REVISTA MEXICANA DE ENDOCRINOLOGÍA, METABOLISMO & NUTRICIÓN ORIGINAL ARTICLE

Lixisenatide versus exenatide on metabolic control, insulin secretion and insulin sensitivity in patients with impaired glucose tolerance

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ABSTRACT

Aim: To evaluate the effect of lixisenatide versus exenatide on metabolic control, insulin secretion, and insulin sensitivity in patients with impaired glucose tolerance. **Materials and methods:** A randomized, open-label clinical trial in parallel groups was carried out in 24 adults with impaired glucose tolerance. Subjects received lixisenatide (10 µg once daily for two weeks and then 20 µg once daily) or exenatide (5 µg twice daily for four weeks and then 10 µg twice daily) for 12 weeks. At the beginning and at the end of the study, metabolic control, insulin secretion, and insulin sensitivity were evaluated. **Results:** Both groups demonstrated a decrease in weight, body mass index, waist circumference, blood pressure, glucose and insulin at 120 min, increasing insulin sensitivity. Lixisenatide also decreased fasting glucose (5.7 ± 0.8 vs. 5.0 ± 0.5 mmol/l; p = 0.008), area under the curve of glucose (1,252 ± 150 vs. 1,032 ± 157 mmol/l; p = 0.008) and high-density lipoprotein cholesterol (1.1 ± 0.1 vs. 1.0 ± 0.1 mmol/l; p = 0.025), and increased low-density lipoprotein cholesterol (2.5 ± 0.8 vs. 3.0 ± 0.9 mmol/l;

RESUMEN

Objetivo: Evaluar el efecto de lixisenatida versus exenatida sobre el control metabólico, la secreción de insulina y la sensibilidad a la insulina en pacientes con intolerancia a la glucosa (IG). **Material y métodos:** Ensayo clínico, abierto, aleatorizado, de grupos paralelos, realizado en 24 pacientes con IG. Durante 12 semanas los pacientes recibieron lixisenatida (10 µg una vez al día durante dos semanas y posteriormente 20 µg/día) o exenatida (5 µg dos veces al día durante cuatro semanas y posteriormente 10 µg dos veces al día). Al inicio y al final del estudio se midieron el control metabólico, la secreción de insulina y la sensibilidad a la insulina. **Resultados:** Los pacientes de ambos grupos disminuyeron el peso, el índice de masa corporal, la circunferencia de cintura, la presión arterial, la glucosa y la insulina al minuto 120 e incrementaron la sensibilidad a la insulina. Lixisenatida disminuyó además la glucosa en ayunas (5.7 ± 0.8 vs. 5.0 ± 0.5 mmol/l; p = 0.008), el área bajo la curva (ABC) de glucosa (1,252 ± 150 vs. 1,032 ± 157 mmol/l; p = 0.008) y el colesterol unido a lipoproteínas de alta densidad (C-HDL)

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Received for publication: 24-08-2016
Accepted for publication: 09-10-2016

p = 0.016), whereas exenatide decreased triglycerides (2.4 ± 1.0 vs. 2.1 ± 1.0 mmol/l; p = 0.050). **Conclusion:** Lixisenatide and exenatide decreased the same metabolic measurements. Lixisenatide also decreased fasting glucose, area under the curve of glucose, and high-density lipoprotein cholesterol, and increased low-density lipoprotein cholesterol, and exenatide decreased triglycerides. Both groups increased insulin sensitivity. (REV MEX ENDOCRINOL METAB NUTR. 2017;4:17-23)

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Key words: Exenatide. Impaired glucose tolerance. Insulin secretion. Insulin sensitivity. Lixisenatide. Metabolic control.

(1.1 ± 0.1 vs. 1.0 ± 0.1 mmol/l; p = 0.025), e incrementó el colesterol unido a lipoproteínas de baja densidad (C-LDL) (2.5 ± 0.8 vs. 3.0 ± 0.9 mmol/l; p = 0.016), mientras que exenatida disminuyó los triglicéridos (2.4 ± 1.0 vs. 2.1 ± 1.0 mmol/l; p = 0.050). **Conclusión:** Lixisenatida y exenatida disminuyeron las mismas mediciones metabólicas; lixisenatida también disminuyó la glucosa en ayunas, el ABC de glucosa y el C-HDL, y aumentó el C-LDL, y exenatida disminuyó los triglicéridos. Ambos grupos incrementaron la sensibilidad a la insulina.

