Exenatide – A Novel Treatment to Manage Type 2 Diabetes Mellitus

a report by

Manel Puig-Domingo,[1] Alicia Gervás-Ríos,[2] Cristián Fernández-Fernández[1] *and* Jesús Reviriego[2]

1. Endocrinology, Nutrition and Diabetes Service, Hospital Clínic, Barcelona; 2. Department of Clinical Investigation, Lilly SA, Madrid

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The epidemic characteristics of type 2 diabetes mellitus (T2DM) pose a challenge to the healthcare resources needed to treat this chronic disease and also to prevent its associated cardiovascular (CV) complications, the number one cause of T2DM-associated morbi-mortality and its social and personal impact. There is currently a growing number of available treatments that make it possible to achieve targeted glycaemic control in most patients, albeit only temporarily in many patients due to the progressive nature of the disease. Current therapies often entail undesirable side effects, such as weight gain or hypoglycaemia, limiting their optimisation. Recently, a new class of drugs has become available for the treatment of T2DM: incretin mimetics. Exenatide is the first incretin mimetic available to date. It acts in a similar way to glucagon-like peptide-1 (GLP-1), an intestinal incretin hormone that is naturally secreted following the intake of nutrients. Unlike GLP-1, which has a half-life too short to make it viable for treatment, exenatide is resistant to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). Exenatide has shown to increase glucose-dependent insulin secretion, decrease glucose-dependent post-prandial secretion of glucagon, slow gastric emptying and reduce food intake. Furthermore, some of these effects represent mechanisms that have a significant positive impact on glucose homeostasis and a beneficial effect on bodyweight. Clinical trials (phase III triple-blind studies) have shown that exenatide can decrease glycated haemoglobin (HbA_{1C}) by 1%, together with weight loss and infrequent hypoglycaemic episodes in patients not well controlled with previous metformin and/or sulphonylurea treatment. Nausea is the main side effect when starting treatment with exenatide and can decrease with continued use of exenatide. Moreover, pre-clinical studies in experimental models suggest that exenatide might have a promising effect on pancreatic islet ß–cell function and mass. Overall, exenatide provides a treatment option for patients with T2DM who have not achieved adequate glycaemic control while on maximum tolerated doses of metformin and/or sulphonylurea therapy.

Background

T2DM affects more than 150 million people worldwide.[1,2] The World Health Organization predicts that by 2025 the number of people affected will double, largely due to demographic growth, the ageing population, unhealthy eating, obesity and sedentary lifestyles in most developed countries.[2–4] T2DM is associated with a series of macro- and micro-vascular complications that lead to disabilities, loss of employment and premature death, resulting in increased utilisation of healthcare resources.[1]

It is widely accepted that the current treatment of T2DM requires a progressive pharmacological approach, as pointed out recently by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[5] The first step in T2DM treatment is to improve the glycaemic control of patients by implementing lifestyle changes, such as dietary modifications and increased physical activity. Once the first intervention is no longer effective, other drugs such as metformin, sulphonylureas, thiazolidinadiones (TZDs), meglitinides and α-glucosidase inhibitors are added to achieve the desired targets. These groups of drugs lower glucose levels by means of different mechanisms of action and can be used in mono- or combination therapy.[3]

The initial and subsequent dose titration may be limited by the emergence of adverse effects. Nevertheless, despite the many treatment options currently available, for many T2DM patients glycaemic control continues to be inadequate.

It is well-known that after a variable period of time of treatment with oral medications (roughly 5–7 years), and given the progressive nature of the illness, ß-cell function declines sharply, making insulin necessary in approximately half the cases.[6]

Most existing therapeutic options have been developed without prior definition of molecular targets. The advances being made in understanding the pathogenesis of T2DM provide the opportunity to develop new treatment interventions,[7] such as using glucose-regulating peptides known as incretins.[8]

Concept and Physiology of the Incretin Effect

Incretins are hormones that are released into the circulation by gut cells in response to food intake, and exert a significant number of glucose regulating actions including an insulinotropic effect – that is, an increased glucose-dependent secretion of insulin.[9,10] These hormones include the glucose-dependent insulinotropic polypeptide (GIP) secreted by intestinal K cells, mainly located in the jejunum, and also throughout the rest of the

