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Article

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Efficacy and Safety of Exenatide versus Insulin in Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis

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Exenatide is one of a new class of medications (incretin mimetics) for the treatment of type 2 diabetes mellitus and was approved in April 2005 by the U.S. Food and Drug Administration. We undertook a systematic review and meta-analysis of exenatide therapy compared to both placebo and insulin therapy in terms of main efficacy parameters and safety. We searched PubMed for randomized controlled clinical studies of type 2 diabetes mellitus of at least 12 weeks' duration published from June 2003 to July 2010. Exenatide reduced the mean differences of HbA1c comparing with both placebo (-0.88% [95% CI -0.98 to -0.79]) and insulin (0.05% [95% CI -0.11 to 0.21]). And, mean differences of body weight were reduced for exenatide comparing with both placebo (-1.18 kg [95% CI -1.44 to -0.93]) and insulin (-5.42 kg [95% CI -5.89 to -4.95]). Exenatide has beneficial effects on glycemic control and is relatively safe in terms of the adverse events studied. The glycemic control effects of exenatide and insulin are similar, but the body weight reduction effects of exenatide are greater. This indicates that exenatide provides another choice for type 2 DM patients who have weight control problems.

Keywords: Exenatide, diabetes mellitus, meta-analysis, evidence based medicine

JEL: I10

Diabetes mellitus (DM) is one of the most common chronic diseases and has an increasing incidence worldwide. Recent estimates suggest that there were 171 million people throughout the world living with diabetes in the year 2000, and this number is projected to increase to 366 million by 2030 (Wild *et al.*, 2004). Moreover, most of these people were or will be diagnosed with type 2 DM. This chronic and progressive disease has no established cure, but there are well-established treatments for it which can delay or prevent entirely the formerly inevitable consequences of the condition. Successful management of type 2 DM requires strict control of glycemia as well as other risk factors to prevent disease complications (UK Prospective Diabetes Study Group, 1998).

Body weight management is one of the major issues of type 2 DM patients. Successful weight management not only affects glycemic control, but also improves overall health (Seagle *et al.*, 2009). All the oral anti-diabetic medications (sulfonylurea (SU), α – glucosidase inhibitor, thiazolidinediones,

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etc) may cause weight gain, except for metformin (Bjorkhem-Bergman, Asplund and Lindh, 2010; Nathan *et al.*, 2009a). Insulin therapy is commonly used to help type 2 DM patients achieve adequate glycemic control, especially for cases in which the control provided by an oral medication is insufficient (Nathan *et al.*, 2009b). Nevertheless, insulin therapy results in weight gain (Swinnen *et al.*, 2010). This makes body weight management difficult for type 2 DM patients.

Exenatide (Byetta®, Amylin Pharmaceuticals) is one of a new class of anti-diabetic medications called incretin mimetics. This injectable prescription medicine is currently available as an adjunctive therapy in many countries, including the United States and the member states of the European Union, for type 2 DM patients who are taking MET, SU, or a combination of MET and SU, but have not achieved adequate glycemic control. Exenatide imitates the actions of naturally occurring GLP-1 (glucagon-like peptide 1), which binds to the pancreatic GLP-1 receptor and improves glucose homeostasis. It stimulates insulin release in a glucose-dependent manner, improves first-phase insulin release, induces a delay of gastric emptying, decreases food intake, and ultimately results in body weight reduction (Verspohl, 2009).

Both exenatide and insulin are injectable and can be prescribed for patients with inadequate glycemic control on oral medications (Nathan *et al.*, 2009b). Some reviews have examined the efficacy of exenatide but only in comparison to placebo (Amori, Lau and Pittas, 2007; Norris *et al.*, 2009). In the present study, we provide an update on those reviews by including the relevant randomized controlled trials published up through 2010 in our meta-analysis. In addition, the aim was to compare exenatide not only to placebo but also to insulin therapy in terms of efficacy and safety in type 2 diabetes, especially with regard to body weight changes.

METHODOLOGY

-Data Sources and Search

We conducted a search of PubMed for clinical trials of exenatide for type 2 diabetes published from June 2003 to July 2010 using the following search terms: "exenatide" [Substance Name] and "Diabetes Mellitus, Type 2" [MeSH] and "humans" [MeSH Terms] and "Clinical Trial" [ptyp].