Palabras clave: Control metabólico. Exenatida. Intolerancia a la glucosa. Lixisenatida. Secreción de insulina. Sensibilidad a la insulina.

INTRODUCTION

Impaired glucose tolerance (IGT) is an intermediate metabolic state between normal glucose tolerance and diabetes mellitus and is defined as a two-hour response to a 75 g oral glucose tolerance test (OGTT) of ≥ 7.8 mmol/l and < 11.1 mmol/l[1]. Impaired glucose tolerance reflects failing pancreatic islet beta-cell compensation for an underlying state of insulin resistance[2]. The natural history of IGT predicts that the majority of persons with the condition progress to diabetes in the long term. In addition to the risk of progression to diabetes, IGT has been reported to increase the risk for certain micro- and macrovascular complications typically associated with diabetes[3]. Thus, it is clear that IGT is not a benign condition. Pharmacological interventions reduce the rate of progression to type 2 diabetes mellitus (T2DM) by 10-60% in persons with IGT. Lifestyle interventions are likely to be at least as effective as drug treatment, but are often difficult to successfully carry out, and lifestyle advice needs to be reinforced on a regular basis[4]. Medications that attenuate postprandial glucose spikes may be particularly attractive in individuals with IGT because these glucose excursions are associated with endothelial dysfunction, inflammation, oxidative stress, and atherosclerosis[5]. In this regard, the class of glucagon-like peptide-1 receptor agonists (GLP-1 RA) may be an ideal candidate due to its primary mechanisms of action: reduction of postprandial glucose via increasing insulin secretion, decreasing glucagon secretion, and slowing gastric emptying[6], which leads to improved glycemic control[7]. According to the consensus statement by the American Association of Clinical Endocrinologists and the American College of Endocrinology on the comprehensive T2DM management algorithm, GLP-1 RAs can be considered in patients with IGT[2]. Lixisenatide and exenatide are short-acting GLP-1 RAs that share the same basic mechanism of action. However, each has a distinct pharmacokinetic profile and molecular structure with potential clinical implications[8] in terms of efficacy against metabolic control, insulin secretion, and insulin sensitivity. To the best of our knowledge, there is no current information about the use of lixisenatide versus exenatide in patients with IGT. Therefore, the aim of this study was to evaluate the effect of lixisenatide versus exenatide on metabolic control, insulin secretion, and insulin sensitivity in patients with IGT.

PATIENTS AND METHODS

A randomized, open-label clinical trial in parallel groups was carried out in 24 patients (31-60 years of age) with IGT in accordance with the American Diabetes Association (ADA) criteria. At screening visit, an oral glucose tolerance test was done to diagnose IGT and overweight or obesity (body mass

index [BMI] 25.0-39.9 kg/m^2). Subjects were selected from the same residential area and socioeconomic status. No participant was excessively sedentary or participated in heavy physical activity. All individuals were nonsmokers and had stable body weight for at least three months prior to the study. Subjects had not consumed any medication known to affect glucose or lipid metabolism during the previous six months. The main exclusion criteria were as follows: pregnant patients; those who were breastfeeding; patients with diabetes mellitus, hypertension, thyroid, renal, or liver disease; history of pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery, or inflammatory bowel disease; and clinically relevant history of gastrointestinal disease. In addition, patients were excluded from the study if they exhibited any other contraindication for the use of lixisenatide or exenatide.

