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REVIEW ARTICLE

Effects of Exenatide on Diabetes, Obesity, Cardiovascular Risk Factors, and Hepatic Biomarkers in Patients with Type 2 Diabetes

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Abstract

Obesity increases the risk of diabetes up to 90-fold and worsens hyperglycemia, hyperinsulinemia, insulin resistance, dyslipidemia, and nonalcoholic fatty liver disease. For patients with type 2 diabetes, weight loss can trigger improvements in all these conditions and decrease the need for glucose-lowering agents. The incretin mimetic exenatide shares many glucoregulatory properties with native glucagon-like peptide-1, including enhancement of glucose-dependent insulin secretion, glucose-dependent suppression of inappropriately high glucagon secretion, slowing of gastric emptying, and reduction of food intake in patients with type 2 diabetes. Exenatide treatment was associated with progressive weight loss in the majority of patients in clinical trials. In addition, patients with elevated markers of liver injury at baseline showed improvements. Therefore, exenatide represents a unique option for adjunctive therapy for patients with type 2 diabetes not achieving adequate glycemic control on oral antidiabetic agents, especially in patients for whom weight gain would be an additional contraindication.

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Background

Obesity increases the risk of diabetes up to 90-fold.[1–3] Results of the Behavioral Risk Factor Surveillance System indicate that for every 1-kg increase in weight the risk of diabetes is increased by 9%.[4] Therefore, it is not surprising that the prevalence of diabetes in the United States has risen (from 4.9% in 1990 to 7.9% in 2001) in concert with the prevalence of obesity (doubled over the past 30 years).[4,5] Obesity is a risk factor for the development of diabetes and worsens hyperglycemia, hyperinsulinemia, insulin resistance, and dyslipidemia.[2] Obesity is also a risk factor for nonalcoholic fatty liver disease (NAFLD), hypertension, and cardiovascular disease.[5–8]

Traditionally, type 2 diabetes has been treated first with dietary counseling and increased exercise, followed by the stepwise addition of oral antidiabetic agents as glycemic control worsens and finally exogenous

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Abbreviations: (ALT) alanine aminotransferase, (BMI) body mass index, (GLP 1) glucagon-like peptide-1, (HbA1c) glycated hemoglobin, (HDL-C) high-density lipoprotein cholesterol, (LAR) long-acting release, (MET) metformin, (NAFLD) nonalcoholic fatty liver disease, (SFU) sulfonylureas, (TZD) thiazolidinedione

Keywords: exenatide, NAFLD, obesity, type 2 diabetes

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insulin.[9] Unfortunately, these therapies do not prevent the inevitable decline in pancreatic β cell function.[10] Patients commonly experience substantial weight gain as a side effect of many antidiabetic agents.[11] The risk of hypoglycemia also increases with increased therapeutic interventions, e.g., sulfonylureas (SFU) and insulins. For patients with type 2 diabetes, weight loss can improve fasting hyperglycemia, glycated hemoglobin (HbA1c) levels, dyslipidemia, and hypertension and decrease the need for glucose-lowering agents.[2,8] Patients with type 2 diabetes have twice the risk of myocardial infarction and stroke as the general population, and these cardiovascular complications account for up to 80% of the risk of mortality.[8] Weight loss in patients with type 2 diabetes has been associated with a 25% reduction in total mortality and a 28% reduction in cardiovascular disease and diabetes mortality.[12]

Obesity, type 2 diabetes, and NAFLD often coexist. According to the American Gastroenterological Association, the likelihood of NAFLD is directly proportional to body weight, with resolution of fatty liver often occurring in parallel with gradual weight loss.[13] Although NAFLD is generally asymptomatic, elevated concentrations of serum alanine aminotransferase (ALT), a biochemical marker of hepatic injury, are indicative of NAFLD.[13] NAFLD can cause progressive fibrosis, leading to cirrhosis and its complications, including portal hypertension and liver failure.[13] Progressive fatty liver disease is associated with a decreased insulin-mediated suppression of lipolysis. The resulting elevation in serum-free fatty acid concentrations contributes to impaired pancreatic β-cell function and increased cardiovascular morbidity and mortality.[7,13,14] In a study of 2839 patients with type 2 diabetes, 85% had hepatic steatosis and 70% had NAFLD as measured by a liver ultrasound, although the majority had normal concentrations of serum ALT.[15] Forty-four percent had cardiovascular disease, and the NAFLD incidence increased to 75% in patients 60 years of age or older.