-Study Selection

Publications were included in the meta-analysis if they (1) were prospective, randomized, and controlled with placebo or insulin therapy, (2) were at least 12 weeks in duration, (3) included non-pregnant adults with type 2 diabetes mellitus, (4) examined the efficacy of exenatide alone or in combination with other oral agents, and (5) had reported hemoglobin A1c (HbA1C) outcomes in a manner that allowed data analysis.

We excluded studies of less than 12 weeks' duration because such studies would not give an adequate assessment of the change in glycemic efficacy, as HbA1c concentrations reflect glycemic control during the previous 3 months. We also excluded publications that assessed exenatide in terms of pharmacokinetics or economics.

–Data Extraction and Quality Assessment

For the included studies, we extracted information about the following variables: sample size, study duration, participants' baseline characteristics, drug interventions, study design, and dropout rate (see Table 1–Appendix–I). For glycemic efficacy, we extracted the mean change in the HbA1C and fasting plasma glucose (FPG) levels from baseline to study endpoint, as well as the percentage of participants achieving HbA1C concentrations of less than 7 percent. Other variables extracted were the mean change in body weight and the occurrence of reported adverse effects.

–Data Synthesis and Analysis

The primary outcome was the mean change in HbA1C concentrations from baseline to study endpoint. The secondary outcomes were the mean change from baseline to study endpoint in FPG levels, the proportion of participants reaching HbA1C concentrations of less than 7 percent, body weight, and the occurrence of all reported adverse events. For continuous variables (HbA1c concentration, FPG level, and body weight), mean differences and 95 percent confidence intervals (CIs) were obtained using the fixed effect inverse variance (IV) method. For dichotomous variables (percentages achieving HbA1c concentrations of less than 7 percent and percentages with adverse events), the odds ratios (OR) and 95% CIs were calculated by the fixed effect Mantel–Haenszelor (M–H) method. The I2 statistic was used to evaluate statistical heterogeneity in each meta–analysis. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. An I2 value greater than 50% was considered indicative of at least moderate heterogeneity (Higgins *et al.*, 2003). Statistical analyses were performed using Review Manager (RevMan) version 5.0.22 for Windows (The Nordic Cochrane Centre, Copenhagen).

RESULTS

Search Results and Study Characteristics

The search results are summarized in Figure 1. A total of 57 publications were identified in our PubMed search. After critical evaluation, it was found that 11 publications met all the inclusion criteria for the meta–analysis. The characteristics of the 11 included trials are summarized in Table 1. Six publications evaluated exenatide with a dosage of 10 μg BID in combination with metformin, sulfonyl–

urea, combined metformin/sulfonylurea, or combined thiazolidinedione/metformin therapy in randomized placebo-controlled trials (Buse *et al.*, 2004; DeFronzo *et al.*, 2005; Gao *et al.*, 2009; Kendall *et al.*, 2005; Moretto *et al.*, 2008; Zinman *et al.*, 2007). Four of them also had a parallel group of exenatide with a dosage of 5 μg BID. There was only one trial for LAR (long-acting release) exenatide (Kim *et al.*, 2007). Four publications compared the efficacy of exenatide with open-label subcutaneous insulin (glargine and biphasic aspart) (Bergenstal *et al.*, 2009; Davis *et al.*, 2007; Heine *et al.*, 2005; Nauck *et al.*, 2007).