Before testing, an isocaloric diet of at least 250 g of carbohydrates/day was given for three days, as confirmed by dietary history. Women were in the first phase of their menstrual cycle (3-8 days). Testing was initiated at 8:00 AM after a 12-hour overnight fast. Height and weight were recorded with the individuals wearing light clothing and without shoes. Values were used to calculate BMI according to the following formula: weight (kg)/height (m^2). Waist circumference was taken at the midpoint between the highest point of the iliac crest and the lowest rib in the mid-axillary line. Adiposity (% of fat mass) was assessed by bioelectrical impedance analysis using a contact electrode foot-to-foot body fat analyzer system (TBF-300 A, Tanita Corporation of America, Arlington Heights, IL, USA). The investigator evaluated blood pressure after a five-minute resting period with the individual sitting in a chair and determined with a digital sphygmomanometer.

A venous blood sample was obtained with the subject in a supine position in a quiet room. A catheter was placed in order to accomplish sampling at 0, 30, 60, 90, and 120 minutes after a 75 g oral dextrose load. After that, samples were centrifuged.

The resulting serum was placed into two aliquots: one of the aliquots was immediately used for glucose determination; the second was frozen at –20º C for insulin measurement within the following 30 days.

At time 0 minutes, an extra blood tube was taken to measure high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride (TG) concentrations.

Glucose concentration was determined by the glucose oxidase method; TC, TG, and HDL-C were measured enzymatically. In particular, HDL-C was assessed after selective precipitation of non-HDL-C fractions. Determinations were performed with commercially available equipment (Vitros® Ortho-Clinical Diagnostics, Johnson & Johnson, Rochester, NY) with an intra- and inter-assay coefficient of variation of < 2%. Insulin concentrations were measured by a chemiluminescent immunoassay technique (Beckman Coulter, Fullerton, CA) with an intra- and inter-assay coefficient of variation of 3.8 and 4.2, respectively. Area under the curve (AUC) 0-120 minutes of glucose and insulin was calculated with the polygonal formula. Total insulin secretion was evaluated with the insulinogenic index (ΔAUC insulin/ΔAUC glucose). The first phase of insulin secretion was estimated using the Stumvoll index (1,283 + 1.829 x insulin 30′ – 138.7 x glucose 30′ + 3.772 x insulin 0′) and insulin sensitivity with the Matsuda index (10,000/√ (glucose 0′ x insulin 0′) (mean glucose taken from the OGTT x mean insulin OGTT)[9-11]. The low-density lipoprotein cholesterol (LDL-C) concentration was estimated using the Friedewald formula[12].

Participants were randomized at a 1:1 ratio to receive either lixisenatide or exenatide using a table of random numbers. Treatment numbers were allocated according to a predefined randomization list.

After random allocation of the intervention, 12 patients received lixisenatide (Lyxumia®, Sanofi, Mexico City, Mexico) 10 µg once daily for two weeks and then 20 µg once daily. The other group of 12 patients received exenatide (Byetta®, Eli Lilly Co, Mexico City, Mexico) 5 µg twice daily for four weeks and then 10 µg twice daily. Treatments were administered subcutaneously within one hour before the morning meal (lixisenatide) or before the morning and evening meals (exenatide). Both groups followed the treatments for 12 weeks. All patients received general nutritional recommendations and were instructed to not modify their usual exercise habits.

Statistical analyses

Sample size was calculated using a formula for mean differences[13] with a statistical confidence of 95%, statistical power of 80%, standard deviation (SD) for the Matsuda index of 1.75, and an expected between-group difference of at least 2.3 of the Matsuda index, obtaining a total of 12 patients for each group that included 20% of expected loss. For insulin secretion, sample size calculation was lower. Values were converted to the International System of Units and are presented as mean ± SD. Shapiro-Wilk test was used to evaluate normal and intra- and inter-group distribution. 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 the Institutional Ethics Committee (DF/CB052/13) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all volunteers prior to any procedures.

RESULTS

Twenty-two patients completed the 12-week period of pharmacological intervention with an adherence > 80%. There were 11 patients (seven females and four males) in each group. One patient in each group did not complete the study due to early withdrawal. There was no significant difference in age between groups (47.6 ± 7.5 vs. 45.2 ± 6.5 years old, lixisenatide and exenatide group, respectively; $p = 0.266$). No significant differences were shown at baseline in clinical and laboratory characteristics between groups (Table 1).

