 ± 6	77 ± 4
Fasting glucose, mmol/l	6.0 ± 0.5	5.4 ± 0.4¶	5.8 ± 0.6	4.9 ± 0.9*
Post-load glucose, mmol/l	7.8 ± 1.5	5.8 ± 1.2¶	7.8 ± 1.7	5.8 ± 0.9*
Total cholesterol, mmol/l	4.9 ± 0.8	4.9 ± 1.1	5.7 ± 0.9	4.5 ± 0.9‡
HDL-C, mmol/l	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.0 ± 0.2
LDL-C, mmol/l	2.9 ± 0.5	3.0 ± 0.9	3.6 ± 0.8	2.7 ± 0.5‡
Triglycerides, mmol/l	1.7 ± 0.6	1.7 ± 0.7	2.0 ± 0.6	1.4 ± 0.2

Statistical analyses before and after interventions: *p = 0.05; †p = 0.02; ‡p = 0.01; ¶p = 0.008.
Conversion factors:
Glucose in mg/dl = glucose in mmol/l * 18.
Total, HDL- or LDL-cholesterol in mg/dl = total, HDL or LDL-cholesterol in mmol/l * 38.67.
Triglycerides in mg/dl = triglycerides in mmol/l * 88.57.
BMI: body mass index; BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

reported during the study were mainly nausea (three patients in the placebo group and four in the metformin group) and headache (two patients in each group). Adherence to treatment was > 80% in all patients.

DISCUSSION

Obesity is a global health problem with a gradual worldwide effect. This is a heterogeneous disorder associated with cardiovascular risk and other adverse health effects including prediabetes. The biological causes of obesity are complex. The rapid increase in obesity prevalence during the past few decades is due primarily to major societal changes, leading to an increase in the diabetic population[9].

It is fundamental to find treatment strategies for obtaining and maintaining long-term body weight reduction. One strategy could be use of the combination of several pharmacological medications with different and complementary mechanisms of actions, achieving greater body weight loss among other beneficial metabolic effects[10].

The effect of metformin to decrease body weight in obese diabetic and nondiabetic patients is controversial; however, decreases of > 1 kg at one year and 0.5 kg at two years have been observed[11]. In patients with prediabetes at 2.8 years, the average body weight loss was 2.1 kg, with a 31% reduction in diabetes incidence[12]. Long-term data on body weight reduction in diabetic patients are available from the United Kingdom Prediabetes Study (UKPDS)[13]. In obese insulin-resistant children, six-months administration of metformin decreased total body fat mass by 1.4 kg[14]. The effect of metformin to decrease appetite is likely to be multifactorial. Changes in hypothalamic physiology including leptin and insulin sensitivity have been documented. In addition, the gastrointestinal physiology and circadian rhythm changes by metformin not only affect food intake but also the regulation of fat oxidation and storage in liver, skeletal muscle, and

adipose tissue that could be participating in loss of body weight[15].

Metformin had a beneficial effect on total cholesterol, glucose control, and systolic and diastolic blood pressures, decreasing all-cause mortality and myocardial infarction-related mortality[16].

The mechanisms involved in the pleiotropic effects of GLP1 RA have yet to be completely elucidated; however, satiety is stimulated, leading to reductions in food intake and body weight. Gastric distension, peripheral vagal nerve activation, and central regulation of feeding have been proposed[17].

In prediabetic and obese patients, administration of exenatide for six months decreased body weight > 5 kg[18]. One-month administration of exenatide has shown a significant (4.4%) decrease of subcutaneous fat deposition in patients with metabolic syndrome[19]. Exenatide/metformin-treated patients with type 2 diabetes display progressive dose-dependent body weight loss up to –2.8 kg after 30 weeks[20]. For patients with diabetes and BMI > 30 kg/m^2, body weight change from baseline with the administration of exenatide for three years in patients with previous treatment of metformin or sulfonylureas was –5.8 kg[21].

Our results showed that administration of exenatide alone or in combination with metformin decreased BMI at the same magnitude, probably due to the fact that the effect of exenatide in decreasing total body weight was more powerful in both groups than that offered by the addition of metformin in this short period of time. Therefore, we believe that administration of exenatide alone is adequate if the purpose is to decrease body weight as an inducer only. However, this could be considered as a limitation of our study, and long-term investigations should be carried out to prove such affirmation. There is no information about the effect of the combination of exenatide plus metformin on fat deposition in diabetic patients and less information in nondiabetic individuals. In our study, adiposity was improved only with the combinations of metformin. One possible explanation may be that, in similar populations, exenatide administration as monotherapy has shown to only reduce subcutaneous fat[19] unlike metformin as monotherapy, which has decreased total body fat mass[14]. In regard to glucose control, fasting and post-load levels were decreased in both groups as expected. The results observed in the lipid profile were also as expected in accordance with the short time of metformin administration.