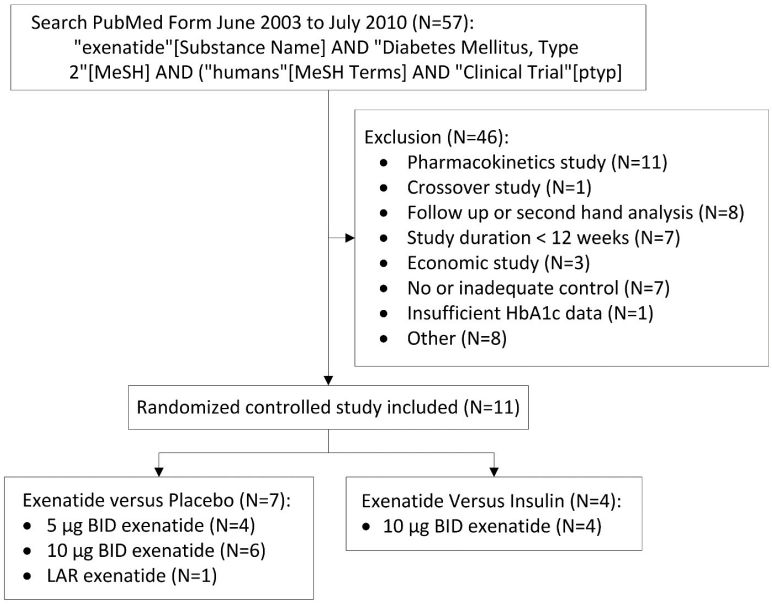

Figure 1. Study Design

Methodological Quality

Six of the 11 publications (55%) were triple-blind or double-blind placebo-controlled trials, and the other 5 publications (45%) were open-label. The range of dropout rates from intervention prior to the conclusion of the study was 0-31 percent, and only 3 (27%) studies had dropout rates over 20 percent (Table 1).

Glycemic Outcomes: Hemoglobin A1c (HbA1c)

Combining data from the studies comparing exenatide with placebo showed statistically significant differences in HbA1c concentration declines from baseline favoring exenatide therapy in doses of both 5 μg BID (mean difference −0.63% [95% CI −0.76 to −0.50]; see Figure 2a-Appendix-II) and 10 μg

BID (mean difference −0.88% [95% CI −0.98 to −0.79]). There was no statistically significant difference in HbA1c concentration declines between exenatide and insulin (mean difference 0.05 percent [95% CI −0.11 to 0.21]). There was only one trial for LAR exenatide, but the two dosages of LAR exenatide both reduced HbA1c concentrations compared with the same dosages of placebo (mean difference −1.8% [95% CI −2.63 to −0.97] (0.8 mg) and −2.10% [95% CI −2.93% to 1.27%] (2.0 mg); data not shown) (Kim *et al.*, 2007).

Patients receiving exenatide were more likely to reach the goal of an HbA1c concentration of less than 7% than those receiving placebo (odds ratio 3.54 [95% CI 2.49 to 5.05] (5 μg BID) and 5.15, [95% CI, 4.03 to 6.59] (10 μg BID); see Figure 2b-Appendix-II). However, when exenatide was compared with insulin, the odds ratio of achieving that HbA1c concentration goal favored insulin (0.99 [95% CI 0.79 to 1.25]).

Glycemic Outcomes: Fasting Plasma Glucose (FPG)

The reductions in fasting plasma glucose levels favored exenatide over placebo (weighted mean difference −0.99 mmol/L [95% CI −1.31 to −0.68] (5 μg BID); −1.25 mmole/L [95% CI −1.49 to −1.01] (10 μg BID); see Figure 3-Appendix-III). Comparing exenatide with insulin, the declines in fasting plasma glucose levels favored insulin (weighted mean difference 2.24 mmole/L [95% CI 2.16 to 2.32]).

Nonglycemic Outcomes: Weight

The body weight reductions from baseline were significantly in favor of exenatide over placebo (weighted mean difference −0.85 kg [95% CI −1.22 to −0.47] (5 μg BID); −1.18 kg [95% CI −1.44 to −0.93] (10 μg BID); see Figure 4-Appendix-IV). Compared with insulin, the declines in body weight were significantly greater for exenatide (weighted mean difference −5.42 kg [95% CI −5.89 to −4.95]).

Nonglycemic Outcomes: Adverse Events

Hypoglycemia was commonly reported in the analyzed exenatide trials. Compared with placebo, the odds ratios for hypoglycemia with exenatide treatment were greater than 1 (1.92 [95% CI 1.28 to 2.88] (5 μg BID); 3.17 [95% CI 2.24 to 4.48] (10 μg BID); see Table 2-Appendix-V). There was only one trial that compared exenatide with insulin in this regard, and it showed that, in comparison, the odds ratio for hypoglycemia with exenatide was smaller than 1 (0.63 [95% CI 0.41 to 0.97]). Gastrointestinal-related adverse events like nausea, vomiting, and diarrhea all had odds ratios greater than 1 for 10 μg BID exenatide compared with both placebo (5.25 [95% CI 4.07 to 6.77], 6.71 [95% CI 4.13 to 10.89], 5.36 [95% CI 3.18 to 9.04], respectively) and insulin (20.89 [95% CI 13.04 to

33.49], 5.36 [95% CI 3.18 to 9.04], 3.80 [95% CI 2.03 to 7.10], respectively).