Manel Puig-Domingo is a Consultant in the Endocrinology, Nutrition and Diabetes Service at the Hospital Clínic, Barcelona. His primary research interests include the prevention of type 1 diabetes, the treatment of type 2 diabetes, the endocrinology of ageing and thyroid cancer. Dr Puig-Domingo is Vice-President of both the Catalan Society of Endocrinology and the Spanish Society of Endocrinology. He has authored 68 peer-reviewed papers, 18 reviews and 22 chapters of books. Dr Puig-Domingo obtained his PhD in Endocrinology at the Universidad Autónoma de Barcelona in 1988, and was Associate Professor of Medicine at the same institution from 1991 to 2000. Earlier in his career he spent two years at the University of Texas Health Science Center at San Antonio, from 1986 to 1988, where he was a Research Fellow in the Department of Cellular and Structural Biology and Assistant Professor at their School of Medicine. Prior to this, Dr Puig-Domingo was a Resident in Endocrinology at Hospital de Sant Pau, Barcelona.

gut,[11] and GLP-1, secreted by intestinal glucose-responsive neuroendocrine (L) cells, mainly located in the ileum and the colon, and in the duodenum and jejunum. The incretin effect is the phenomenon by which greater insulin secretion results after oral glucose intake than after infusion of comparable amounts of intravenous glucose.[12]

Role of Incretins in Regulating Glucose Homeostasis

Different studies have consistently demonstrated the glucose-regulating effects of GLP-1. The underlying mechanisms were discovered by administering GLP-1 and GLP-1 antagonists in animal models. These glucose-regulatory effects include glucose-dependent insulinotropic effect, inhibition of glucagon secretion, slowed gastric emptying and cytoprotection of cells (in experimental models).[13–20]

Glucose-dependent Insulinotropic Effect

The incretin effect of GLP-1 – increasing glucose-dependent insulin secretion – is mediated by the interaction of GLP-1 with its specific receptor bound to a G protein in ß cells that stimulates adenylcyclase and increases the generation of cyclic adenosine-3', 5'-monophosphate (cAMP), which increases intracellular Ca++, ultimately triggering insulin secretion.[21–23] These actions depend on glucose levels, so that the insulinotropic effects of GLP-1 decrease as plasma concentrations of glucose approach normal values.[24] Furthermore, GLP-1 has been shown to enhance the first phase of insulin secretion in patients with T2DM, which is generally absent in these patients.[25]

> Unlike most antidiabetic medications, incretin mimetics also suppress post-prandial secretion of glucagon, slow gastric emptying and reduce food intake and bodyweight, thus providing a positive scenario for a comprehensive amelioration of metabolic status in type 2 diabetes mellitus patients.

Inhibition of Glucagon Secretion

GLP-1 suppresses glucagon secretion by pancreatic cells when glucose concentrations are elevated.[26] This glucagon-static effect of GLP-1 is accompanied by a decrease in hepatic glucose production. There is no consensus as to whether GLP-1 exerts a direct effect on α cells, since it is not known whether α cells express receptors for GLP-1, or whether there is an alternative paracrine regulation by means of somatostatin.[27]

Gastric Emptying Effect

The rate of gastric emptying is the main regulatory mechanism of the amount of nutrients that reach the small intestine. GLP-1 is one of several factors that modulate the rate of gastric emptying.[28] It has been postulated that GLP-1 regulation of gastric emptying is mediated by specific receptors in the brain, promoting vagal stimulation.[29,30]

Cytoprotection of β Cells

Studies *in vitro* and *in vivo* have demonstrated that GLP-1 increases cell mass and maintains ß cell function. The effects of GLP-1 on ß cells have been categorised as:

- acute: GLP-1 increases glucose-dependent insulin secretion;
- subacute: GLP-1 stimulates pro-insulin transcription and insulin biosynthesis; and
- chronic: GLP-1 stimulates both the proliferation and neogenesis of ß cells from ductal precursor cells and decreases their apoptosis.[31–33]

Limitations of Therapeutic Use

GLP-1 has been investigated in some short-term clinical trials to explore its therapeutic potential for patients with T2DM.[34] However, because of the rapid degradation of the molecule by the DPP-4 enzyme, the therapeutic usefulness of GLP-1 is limited by the need for chronic infusion and the temporary nature of its effects once infusion is suspended.