Both groups significantly decreased weight, BMI, waist circumference, and systolic and diastolic blood pressures as well as glucose and insulin at 120 minutes in addition to a significant increase in the Matsuda index. In the lixisenatide group, there were also significant reductions of fasting glucose, AUC of glucose, and HDL-C, and a significant increase of LDL-C, whereas the exenatide group significantly decreased triglyceride levels (Table 1). Normalization of glucose at 120 minutes was observed in 45 vs. 36% of the lixisenatide and exenatide groups, respectively; $p = 0.665$. There were no significant differences in adverse events (AE) observed between groups. The most common AE in both groups were gastrointestinal in nature, mainly nausea (42% of the participants in the lixisenatide group vs. 50% in the exenatide group). This nausea resolved during the first eight weeks of treatment.

DISCUSSION

IGT reflects failing pancreatic islet beta-cell compensation for an underlying state of insulin resistance, most commonly caused by excess body weight or obesity[2].

In this regard, the use of a short-acting GLP-1 RA such as lixisenatide and exenatide may be an option for the treatment of IGT because these drugs have been shown to improve glycemic control with the additional benefit of clinically relevant weight loss in the population with T2DM[14].

A previous study compared the effect of lixisenatide and exenatide in patients with T2DM in relation to the effectiveness on reducing A1C; however, to date there is no information about the comparison of these drugs in relation to metabolic control, insulin secretion, and insulin sensitivity in a patient population with IGT, which could help to choose the best drug therapy in clinical practice[8].

In our study, body weight (–2.0 ± 2.2 vs. –1.8 ± 1.3 kg, lixisenatide and exenatide group, respectively; $p = 0.651$), BMI, and waist circumference decreased significantly from baseline in both groups. These results are consistent with what has been reported in the literature. In a meta-analysis that included 21 trials and 3,395 participants with T2DM randomly assigned to GLP-1 RAs, all trials showed a reduction in weight ranging from –0.2 to –7.2 kg[15]. This could be explained