DISCUSSION

Compared to placebo, both dosages of exenatide (5 μg BID and 10 μg BID) had beneficial effects on glycemic control, including in terms of HbA1c concentration reductions, the number of patients achieving the goal of an HbA1c concentration of less than 7 percent, and fasting plasma glucose levels. Moreover, exenatide was shown to be relatively safe in regard to adverse events and the ability to reduce body weight. When compared to insulin, exenatide had a similar effect on glycemic control, but exenatide was associated with significantly greater reductions in body weight.

In addition to glycemic control, body weight reduction is the most obvious effect of exenatide. Insulin therapy regulates the absorption of glucose by diabetes patients, but it also has the commonly occurring side effect of weight gain. Insulin injections directly control blood sugar levels by inducing glucose to be stored in cells and reducing glucose levels in urine. The glucose taken in by cells will be used as an energy source or stored as fat; therefore, the overall utilization of fat will be decreased. As such, by continuing to eat as before, patients will likely gain weight after they start taking insulin. Relatedly, this study found that the most significant advantage of exenatide in comparison to insulin is the reduction in body weight. Furthermore, body weight reduction also helps to lower blood glucose, blood pressure, and cholesterol levels (Feldstein *et al.*, 2008). Finally, it can improve the overall health of patients with diabetes.

Hypoglycemia is one of the common adverse effects of exenatide treatment in comparison to placebo therapy. However, we found that hypoglycemia was less commonly induced by exenatide than by insulin injection. Exenatide stimulates insulin secretion in response to food intake, and the result is the release of higher, more moderate amounts of insulin that help reduce the increase of blood sugar caused by eating meals. Once blood sugar levels fall nearer to normal values, the pancreatic response to produce insulin is decreased. Meanwhile, although injectable insulin is effective in lowering blood sugar, it can also cause blood sugar to drop too low, resulting in the dangerous situation of hypoglycemia (Heine *et al.*, 2005). The use of exenatide can thus reduce the risk of hypoglycemia from insulin therapy for type 2 diabetes patients.

CONCLUSION

In this meta-analysis, gastrointestinal tract symptoms, including nausea, vomiting, and diarrhea, were the other common adverse effects. There were two warnings from the U.S. Food and Drug Administration (FDA) in post-marketing reports for exenatide, and those warnings were in regard to

acute pancreatitis and renal failure (U.S. Food and Drug Administration, 2007, 2009). Relatedly, the serious effects of renal failure may be associated with the aforementioned common adverse effects, such as vomiting and nausea (Weise *et al.*, 2009). This indicates that a patient who has kidney dysfunction or a history of pancreatic disease, as well as serious adverse effects of vomiting and nausea, should be more careful when using exenatide.

The effects of exenatide on blood glucose control and body weight lowering were obvious. Since exenatide has a glycemic control effect similar to that of insulin and also has the ability to lower body weight, for type 2 DM patients who cannot achieve adequate glycemic control from oral anti-diabetic medications, especially those who have body weight problems, exenatide offers another choice of