Incretin Mimetics

Incretin mimetics are molecules that mimic different physiological effects of the incretin GLP-1, such as glucose-dependent insulin secretion in clinical and pre-clinical models. Unlike most antidiabetic medications, incretin mimetics also suppress post-prandial secretion of glucagon, slow gastric emptying and reduce food intake and bodyweight,[35,36] thus providing a positive scenario for a comprehensive amelioration of metabolic status in T2DM patients. Likewise, beneficial actions have been revealed in cell lines and in animal models, such as a promoting ß–cell proliferation and neogenesis.

Exenatide

In 2006, the European Commission approved an exenatide injection called Byetta™ used for treatment of T2DM in combination with metformin and/or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.[37]

Pharmacology

Exendin-4, a natural peptide containing 39 amino acids, was identified and isolated from the saliva of a lizard commonly known as the gila monster (*Heloderma suspectum*), native to the Gila river valley in Arizona and New Mexico. Exendin-4 shares several glucoregulatory actions with GLP-1.[38,39] Exenatide is the synthetic form of exendin-4. Exenatide is not an analogue of the GLP-1 hormone, although it shares 53% of its amino acid sequence. Unlike GLP-1, exenatide is resistant to the action of DPP-4 due to substitution of glycine for alanine in position 2, and therefore has a longer half-life.[40]

In various pre-clinical studies, exenatide has been shown to exert antidiabetic actions similar to those described for the incretin GLP-1, such as enhancing glucose-dependent insulin secretion, suppressing the concentration of high glucagon levels, slowing gastric emptying, decreasing food intake and inducing neogenesis of pancreatic islets.[41–49]

Pharmacokinetics/Pharmacodynamics

The pharmacokinetic profile of exenatide has been researched clinically in healthy volunteers[50,51] and in patients with T2DM.[52,53] Peak plasma concentrations are reached after 2.1 hours, with similar bioavailability following subcutaneous administration in the abdomen, thigh or upper arm.[51] Results of pre-clinical studies indicate that the drug is eliminated primarily by glomerular filtration, followed by proteolytic degradation.[54,55] Exenatide has a half-life of 2.4 hours, and plasma concentrations are

Table 1: Efficacy of Exenatide (5–10µg) for AMIGO Clinical Trials

	AMIGO I			AMIGO II			AMIGO III		
Drug	Exenatide+metformin			Exenatide+sulphonylurea			Exenatide+(sulphonylurea+metformin)		
Treatment	Placebo	5µg	10µg	Placebo	5µg	10µg	Placebo	5µg	10µg
Treatment ITT (n)	113	110	113	123	125	129	247	245	241
Population evaluated (n)	89	90	91	73	93	89	184	205	188
Baseline A1C (%)	8.2	8.3	8.2	8.7	8.5	8.6	8.5	8.5	8.5
Change at week 30	+0.1	-0.4	-0.8	+0.1	-0.5	-0.9	+0.23	-0.55	-0.77
A1C <7%									
Evaluated (%)	13	32	46	9	33	41	9	27	34
ITT (%)*	11	27	40	8	27	34	7	24	30
Baseline FPG (mmol/l)	9.4	9.8	9.3	10.8	10	9.9	10	10.1	9.9
Change at week 30	+0.8	-0.4	-0.6	+0.4	-0.3	-0.6	+0.8	-0.5	-0.6
Baseline weight (kg)	100	100	101	99	95	95	99	97	98
Change at week 30	-0.3	-1.6	-2.8	-0.6	-0.9	-1.6	-0.9	-1.6	-1.6

ITT = intent to treat population; FPG = fasting plasma glucose.
** Numbers have been rounded to the nearest whole value.*

detectable up to 10 hours following subcutaneous administration.[51,55]

Other pharmacokinetic studies of exenatide in male and female Caucasian, Hispanic, Japanese and black patients aged 22–73 years have shown that age, sex and race have no significant effects on the pharmacokinetics of subcutaneous administration of exenatide.[37,56] Furthermore, obesity (body mass index (BMI) ≥30kg/m^2) does not appear to modify exenatide's pharmacokinetic profile.[55] Experience in patients with BMI ≤25 is limited.[37]

In patients with mild renal impairment (creatinine clearance 50–80ml/min) or moderate renal impairment (creatinine clearance 30–50ml/min), exenatide clearance is slightly decreased compared with clearance in individuals with normal renal function (13% reduction in mild and 36% reduction in moderate renal impairment). No dosage adjustment is required in these cases, but in patients with moderate renal impairment, dosage escalation from 5 to 10µg should proceed conservatively.[37,57] In patients with severe renal dysfunction treated with dialysis (creatinine clearance <30ml/min), the clearance of exenatide is reduced by more than 10-fold (0.9l/h compared with 9.1l/h in healthy subjects); hence, its use is not recommended for this group of patients.[55] At present, there are no available data on the effects of exenatide administration in subjects with severe hepatic insufficiency. Exenatide is cleared primarily by the kidney; therefore, hepatic dysfunction is not expected to affect blood concentration of exenatide.[37]