Table 1. Clinical and laboratory characteristics of both groups

	Lixisenatide*		Exenatide*	
	Baseline	12 weeks	Baseline	12 weeks
Weight (kg)	83.8 ± 11.7	81.9 ± 12.1†	91.8 ± 16.1	89.1 ± 16.7†
BMI (kg/m^2)	31.9 ± 3.5	31.6 ± 3.6†	34.5 ± 4.5	33.6 ± 4.8
WC (cm)	106 ± 11	102.6 ± 10.8†	109 ± 13	107 ± 13†
SBP (mmHg)	120 ± 15	111 ± 12†	121 ± 11	113 ± 11†
DBP (mmHg)	78 ± 11	73 ± 12†	76 ± 8	72 ± 10†
Glucose 0-min,	5.7 ± 0.8	5.0 ± 0.5	5.9 ± 0.7	5.6 ± 0.8
mmol/l (mg/dl)	(103.5 ± 14.1)	(90.1 ± 9.6)	(106.3 ± 13.4)	(100.9 ± 13.9)
Glucose 120-min,	9.7 ± 1.0	7.8 ± 1.7†	9.6 ± 1.2	8.1 ± 1.7†
mmol/l (mg/dl)	(175.0 ± 17.3)	(141.2 ± 31.4)	(173.4 ± 22.3)	(146.1 ± 30.7)
Insulin 0-min,	83.4 ± 37.8	79.2 ± 52.8	77.4 ± 57.0	70.2 ± 64.2
pmol/l (µUI/ml)	(13.9 ± 6.3)	(13.2 ± 8.8)	(12.9 ± 9.5)	(11.7 ± 15.7)
Insulin 120-min,	891.6 ± 526.8	577.2 ± 285.0†	987.6 ± 578.4	580.2 ± 386.4†
pmol/l (µUI/ml)	(148.6 ± 87.8)	(96.2 ± 47.5)	(164.6 ± 96.4)	(96.7 ± 64.4)
TC,	4.8 ± 0.8	4.9 ± 0.9	5.2 ± 1.0	5.0 ± 1.3
mmol/l (mg/dl)	(186.8 ± 31.4)	(190.4 ± 34.7)	(202.1 ± 40.5)	(193.0 ± 50.1)
LDL-C,	2.5 ± 0.8	3.0 ± 1.0†	2.3 ± 0.8	2.5 ± 1.2
mmol/l (mg/dl)	(95.6 ± 30.9)	(116.8 ± 37.5)	(111.0 ± 31.1)	(97.0 ± 47.4)
HDL-C,	1.1 ± 0.2	1.0 ± 0.1†	1.2 ± 0.2	1.3 ± 0.3
mmol/l (mg/dl)	(44.4 ± 6.3)	(40.5 ± 5.8)	(46.6 ± 9.1)	(49.6 ± 11.3)
TG,	2.6 ± 1.2	1.8 ± 1.1	2.5 ± 1.0	2.1 ± 1.0†
mmol/l (mg/dl)	(234.0 ± 103.7)	(165.1 ± 98.3)	(222.3 ± 92.7)	(192.0 ± 94.5)
VLDL,	0.5 ± 0.2	0.4 ± 0.2	0.5 ± 0.2	0.4 ± 0.2
mmol/l (mg/dl)	(46.8 ± 20.7)	(33.0 ± 19.6)	(44.4 ± 18.5)	(37.3 ± 19.4)
AUC glucose,	1252 ± 150	1032 ± 157†	1259 ± 144	1194 ± 186
mmol/l (mg/dl)	(22,563 ± 2,703)	(18,600 ± 2,837)	(22,688 ± 2,595)	(21,518 ± 3,358)
AUC insulin (pmol/l)	83,182 ± 46,602	71,696 ± 36,793	88,120 ± 54,857	70,992 ± 37,356
pmol/l (µUI/ml)	(13,863 ± 7,767)	(11,949 ± 6,132)	(14,686 ± 9,143)	(11,832 ± 6,226)
Insulinogenic index	0.62 ± 0.34	0.58 ± 0.38	0.64 ± 0.40	0.56 ± 0.28
Stumvoll index	1,140 ± 586	1,320 ± 658	1,322 ± 1092	944 ± 854
Matsuda index	2.3 ± 1.0	3.5 ± 2.4†	2.6 ± 1.8	5.6 ± 4.0

*No significant basal differences between groups. †$p < 0.05$ between baseline and 12 weeks.
AUC: area under the curve; BMI: body mass index; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; TG: triglycerides; VLDL: very low-density lipoprotein; WC: waist circumference.

by several pathways such as GLP-1 decreasing gastrointestinal motility, which increases the time that nutrients can be absorbed. It also increases satiety, increases resting metabolic rate, and lowers plasma concentrations of free fatty acids[16].

The GLP-1 RAs also have demonstrated positive effects on blood pressure. Most data are related to liraglutide and exenatide because they have been available for the longest period. In clinical trials, exenatide reduced systolic blood pressure (SBP) from 2.9 to 4.7 mmHg and diastolic blood pressure (DBP) from 0 to 1.9 mmHg[17-20]. We report that both groups showed a significant decrease of SBP and DBP. The possible mechanisms of blood pressure reduction may involve direct stimulation of GLP-1 receptors through signal transduction, GLP-1 receptor-independent activation of a nitric oxide/cyclic guanosine 3′,5′-monophosphate (NO/cGMP)-associated pathway, adrenergic receptor activation, renin-angiotensin-aldosterone system

inhibition, and an increase in urinary sodium excretion or neural pathway activation, leading to decreased sympathetic nervous system activity[21].