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Appendix–I

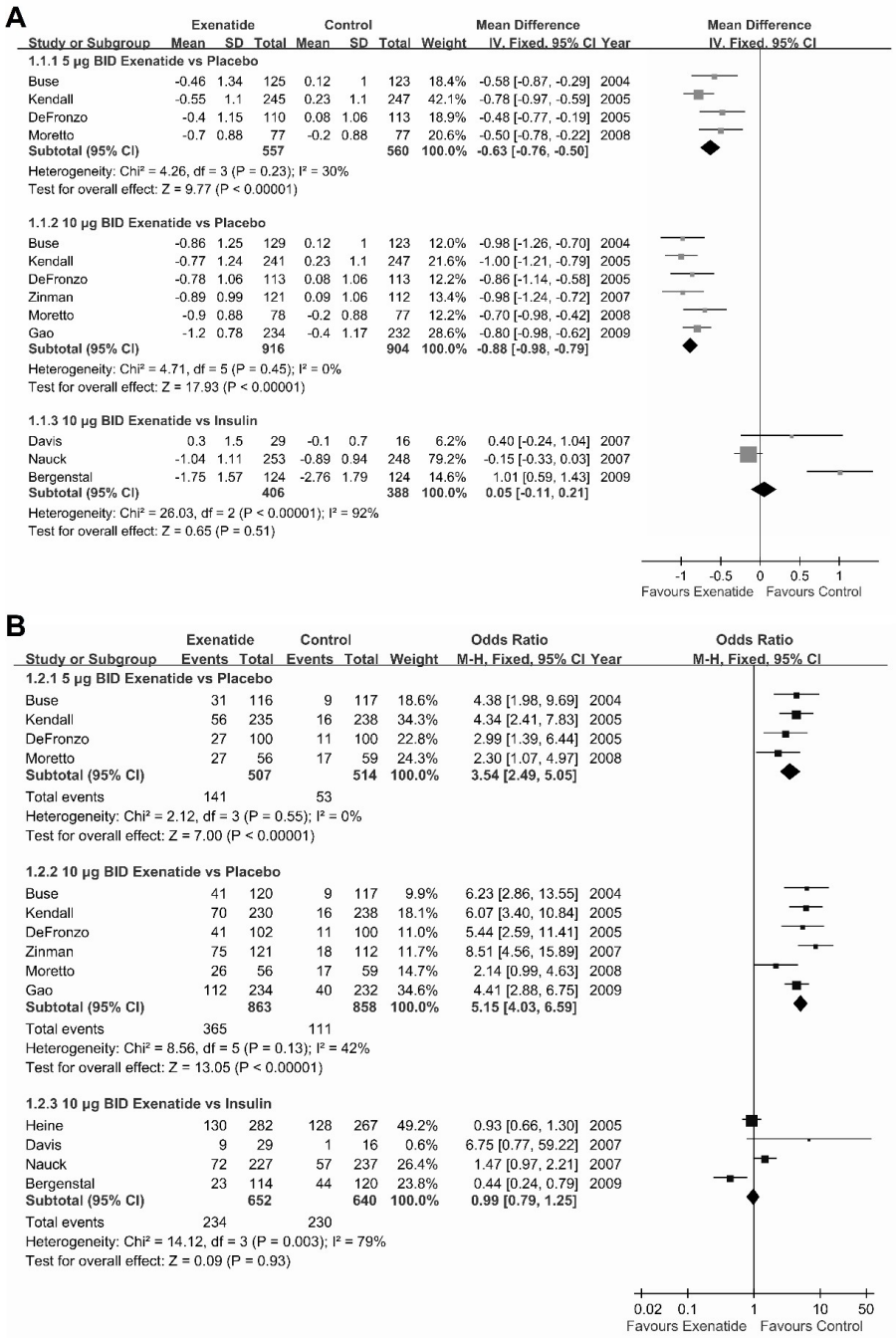
Study	Patients, n/ Duration, wk	Mean age, y/ Women, %/ White, %	BMI, kg/cm^2/ Diabetes Duration, y/ HbA1c, %	Exenatide therapy groups	Control groups	Study design	Drop out rate, %
Buse 2004	377/30	55/40/63	33/6.6/8.6	SU + 5 µg BID exenatide SU + 10 µg BID exenatide	SU + placebo	R, MC, ITT, TB, PC	31
DeFronzo 2005	336/30	53/43/76	34/5.9/8.2	MET + 5 µg BID exenatide MET + 10 µg BID exenatide	MET + placebo	R, MC, ITT, TB, PC	19
Kendall 2005	733/30	55/42/68	34/8.9/8.5	MET and/or SU + 5 µg BID exenatide MET and/or SU + 10 µg BID exenatide	MET and/or SU + placebo	R, MC, ITT,DB, PC	19
Moretto 2008	232/24	54/45/68	31/2/7.8	5 µg BID exenatide 10 µg BID exenatide	placebo	R, MC, ITT, OL, PC	13
Zinman 2007	233/16	56/45/82	34/8.2/7.9	TZD and/or MET + 10 µg BID exenatide	TZD and/or MET + placebo	R, MC, DB, PC	22
Gao 2009	466/16	54/56/Asian	26/8/8.3	MET and/or SU + 10 µg BID exenatide	MET and/or SU + placebo	R, MC, DB, PC	14
Kim 2007	45/15	54/40/60	36/5/8.5	MET + 0.8 mg LAR exenatide MET + 2.0 mg LARexenatide	MET + placebo	R, MC, ITT, DB, PC	4
Heine 2005	551/26	58/44/80	31/9.6/8.2	MET and SU + 10 µg BID exenatide	MET and SU + insulin glargine	R, MC, ITT, OL	15
Bergenstal 2009	372/24	53/52/64	34/9/10.2	MET and SU + 10 µg BID exenatide	MET and SU + BIAsp 30 BID MET + BIAsp 30 QD	R, MC, OL	22
Nauck 2007	501/52	59/49/NA	30/10/8.6	MET and SU + 10 µg BID exenatide	MET and SU + BIAsp 30 BID	R, MC, ITT, OL	11
Davis 2007	49/16	53/53/NA	34/11/8.1	MET and SU + 10 µg BID exenatide	MET and SU + insulin	R, MC, OL	0