Drug Interactions

The ability of exenatide to slow gastric emptying may reduce the extent and rate of absorption of orally administrated drugs. This fact should be taken into account when administering oral drugs that require rapid gastrointestinal absorption. For example, contraceptives and antibiotics, which are particularly dependent on threshold concentrations for efficacy, should be taken at least one hour before exenatide injection.[37] Exenatide is not expected to have any clinically relevant effects on the pharmacokinetics of metformin or sulphonylureas. Hence, no restriction in the timing of the intake of these drugs in relation to exenatide injection is needed.[37]

Paracetamol was used as a model drug to evaluate the effect of exenatide on gastric emptying. In a drug interaction study, when 1,000mg paracetamol was given with 10µg exenatide at 0h, +1h, +2h and +4h, the maximum decrease of paracetamol area under the concentration-time curve (AUC) and maximum drug concentration (C_{max}) was observed between one and two hours post-exenatide administration. Paracetamol AUC, C_{max} and time to C_{max} (T_{max}) were not significantly changed when paracetamol was given one hour before exenatide injection. Based on these study results, no adjustment to paracetamol dosing is required.[37,50]

Many patients with T2DM have dyslipidaemia, which requires treatment with three hydroxyl-3-methylglutaryl coenzyme (HMG CoA) reductase inhibitors (statins). The potential interaction between exenatide and statins has been evaluated in two studies.[58] In an open-label, fixed-sequence, clinical pharmacology study in which healthy subjects received 10µg twice daily (BID) of exenatide and lovastatin (40mg) or lovastatin (40mg) alone, lovastatin AUC and C_{max} were decreased by approximately 40% and 28%, respectively, and T_{max} was delayed by about four hours in the exenatide plus lovastatin group. In the 30-week placebo-controlled clinical trials, described in the clinical experience section, concomitant use of exenatide and HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles. Although no pre-determined dose adjustment is required, one should be aware of possible changes in low-density lipoprotein cholestrol (LDL-C) or total cholesterol. Lipid profiles should be monitored regularly.[37]

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Exenatide has been also administered and studied in combination with digoxin,[59] lisinopril and warfarin. A delay in T_{max} of about two hours was observed when digoxin, lisinopril or warfarin were administered

Table 2: Adverse Events in the AMIGO Clinical Trials

Adverse Events	+Metformin			+Sulphonylureas			+Sulphonylureas+Metformin		
	Placebo	5µg	10µg	Placebo	5µg	10µg	Placebo	5µg	10µg
Nausea	23%	36%	45%	7%	39%	51%	20.6%	39.2%	48.5%
Hypoglycaemia	5%	5%	5%	3%	14%	36%	12.6%	19.2%	27.8%
Diarrhoea	8%	12%	16%	4%	11%	9%	6.5%	10.2%	17.4%
URTI	11%	14%	10%				19.4%	11.,4%	17.4%
Vomiting	4%	11%	12%	2%	10%	13%	4.5%	14.7%	13.7%
Dizziness	6%	9%	4%	7%	15%	15%	0	0	0
Sinusitis	5%	5%	6%	0	0	0	0	0	0
Feeling jittery	0	0	0	2%	12%	15%	6.9%	8.6%	11.6%
Headache	0	0	0	7%	9%	8%	4.9%	11%	7.5%
Serious treatment-emergent adverse events	3.5%	4.5%	2.7%	8%	3%	4%	6%	6%	5.%

URTI = upper respiratory tract infection.

30 minutes after exenatide. No clinically relevant effects on C_{max} or AUC were observed. On the other hand, post-marketing reports in the US have described increases in international normalized ratio (INR) when exenatide and warfarin are used concomitantly. INR should be monitored closely during initiation and dose increase of exenatide therapy in patients on warfarin and/or cumarol derivatives.[37]

Dosage and Administration

Exenatide is a peptide and therefore cannot be administered orally. It has to be administrated via subcutaneous injection in the abdomen, thigh or upper arm at any time within the 60-minute period before the morning and evening meals. Exenatide should not be administered after a meal. If a dosage is missed, the treatment should be continued with the next regularly scheduled dosage.[37] Exenatide treatment should be initiated at a dosage of 5µg administered BID for at least one month to improve tolerability. Then, the dosage may be increased to 10µg BID to further improve glycaemic control. Doses higher than 10µg BID are not recommended.