The GLP-1 RAs offer effective glycemic control. This class of injectable antihyperglycemic agents acts in a glucose-dependent manner and reduces both fasting and postprandial blood glucose levels. In particular, short-acting GLP-1 RAs lead to a strong reduction in postprandial glucose and postprandial insulin secretion, with a modest reduction of fasting blood glucose levels and fasting insulin secretion[22]. In our study, a comparable reduction in glucose 120' and insulin 120' from baseline in both groups was demonstrated, and only the lixisenatide group significantly decreased fasting glucose and AUC of glucose. The effects of these drugs on fasting glucose levels or fasting measures of insulin secretion are less pronounced than those of long-acting analogues[8]. In contrast, rapid increases in plasma levels of these short-acting receptor agonists lead to substantial retardation of gastric emptying, thereby markedly blunting postprandial glucose excursions[23,24]. Although the two short-acting receptor agonists stimulate insulin secretion in the fasting state and under experimental conditions, their effects on postprandial blood glucose levels do not seem to be mediated by stimulation of insulin secretion. In fact, postprandial insulin secretion is dose-dependently reduced by exenatide and lixisenatide. Indeed, the postprandial reduction of blood glucose levels induced by short-acting GLP-1 RAs seems to be primarily the result of delayed gastric emptying, which leads to a decreased rate of glucose entry into the duodenum and, subsequently, into the circulation[25]. This mechanism of action explains why short-acting GLP-1 RAs seem to exert an insulin-lowering effect in the postprandial state despite the well-characterized insulinotropic effect of GLP-1 itself[23].

Lixisenatide and exenatide showed significant increases in insulin sensitivity. Both weight reduction and induced changes in generating cytokine insulin resistance as well as increases in adiponectin provide possible mechanisms that explain the effect of GLP-1 RAs on insulin sensitivity[26]. It has been found that exenatide increases hepatic and muscle glucose uptake. Moreover, it appears that in addition to peripheral mechanisms, central ones are also involved in promoting the effect of insulin sensitivity of GLP-1 RAs in an experimental model[27].

In this study, decrease of insulin secretion was expected, but that was not the case because no significant changes were observed. This is explained because the equations for the Stumvoll and insulinogenic indexes require insulin and glucose in the first minutes and, at this stage, no changes were observed in addition to a possible metabolic compensation in this group of patients[28]. Although both formulas have good correlation with the gold standard, they are generally considered as estimations of insulin metabolism.

In general, GLP-1 RAs have demonstrated positive effects on lipid parameters.

The GLP-1 RAs generally induce a favorable lipid profile because they reduce the plasma concentration of total cholesterol, LDL-C, and triglycerides. However, meta-analyses indicate that they do not lead to a significant improvement in HDL-C[29]. Reduction of intestinal secretion of triacylglycerol, cholesterol and apolipoprotein B48 as well as the effects of the improvement in glycemic control and weight reduction are elements that could contribute to the effect on dyslipidemia[30]. We only report a positive change in the concentration of triglycerides in the exenatide group. This is according to a study in T2DM patients treated for 82 weeks with exenatide plus sulfonylurea and/or metformin, finding a significant change of triglyceride concentrations (–0.43 mmol/l)[31]. Regarding lixisenatide, we observed a decrease in HDL-C and an increase in LDL-C. However, no other studies have evaluated the effect of lixisenatide on lipid profile and, therefore, we cannot compare our results.

At the end of the study, normalization of glucose at 120 minutes was observed in more than one-third of the patients after lixisenatide or exenatide administration as monotherapy, indicating that the multi-pleiotropic activity of those compounds could be explored in the routine treatment of IGT.

Our results, as well as other reports in the medical literature (in diabetic populations), showed that

lixisenatide and exenatide administration improved metabolic control, increasing insulin sensitivity.

Despite our results, further long-term studies with a larger sample size are necessary in order to continue with the recommendation of the use of GLP-1 RAs in patients with IGT.

In conclusion, both lixisenatide and exenatide lead to an improvement in metabolic control (weight, BMI, waist circumference, systolic and diastolic blood pressure, postprandial glucose and insulin) and insulin sensitivity with a different effect on the lipid profile.

ACKNOWLEDGMENTS

We thank Sharon Morey, Executive Editor, Scientific Communications, for English editorial assistance.

DISCLOSURE OF INTEREST

No conflict of interest is reported with regard to this manuscript. The authors declare no competing interests with the mentioned pharmaceutical companies.

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