Source: Developed for this study

SU, sulfonylurea; MET, metformin; TZD, thiazolidinedione; BIAsp, biphasic insulin aspart 30/70; BID, twice daily; QD, once daily; LAR, long-acting release; R, randomized; MC, multicenter; ITT, intent-to-treat; TB, triple-blind; DB, double-blind; OL, open-label; PC, placebo-controlled; NA, not available.

Table 1. Characteristic of Randomized Controlled Trials of Exenatide included in the Systematic Review

Appendix–II

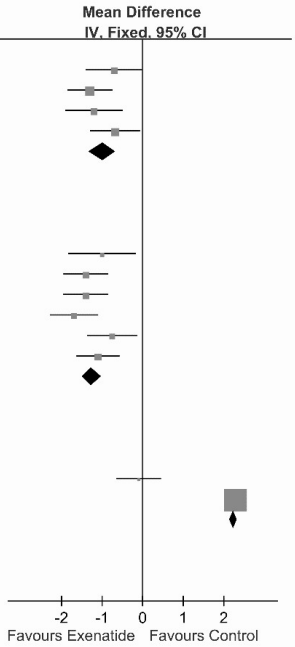


Source: Developed for this study

Figure 2. HbA1c Changes for Exenatide vs. Control in Patients with Type 2 Diabetes. (A) Mean difference in HbA1c (%) (B) Odds ratio for reaching target HbA1c concentration of less than 7%. The forest plot presents the meta-analysis data pooled by the fixed effect Mantel-Haenszel (M-H) method. The I2 value describes the percentage of total variation across the studies due to heterogeneity