Clinical Experience – Efficacy and Safety Studies

The efficacy and safety of 5µg and 10µg exenatide administered BID have been evaluated in three phase III trials entitled: 'AC2993: Diabetes Management for Improving Glucose Outcomes' (AMIGO Studies). All studies were multicentre, randomised, triple-blind, placebo-controlled 30-week trials that enrolled more than 1,400 patients with T2DM. Study participants had inadequate glycaemic control with metformin,[60] sulphonylurea[61] or a combination of both (at maximally effective doses).[62]

After the four-week placebo lead-in period, patients were randomly chosen for treatment with placebo, 5 or 10µg of exenatide BID. Patients in the 10µg exenatide group received 5µg of exenatide for the first four weeks of the study to mitigate the feeling of nausea. Placebo and exenatide were administered BID 15 minutes prior to breakfast and dinner by subcutaneous injection into the abdomen.[60–62]

The main efficacy end-point was the change in HbA_{1C} from baseline to week 30. Changes in fasting plasma glucose (FPG) and bodyweight and the percentage of subjects (baseline levels of HbA_{1C} >7%) who achieved HbA_{1C} of ≤7% at week 30 were secondary measures.[60–62] *Table 1* presents the efficacy outcomes for exenatide in the phase III trials.

In the AMIGO studies, nausea was the most common adverse event with most episodes being mild to moderate, and progressive dose escalation lessened the incidence of exenatide-induced nausea. The dropout rate due to nausea varied between 1.8 and 4% in the exenatide-treated patients and was more frequent in the exenatide 10µg treatment groups.[63] There was no increase in the incidence of hypoglycaemia in patients receiving exenatide in combination with metformin.[60] The incidence of hypoglycaemia in relation to placebo was greater in patients treated with sulphonylureas, and was also dependent on the dose of suphonylurea.[60–62]

On the other hand, it is well-known that glucagon, growth hormone, cortisol and catecholamines are important counter-regulatory hormones that offer protection from hypoglycaemia. In a stepwise hypoglycaemic study, the potential effect of intravenous exenatide on counter-regulatory mechanisms to hypoglycaemia was evaluated. The results showed that glucagon, growth hormone, adrenaline and cortisol levels were not affected or, in some cases (i.e. glucagon), were slightly increased during hypoglycaemia, indicating that the physiological counter-regulatory process is not affected by treatment with exenatide during hypoglycaemia.[64] The most commonly reported adverse effects in the AMIGO studies are listed in *Table 2*.

At week 30, patients taking exenatide who lost weight (from baseline -2.1±0.2kg) continued to lose weight at week 82 (-4.4±0.3kg). Post-prandial and fasting plasma glucose levels were also improved.

In a 52-week, open-label extension of the AMIGO studies, 314 patients continued with their oral antidiabetic treatment and 10µg of exenatide BID (82 weeks of total drug exposure).[65] Reduced HbA_{1C} levels observed at week 30 (-0.9±0.1%; mean±SE) were maintained at week 82 (-1.1±0.1%) with 48% of the patients attaining HbA_{1C} ≤7%. At week 30, patients taking exenatide who lost weight (from baseline -2.1±0.2kg) continued to lose weight at week 82 (-4.4±0.3kg). Post-prandial and fasting plasma glucose levels were also improved. The most common adverse effects were similar to those observed in the AMIGO studies (nausea and hypoglycaemia) and tended to be mild to moderate in severity. Exenatide improved some CV risk factors such as high-density lipoprotein cholestrol (HDL-C),[66] triglycerides and diastolic blood pressure

(DBP), particularly in those patients who had the greatest bodyweight loss. Moreover, significant changes in lipid profiles were also observed in patients treated with exenatide who failed to lose a significant amount of weight.[65] This may be of particular interest given that patients with T2DM have a two- to four-fold increased risk of suffering CV disease.[67] Nevertheless, the impact on reduction of CV events associated with decreased CV risk factors with exenatide treatment remains unknown.[65]

