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## No Superiority of Exenatide over Insulin in Diabetic Patients in Terms of Weight Reduction or Incidence of Adverse Effects: A Meta-analysis

<sup>1</sup>Pooneh Salari, <sup>2,3</sup>Shekoufeh Nikfar and <sup>4</sup>Mohammad Abdollahi

<sup>1</sup>Medical Ethics and History of Medicine Research Center,  
Tehran University of Medical Sciences, Tehran, Iran

<sup>2</sup>Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy,  
Tehran University of Medical Sciences, Tehran, Iran

<sup>3</sup>Food and Drug Laboratory Research Center, Deputy for Food and Drug Affairs,  
Ministry of Health and Medical Education, Tehran 1314715311, Iran

<sup>4</sup>Faculty of Pharmacy and Pharmaceutical Sciences Research Center,  
Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences,  
Tehran 1417614411, Iran

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**Abstract:** Recently, exenatide as an incretin mimetic was approved by FDA as an adjunct to diet and exercise in treating type 2 diabetes. Therefore comparing every new medication with insulin can provide more clues about the real benefit of paying extra budget for new drugs. In this meta-analysis we compared the efficacy and tolerability of exenatide to insulin. The literature search provided 1016 articles while only 5 articles were eligible to be included in the meta-analysis with a total of 1404 patients enrolled in the study. The results show that there is no superiority for exenatide over insulin even in its weight reduction advantage. However, the high risk of gastrointestinal side effects including nausea and vomiting is of major concern. Current evidence does not support the advantage of exenatide over insulin but more clinical trials are needed to reach a convincing conclusion.

**Key words:** Incretin, obesity, insulin, meta-analysis, systematic review, exenatide

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### INTRODUCTION

Type 2 diabetes mellitus is considered as a chronic disease in the middle-aged and elderly nevertheless its incidence is increasing in adolescents (Pinhas-Haniel and Zeitler, 2005; American Diabetes Association, 2000; Alberti *et al.*, 2004; Esteghamati *et al.*, 2008). Therefore, the younger patients with diabetes are likely to experience more complications that are mostly originated by uncontrolled diabetes (Hillier and Pedula, 2003).

Obesity is known to increase the risk of diabetes up to 90-fold (Anderson *et al.*, 2003; Maggio and Pi-Sunyer, 2003; Stein and Colditz, 2004) and complications like insulin resistance, dyslipidemia (Maggio and Pi-Sunyer, 2003) and cardiovascular diseases (Bray, 2004). In the recent years, several classes of drugs have been tried as hypoglycemic agents and anti-obesity medications; however there is no fully efficient tolerable drug without side effects (Larijani *et al.*, 2006; Vosough-Ghanbari *et al.*, 2010; Hasani-Ranjbar *et al.*, 2008, 2009; Malihi *et al.*, 2009; Radfar *et al.*, 2005).

In the recent years, incretin pathway has been considered as one of the interactive lines of investigation into glucose control in diabetes because of its mechanism of action including induction of glucose-dependent insulin secretion, diminishing postprandial glucose secretion, decreasing gastric emptying and decreasing food intake (Buse *et al.*, 2004; DeFronzo *et al.*, 2005; Kendall *et al.*, 2005; Klonoff *et al.*, 2008). In addition, exenatide enhances  $\beta$ -cell proliferation and islet neogenesis *in vitro* and *in vivo* (Fehse *et al.*, 2005; Nielsen *et al.*, 2004; Gedulin *et al.*, 2005). A recent study indicated benefit of exenatide through reduction of oxidative stress and inflammatory markers in patients of type 2 diabetes having inadequate glucose control (Wu *et al.*, 2011) that adds new hopes for its efficacy in reduction of diabetic complications that occur through oxidative stress (Rahimi *et al.*, 2005; Momtaz and Abdollahi, 2010; Hasani-Ranjbar *et al.*, 2010).