Appendix–III

Study or Subgroup	Exenatide Mean	Exenatide SD	Exenatide Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
1.3.1 5 µg BID Exenatide vs Placebo									
Buse	-0.3	2.24	125	0.4	3.33	123	20.2%	-0.70 [-1.41, 0.01]	2004
Kendall	-0.5	3.13	245	0.8	3.14	247	32.9%	-1.30 [-1.85, -0.75]	2005
DeFronzo	-0.4	3.15	110	0.8	2.13	113	20.2%	-1.20 [-1.91, -0.49]	2005
Moretto	-0.97	1.95	77	-0.29	1.95	77	26.7%	-0.68 [-1.30, -0.06]	2008
Subtotal (95% CI)			**557**			**560**	**100.0%**	**-0.99 [-1.31, -0.68]**	
Heterogeneity: Chi² = 3.16, df = 3 (P = 0.37); I² = 5%									
Test for overall effect: Z = 6.12 (P < 0.00001)									
1.3.2 10 µg BID Exenatide vs Placebo									
Buse	-0.6	3.41	129	0.4	3.33	123	8.5%	-1.00 [-1.83, -0.17]	2004
Kendall	-0.6	3.1	241	0.8	3.14	247	19.3%	-1.40 [-1.95, -0.85]	2005
DeFronzo	-0.6	2.13	113	0.8	2.13	113	19.1%	-1.40 [-1.96, -0.84]	2005
Zinman	-1.59	2.42	121	0.1	2.22	112	16.6%	-1.69 [-2.29, -1.09]	2007
Moretto	-1.04	1.96	78	-0.29	1.95	77	15.6%	-0.75 [-1.37, -0.13]	2008
Gao	-1.3	2.73	234	-0.2	3.11	232	20.9%	-1.10 [-1.63, -0.57]	2009
Subtotal (95% CI)			**916**			**904**	**100.0%**	**-1.25 [-1.49, -1.01]**	
Heterogeneity: Chi² = 5.84, df = 5 (P = 0.32); I² = 14%									
Test for overall effect: Z = 10.09 (P < 0.00001)									
1.3.3 10 µg BID Exenatide vs Insulin									
Nauck	-1.8	3.18	253	-1.7	3.15	248	2.1%	-0.10 [-0.65, 0.45]	2007
Bergenstal	-1.19	0.33	124	-3.48	0.32	124	97.9%	2.29 [2.21, 2.37]	2009
Subtotal (95% CI)			**377**			**372**	**100.0%**	**2.24 [2.16, 2.32]**	
Heterogeneity: Chi² = 69.93, df = 1 (P < 0.00001); I² = 99%									
Test for overall effect: Z = 54.84 (P < 0.00001)									

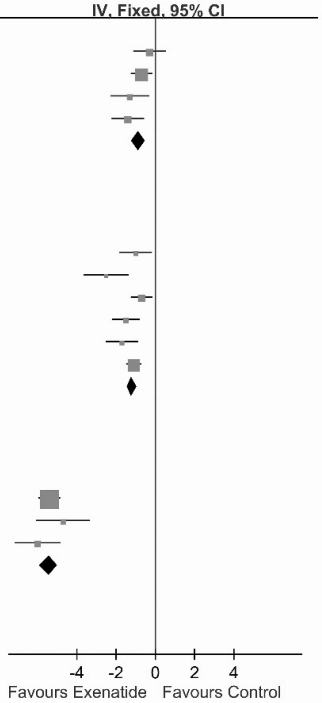


Source: Developed for this study

Figure 3. Mean Differences in Body Weight (kg) Changes for Exenatide vs. Control in Patients with Type 2 Diabetes. The forest plot presents the meta-analysis data pooled by the fixed effect Mantel-Haenszel (M-H) method. The I2 value describes the percentage of total variation across the studies due to heterogeneity.

Appendix–IV

Study or Subgroup	Exenatide Mean	Exenatide SD	Exenatide Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
1.4.1 5 µg BID Exenatide vs Placebo									
Buse	-0.9	3.35	125	-0.6	3.33	123	20.1%	-0.30 [-1.13, 0.53]	2004
Kendall	-1.6	3.13	245	-0.9	3.14	247	45.3%	-0.70 [-1.25, -0.15]	2005
DeFronzo	-1.6	4.2	110	-0.3	3.19	113	14.5%	-1.30 [-2.28, -0.32]	2005
Moretto	-2.8	2.63	77	-1.4	2.63	77	20.1%	-1.40 [-2.23, -0.57]	2008
Subtotal (95% CI)			**557**			**560**	**100.0%**	**-0.85 [-1.22, -0.47]**	
Heterogeneity: Chi² = 4.45, df = 3 (P = 0.22); I² = 33%									
Test for overall effect: Z = 4.45 (P < 0.00001)									
1.4.2 10 µg BID Exenatide vs Placebo									
Buse	-1.6	3.41	129	-0.6	3.33	123	9.3%	-1.00 [-1.83, -0.17]	2004
DeFronzo	-2.8	5.32	113	-0.3	3.19	113	4.9%	-2.50 [-3.64, -1.36]	2005
Kendall	-1.6	3.1	241	-0.9	3.14	247	21.1%	-0.70 [-1.25, -0.15]	2005
Zinman	-1.75	2.75	121	-0.24	2.75	112	12.9%	-1.51 [-2.22, -0.80]	2007
Moretto	-3.1	2.65	78	-1.4	2.63	77	9.3%	-1.70 [-2.53, -0.87]	2008
Gao	-1.2	2.33	234	-0.1	1.95	232	42.4%	-1.10 [-1.49, -0.71]	2009
Subtotal (95% CI)			**916**			**904**	**100.0%**	**-1.18 [-1.44, -0.93]**	
Heterogeneity: Chi² = 10.69, df = 5 (P = 0.06); I² = 53%									
Test for overall effect: Z = 9.14 (P < 0.00001)									
1.4.3 10 µg BID Exenatide vs Insulin									
Nauck	-2.5	3.18	253	2.9	3.15	248	71.9%	-5.40 [-5.95, -4.85]	2007
Davis	-4.2	3	29	0.5	1.7	16	11.7%	-4.70 [-6.07, -3.33]	2007
Bergenstal	-1.9	3.8	124	4.1	5.4	124	16.4%	-6.00 [-7.16, -4.84]	2009
Subtotal (95% CI)			**406**			**388**	**100.0%**	**-5.42 [-5.89, -4.95]**	
Heterogeneity: Chi² = 2.02, df = 2 (P = 0.36); I² = 1%									
Test for overall effect: Z = 22.58 (P < 0.00001)									