Based on the above-mentioned studies among others, the American Association of Clinical Endocrinologists has recommended the use of metformin to reduce the risk of future diabetes in prediabetic patients. On the other hand, glucagon-like peptide receptor agonists have demonstrated to prevent diabetes and restore normoglycemia in the vast of majority of subjects with prediabetes. Both medications are relatively well tolerated and safe and may confer a cardiovascular risk benefit[22].

In conclusion, exenatide alone or in combination with metformin showed similar results in decreasing body weight, BMI, waist circumference, and fasting and post-load glucose levels. The combination with metformin also decreased adiposity and total cholesterol and LDL-C concentrations.

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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 companies.

REFERENCES

1. Quezada AD, Lozada-Tequeanes AL. Time trends and sex differences in associations between socioeconomic status indicators and overweight-obesity in Mexico (2006-2012). BMC Public Health. 2015;15:1244.

2. Balsan GA, Vieira JL, Oliveira AM, Portal VL. Relationship between adiponectin, obesity and insulin resistance. Rev Assoc Med Bras. 2015;61: 72-80.
3. Best JH, Lavillotti K, DeYoung MB, Garrison LP. The effects of exenatide bid on metabolic control, medication use and hospitalization in patients with type 2 diabetes mellitus in clinical practice: a systematic review. Diabetes Obes Metab. 2012;14:387-98.
4. Malin SK, Kashyap SR. Effects of metformin on weight loss: potential mechanisms. Curr Opin Endocrinol Diabetes Obes. 2014;21:323-9.
5. Quan H, Zhang H, Wei W, Fang T. Gender-related different effects of a combined therapy of exenatide and metformin on overweight or obesity patients with type 2 diabetes mellitus. J Diabetes Complications. 2016;30:686-92.
6. Derosa G, Cicero AF, Franzetti IG, et al. Effects of exenatide and metformin in combinations on some adipocytokine levels: a comparison with metformin monotherapy. Can J Physiol Pharmacol. 2013;91;724-32.
7. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care. 2016;39(Suppl 1):S13-22.
8. Jeyaseelan L, Rao PS. Methods of determining sample sizes in clinical trials. Indian Pediatr. 1989;26:115-21.
9. Mandviwala T, Khalid U, Deswal A. Obesity and cardiovascular disease: a risk factor or a risk marker? Curr Atheroscler Rep. 2016;18:21.
10. Balkon N, Balkon C, Zitkus BS. Overweight and obesity: pharmacotherapeutic considerations. J Am Acad Nurse Pract. 2011;23:61-6.
11. Avenell A, Broom J, Brown TJ, et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. Health Tech Assess. 2004;8: 1-182.
12. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393-403.
13. UKPDS Group. Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. Ann Intern Med. 1998;128:165-75.
14. Yanovski JA, Krakoff J, Salaita CG, et al. Effects of metformin on body weight and body composition in obese insulin-resistant children. A randomized clinical trial. Diabetes. 2011;60:477-85.
15. Malin SK, Kashyap SR. Effects of metformin on weight loss: potential mechanisms. Curr Opin Endocrinol Diabetes Obes. 2014;21:323-9.
16. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577-89.
17. van Bloemendaal L, Ten Kulve JS, la Fleur SE, Ijzerman RG, Diamant M. Effects of glucagon-like peptide 1 on appetite and body weight: focus on the CNS. J Endocrinol. 2014;221:T1-16.
18. Rosenstock J, Klaff LJ, Schwartz S, et al. Effects of exenatide and lifestyle modification on body weight and glucose tolerance in obese subjects with and without pre-diabetes. Diabetes Care. 2010;33:1173-5.
19. González-Ortiz M, Martínez-Abundis E, Robles-Cervantes JA, Ramos-Zavala MG. Effect of exenatide on fat deposition and a metabolic profile in patients with metabolic syndrome. Metab Syndr Relat Disord. 2011;9:31-4.
20. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005;28:1092-100.
21. Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors, and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. Curr Med Res Opin. 2008;24:275-86.
22. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2016 executive summary. Endocr Pract. 2016;22: 84-113.