Non-inferiority Studies with Insulin

The efficacy and safety of exenatide compared with insulin glargine and biphasic insulin aspart 30/70 has been examined in three comparative, non-inferiority studies.[68–70] In these studies, exenatide 5µg was administered BID for four weeks prior to administering 10µg for the rest of the study. Insulin glargine treatment was initiated at 10U/day, with subsequent adjustment according to fasting glucose using a pre-established algorithm. Insulin aspart was administered BID with dose modification depending on fasting glycaemia and post-prandial glycaemic levels two hours post-ingestion. In all three studies, exenatide was shown to be as effective as insulin glargine and insulin aspart in lowering mean HbA_{1C} (compared with baseline levels) in all treatment groups, and the percentage of individuals achieving HbA_{1C} was 7%. In contrast, exenatide-treated patients lost between two and three kilograms, whereas insulin-treated subjects gained between 0.35 and 4kg on average. In all studies, exenatide's safety profile was similar to that observed in the AMIGO studies previously described, and the most commonly reported adverse effect was mild or moderate nausea in approximately one-third of the patients.[68–70]

These preliminary data further support a growing interest in the effects of exenatide in the early stages of type 2 diabetes mellitus, with the aim of examining whether or not it protects ß cells and prevents the progression of the disease.

Antiexenatide Antibodies

Patients exposed to recommended doses of exenatide might produce antiexenatide antibodies during the first weeks of treatment. Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop antiexenatide antibodies following treatment with exenatide. In most patients who develop antibodies, antibody titres diminish over time.[37]

The patients who produced antiexenatide antibodies had similar rates and types of adverse events as those who did not. In the AMIGO clinical studies (n=963), 38% of patients showed low titres of antiexenatide antibodies at 30 weeks.[60–62] Within this group, the glycaemic control level (HbA_{1C}) was generally comparable to that observed in those who did not produce antiexenatide antibodies. An additional 6% of patients had higher titres of antibodies at 30 weeks. In about half of these patients (3% of total patients who received exenatide in the controlled clinical studies), no response to exenatide treatment was observed.[60–62] In two non-inferiority clinical studies of exenatide and insulin (n=475), efficacy and adverse events were comparable in patients treated with exenatide regardless of antibody levels.[68,69]

Other Effects of Incretin Mimetics in the Course of Type 2 Diabetes Mellitus

The function of ß cells progressively declines in T2DM, as has been observed in animal models. Muller et al. reported the existence of a deficit in ß- and α-cell secretion in the islets of patients with T2DM.[71] Exenatide has been shown to stimulate ß-cell proliferation and islet neogenesis in stem cells both *in vitro* and *in vivo*.[39] Different *in vitro* studies of exogenous administration of exenatide and GLP-1 provide evidence that exenatide might play an important role in maintaining ß-cell mass and function and stimulating the proliferation and neogenesis of islet cells, as well as inhibiting cell apoptosis.[72] Recent preliminary studies in patients who have undergone pancreatic islet transplants indicated that exenatide enhanced glycaemic response and HbA_{1C} levels.[73–75] These observed effects may be due to the combination of several factors, such as its already known actions of slowed gastric emptying, enhanced glucagon suppression and improved ß-cell function, as seen by the C-peptide levels recorded in these patients. Moreover, exenatide may also contribute to enhancing the first phase of insulin secretion, which is also decreased in this group of patients. Exenatide has been shown to restore the insulin secretion patterns, similar to those observed in subjects with no diabetes, both in the first (0–10 minutes) and second (10–180 minutes) phases of secretion.[76]

On the other hand, glucotoxicity and oxidative stress are two key factors in ß-cell apoptosis in T2DM. Thiorexdoxin-interacting protein (TXNIP) has recently been described as a pro-apoptotic factor in ß cells and a potential mediator of glucotoxicity and oxidative stress.[77] In an *in vitro* study, exenatide demonstrated that it inhibits oxidative stress-induced cell apoptosis and decreases TXNIP expression in pancreatic cells.[77] These preliminary data further support a growing interest in the effects of exenatide in the early stages of T2DM, with the aim of examining whether or not it protects ß cells and prevents the progression of the disease.[78] This new treatment approach based on the glucose-regulating effects of the incretin hormones (mimicking GLP-1 effects or prolonging the length of their action) should be the subject of more extensive clinical evaluation. The introduction of exenatide as the first-in-class drug of incretin mimetics provides physicians with a new and promising treatment option for T2DM. ■

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