Exenatide

The incretin mimetic exenatide is a relatively new option (approved by the Food and Drug Administration in 2005 for the U.S. market) for adjunctive treatment of patients with type 2 diabetes. Exenatide is a synthetic form of exendin 4, a peptide secreted in the saliva of the Gila monster.[16,17] *In vitro*, exendin-4 binds to and activates the known mammalian glucagon-like peptide-1 (GLP-1) receptor and shares many glucoregulatory properties with native GLP-1,[16,18] including enhancement of glucose-dependent insulin secretion, glucose-dependent suppression of inappropriately high glucagon secretion, slowing of gastric emptying, and reduction of food intake.[19–22] Despite their homology and comparable glucoregulatory effects, exendin-4 and GLP-1 are transcribed from separate genes.[23] *In vivo*, exenatide resists proteolysis by the dipetidyl peptidase-4 enzyme, resulting in a half-life of 2.4 hours in the circulation.[24] Exenatide is detectable in the circulation for up to 10 hours after subcutaneous injection.[24] Exenatide restored first- and second-phase insulin secretion in patients with type 2 diabetes[25] and promoted β cell proliferation and islet neogenesis from precursor cells in *in vitro* and in rodent models of diabetes.[26]

In three, 30-week, placebo-controlled trials in patients with type 2 diabetes not achieving glycemic control with metformin (MET) and/or a SFU, treatment with 10 µg exenatide twice daily resulted in mean HbA1c reductions of approximately 1% that were sustained out to 3 years in open-label extensions (**Figure 1**, **Table 1**).[27–32]

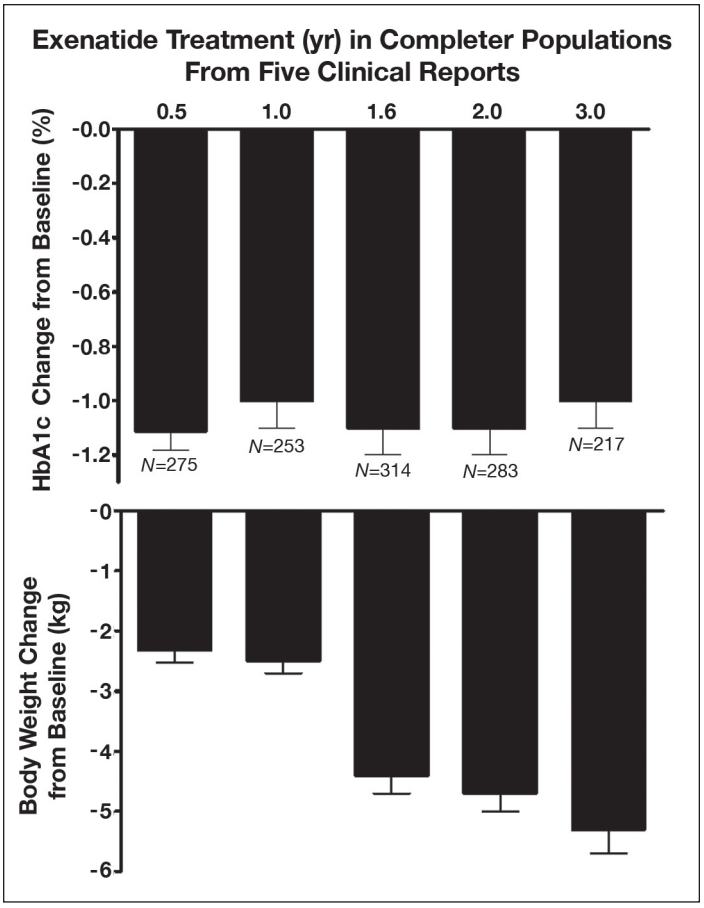

Figure 1. Durable effects of exenatide on patient HbA1c and body weight. Mean ± SEM. Data from Heine 2005[35] (column 1), Nauck 2007[20] (column 2), Blonde 2006[30] (column 3), Buse 2007[31] (column 4), and Klonoff 2008[32] (column 5). Note that the last three references are different time point analyses of the same exenatide open-label extension study.