Source: Developed for this study

Figure 4. Mean Differences in FPG (mmole/L) Changes for Exenatide vs. Control in Patients with Type 2 Diabetes. The forest plot presents the meta-analysis data pooled by the fixed effect Mantel-Haenszel (M-H) method. The I2 value describes the percentage of total variation across the studies due to heterogeneity

Appendix-V

Adverse Events	Studies (n)	Odds ratio (M-H, Fixed, 95% CI)	Exenatide	Control	I^2 (%)*
			Participants (n)		
Hypoglycemia					
5 μg BID exenatide vs placebo	4	1.92 [1.28, 2.88]	557	560	44
10 μg BID exenatide vs placebo	5	3.17 [2.24, 4.48]	682	672	75
10 μg BID exenatide vs insulin	1	0.63 [0.41, 0.97]	253	248	NA
Nausea					
5 μg BID exenatide vs placebo	4	2.92 [2.17, 3.92]	557	560	69
10 μg BID Exenatide vs placebo	6	5.25 [4.07, 6.77]	916	904	79
10 μg BID Exenatide vs insulin	2	20.89 [13.04, 33.49]	535	515	86
Vomiting					
5 μg BID exenatide vs placebo	4	3.82 [2.24, 6.51]	557	560	0
10 μg BID Exenatide vs placebo	6	6.71 [4.13, 10.89]	916	904	43
10 μg BID Exenatide vs insulin	2	5.36 [3.18, 9.04]	535	515	0
Diarrhea					
5 μg BID exenatide vs placebo	3	1.84 [1.15, 2.94]	557	560	0
10 μg BID exenatide vs placebo	6	2.91 [1.93, 4.40]	916	904	0
10 μg BID exenatide vs insulin	2	3.80 [2.03, 7.10]	535	515	0
Headache					
5 μg BID exenatide vs placebo	3	1.91 [1.13, 3.24]	447	447	0
10 μg BID exenatide vs placebo	5	1.24 [0.77, 1.98]	803	791	0
10 μg BID exenatide vs insulin	2	0.98 [0.61, 1.58]	535	515	0
Dizziness					
5 μg BID exenatide vs placebo	2	2.07 [1.08, 3.97]	312	313	0
10 μg BID exenatide vs placebo	4	2.13 [1.22, 3.72]	554	545	36
10 μg BID exenatide vs insulin	1	2.44 [0.93, 6.40]	282	267	NA
Feeling Jittery					
5 μg BID exenatide vs placebo	2	1.99 [1.12, 3.53]	370	370	81
10 μg BID exenatide vs placebo	2	2.69 [1.55, 4.69]	370	370	80

Source: Developed for this study

* The I^2 statistic describes the percentage of total variation across studies and is due to heterogeneity rather than chance; M-H, Mantel-Haenszel; Fixed, fixed effect; IV, inverse variance; NA, not available.

Table 2. Summary of Adverse Events in Patients with Type 2 Diabetes Treated with Exenatide vs. Control