Table 1.
Exenatide Effects on HbA1c and Body Weight in Clinical Trials

Active treatment	Background treatment	Study duration (weeks)	No. of subjects	Diabetes duration (year) ± SD	Baseline HbA1c (%) ± SD	HbA1c Δ from baseline (%) ± SE	Achieved HbA1c ≤7% (%)	Baseline BMI (kg/m²) ± SD	Baseline weight (kg) ± SD	Weight Δ from baseline (kg) ± SE	Ref
Exenatide[a] vs placebo	Diet/ exercise (DE)	4	99	2.7 ± 2.5	7.7 ± 0.9	-0.4 ± 0.1 vs +0.2 ± 0.1	NA	34 ± 5	96 ± 18	NS	37
Exenatide[b] open label	DE or MET	30	30 (DE) 97 (MET)	2.6 ± 3.8 (DE) 4.3 ± 4.6 (MET)	7.5 ± 0.6 (DE) 7.6 ± 0.7 (MET)	-1.0 ± 0.2 (DE) -0.9 ± 0.1 (MET)	69 (DE) 60 (MET)	35 ± 6 (DE) 35 ± 6 (MET)	100 ± 19 (DE) 99 ± 18 (MET)	-4.3 ± 1.3 (DE) -3.7 ± 0.5 (MET)	37
Exenatide[b] vs placebo	SFU	30	377	7 ± 7 vs 6 ± 5	8.6 ± 1.2 vs 8.7 ± 1.2	-0.9 ± 0.1 vs +0.1 ± 0.1	41 vs 9	33 ± 6 vs 34 ± 5	95 ± 18 vs 99 ± 19	-1.6 ± 0.3 vs -0.6 ± 0.3	27
Exenatide[b] vs placebo	MET	30	336	5 ± 5 vs 7 ± 6	8.2 ± 1.0	-0.8 ± 0.1 vs +0.1 ± 0.1	46 vs 13	34 ± 5	101 ± 20 vs 100 ± 19	-2.8 ± 0.5 vs -0.3 ± 0.3	28
Exenatide[b] vs placebo	MET + SFU	30	733	9 ± 6	8.5 ± 1.1	-0.8 ± 0.1 vs +0.2 ± 0.1	34 vs 9	34 ± 6	98 ± 21 vs 99 ± 19	-1.6 ± 0.2 vs -0.9 ± 0.2	29
Exenatide[b] open label	MET, SFU, MET + SFU	82	314	7 ± 6	8.3 ± 1.0	-1.1 ± 0.1	48	34 ± 6	99 ± 21	-4.4 ± 0.3	30
Exenatide[b] open label	MET, SFU, MET + SFU	104	283	8 ± 6	8.3 ± 1.0	-1.1 ± 0.1	50	34 ± 6	100 ± 19	-4.7 ± 0.3	8
Exenatide[b] open label	MET, SFU, MET + SFU	156/182	217/151	8 ± 6/ 8 ± 6	8.2 ± 1.0/ 8.2 ± 0.9	-1.0 ± 0.1/ -0.8 ± 0.1	46	34 ± 5/ 33 ± 5	99 ± 18/ 100 ± 19	-5.3 ± 0.4/ -5.3 ± 0.5	32
Exenatide[b] vs insulin glargine	MET + SFU	26	551	10 ± 6	8.2 ± 1.0	-1.1 vs -1.1	46 vs 48	31 ± 4	88 ± 17	-2.3 vs +1.8	35
Exenatide[b] vs biphasic insulin aspart	MET + SFU	52	501	10 ± 6	8.6 ± 1.1	-1.0 ± 0.1 vs -0.9 ± 0.1	32 vs 24	31 ± 4 vs 30 ± 2	86 ± 16 vs 83 ± 16	-2.5 ± 0.2 vs +2.9 ± 0.2	20
Exenatide[b] vs placebo	TZD, TZD + MET	16	233	7 ± 5 vs 8 ± 6	7.9 ± 0.9	-0.9 ± 0.1 vs +0.1 ± 0.1	62 vs 16	34 ± 5	97 ± 19	-1.8 ± 0.3 vs -0.4 ± 0.3	21
Exenatide[c] vs placebo	Diet, MET	15	45	5 ± 4	8.5 ± 1.2	-1.7 ± 0.3 vs +0.4 ± 0.3	86 vs 0	36 ± 6	106 ± 20	-3.8 ± 1.4 vs -0.03 ± 0.7	37

[a]Subjects dosed with 10 µg twice daily.
[b]Subjects dosed with 5 µg twice daily for 4 weeks during the initiation phase and then 10 µg twice daily thereafter.
[c]Subjects dosed with 2 mg once per week in an extended release formulation.

After 3 years of exenatide therapy, 46% of patients achieved an HbA1c ≤7% and 30% achieved an HbA1c ≤6.5%.[32] These patients also had progressive body weight reductions averaging –5.3 kg. Eighty-four percent of patients lost weight after 3 years of exenatide, with 50% losing at least 5% of baseline body weight. These reductions are especially notable, as no specific diet or exercise counseling or caloric restriction was required by the study protocol. The majority of exenatide-treated patients (68%) had reduced HbA1c combined with weight reductions. For patients with a baseline body mass index (BMI) <30 kg/m² (n = 71), the weight change from baseline was –3.9 ± 0.7 kg (± SEM). For patients with a baseline BMI ≥30 kg/m² (n = 154), the weight change from baseline was –5.8 ± 0.5 kg.

After 3 years of exenatide therapy the 53% of patients with elevated ALT at baseline had reduced ALT (–10.4 ± 1.5 IU/liter; $p < 0.0001$) and 41% achieved normal ALT.[32] They also tended to lose more weight than patients with

normal ALT at baseline (–6.1 ± 0.6 kg vs –4.4 ± 0.5 kg; $p = 0.03$); however, weight change was minimally correlated with baseline ALT ($r = –0.01$) or ALT change ($r = 0.31$). Homeostasis model assessment of β-cell function, blood pressure, and aspartate aminotransferase also improved. A subset of patients achieved 3.5 years of exenatide therapy and had serum lipids available for analysis ($n = 151$): triglycerides decreased 12% ($p = 0.0003$), total cholesterol decreased 5% ($p = 0.0007$), low-density lipoprotein cholesterol decreased 6% ($p < 0.0001$), and high-density lipoprotein cholesterol (HDL-C) increased 24% ($p < 0.0001$). The greatest improvements in cardiovascular risk factors were observed in patients who had the greatest weight reductions. Patients in weight change quartile 1, who had a mean weight reduction of –12.8 kg, had the largest mean changes in systolic blood pressure (–8.1 mmHg), diastolic blood pressure (–5.6 mmHg), HDL-C (+10.6 mg/dl), and triglycerides (–104.2 mg/dl). These improvements in multiple cardiovascular risk factors could have potential patient benefits beyond providing improved glycemic control.

A recent case report described a 59-year-old male with NAFLD and poorly controlled type 2 diabetes treated with metformin.[33] After 44 weeks of exenatide therapy, the patient experienced a 73% reduction in hepatic fat content from a baseline of 15.8% dropping to 4.3%, as measured by proton magnetic resonance spectroscopy. His HbA1c decreased from 8.7 to 8.4%, his weight decreased from 88.5 kg (BMI 28.7 kg/m^2) to 84.3 kg (–4.7%), and his ALT decreased from 46 to 20 IU/liter.

In *ob*/*ob* obese mice, exenatide treatment reduced body weight gain, serum ALT, hepatic lipid content, and plasma glucose compared with placebo-treated mice, while concomitantly improving insulin sensitivity and histological NAFLD.[34] Exenatide reduced the hepatic mRNA concentrations of several regulators of *de novo* lipogenesis and increased peroxisome proliferator-activated receptor ∝ mRNA, a key component in free fatty acid metabolism.

Exenatide in combination with thiazolidinedione (TZD) with or without MET was studied in a 16-week, placebo-controlled trial in patients with type 2 diabetes not achieving adequate glycemic control with a TZD with or without MET.[21] Exenatide treatment reduced HbA1c (mean –0.98% vs placebo) and was also associated with a reduced body weight (mean –1.5 kg vs placebo).

Two published studies demonstrated the noninferiority of exenatide to insulin. In the first trial, 26 weeks of treatment resulted in similar HbA1c reductions for exenatide (mean –1.11% from baseline 8.2%) and insulin glargine (mean –1.11% from baseline 8.3%).[35] However, the exenatide-treated patients lost –2.3 kg in contrast to a weight gain of 1.8 kg for the insulin-treated patients. In the second study, 52 weeks of exenatide resulted in a mean HbA1c reduction of –1.04% accompanied by a mean weight loss of –2.5 kg.[20] Patients treated with biphasic insulin aspart had a mean HbA1c reduction of –0.89% with a mean weight gain of 2.9 kg.

The potential adverse effects of exenatide therapy have been widely reported.[20,21,27–32,35] The most common adverse event has consistently been mild-to-moderate nausea that decreased over time. In general, the risk of mild-to-moderate hypoglycemia was greater in patients when exenatide was coadministered with a sulfonylurea.[27,29] This risk of hypoglycemia was lowered if the dose of sulfonylurea was reduced to a minimally effective dose upon initiation of exenatide treatment.[29] Importantly, the risk of hypoglycemia was not increased when exenatide was administered with metformin[28] or with TZD with or without metformin.[21]

More recently, Kim and colleagues[36] reported the results of a 15-week, phase 2 clinical trial of exenatide formulated for once-weekly dosing (long-acting release, LAR), in contrast to the usual twice-daily dosing. Forty-five patients with type 2 diabetes controlled suboptimally with metformin and/or diet/exercise were studied. The 15 patients treated with the 2-mg LAR dose had a mean HbA1c reduction of –1.7% compared with a mean HbA1c increase of 0.4% for the placebo group. In addition, 86% of the exenatide-treated patients achieved an HbA1c ≤7% compared to none of the placebo-treated patients. Body weight was unchanged in the placebo group, but was decreased in the exenatide group (mean –3.8 kg). Mild nausea was the most frequent adverse event, although no patients withdrew from the study due to nausea.

Conclusion

Exenatide therapy for up to 3.5 years demonstrated sustained and clinically-relevant improvements in glycemic control, cardiovascular risk factors, and hepatic injury biomarkers, coupled with weight reduction. Therefore, exenatide represents a unique option for adjunctive therapy for patients with type 2 diabetes not achieving adequate glycemic control on oral antidiabetic agents, especially in patients for whom weight gain would be an additional contraindication.

Disclosure:

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