Exenatide has been approved by USA Food and Drug Administration (FDA) as an adjunct to diet and exercise but in the recent years there are post-marketing

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**Corresponding Author:** Mohammad Abdollahi, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran 1417614411, Iran

reports of altered kidney function including acute renal failure and insufficiency. The most common side effects of exenatide are nausea, vomiting and diarrhea which may contribute to the development of altered kidney function. In addition there is uncertainty about its effect on hemoglobin A1C (HbA1C) as well as safety profile (Buse *et al.*, 2007). Bearing this in mind we aimed at analyzing all data derived from clinical trials conducted on exenatide. We divided the obtained data into two parts. The first part of analysis devoted to the data derived from placebo-controlled trials and the second part which is discussing in this study is related to the clinical trials comparing exenatide with insulin.

### MATERIALS AND METHODS

PubMed, Web of Sciences (ISI), Scopus, Cochrane and DARE were searched by keywords such as diabetes, exenatide and incretin. We limited our search to the randomized clinical trials written in English. The studies were counted in the meta-analysis if they met the inclusion criteria including trials conducting on patients with type 2 diabetes and trials comparing exenatide with other hypoglycemic agents. Two reviewers evaluated each article independently to lessen the probability of duplication, analyzing reviews, case studies and uncontrolled trials. Studies were precluded if they were uncontrolled or their results did not consider our goals.

**Assessment of trials quality:** Jadad score, which indicates the potentiality of the studies based on their description of randomization, blinding and dropouts (withdrawals), was used to assess the methodological quality of trials (Jadad *et al.*, 1996). The quality scale

ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3. Four trials received Jadad score of 3 and more (Diamant *et al.*, 2010; Bunck *et al.*, 2009; Nauck *et al.*, 2007; Heine *et al.*, 2005) and only one trial obtained Jadad score of 2 (Davis *et al.*, 2007).

**Statistical analysis:** Data from selected studies were extracted in the form of 2×2 Tables. Included studies were weighted and pooled. The data were analyzed using Statsdirect software version 2.7.8. Effect size for weighted mean difference and 95% confidence intervals (95% CI) were calculated using the Der Simonian-Laird method. Relative Risk (RR) and 95% Confidence Intervals (CI) were calculated using the Mantel-Haenszel and Der Simonian-Laird methods. The Cochran Q test was used to test heterogeneity. In case of heterogeneity or probability of few included studies in meta-analysis, the random effects for individual and summary of effect size for weighted mean difference was applied. The event rate in the experimental (intervention) group against the event rate in the control group was calculated using L'Abbe plot as an aid to explore the heterogeneity of effect estimates. Funnel plot analysis was used as publication bias indicator.

### RESULTS

The electronic search provided 1016 articles; 80 from PubMed, 323 from Web of Science, 544 from Scopus and 69 from Cochrane library. Of those, 11 studies were scrutinized in full text, of which, 6 trials were considered unsuitable while 5 trials were analyzed (Fig. 1). Totally 1404 patients were enrolled in the study.

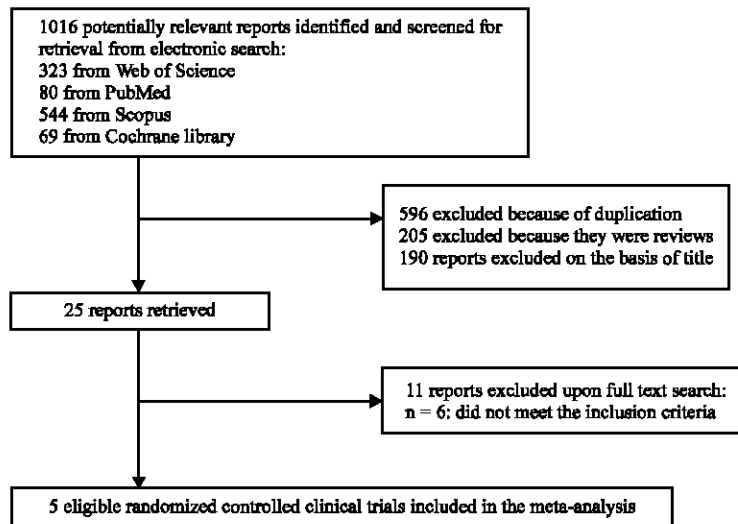


Fig. 1: Flow diagram for study selection

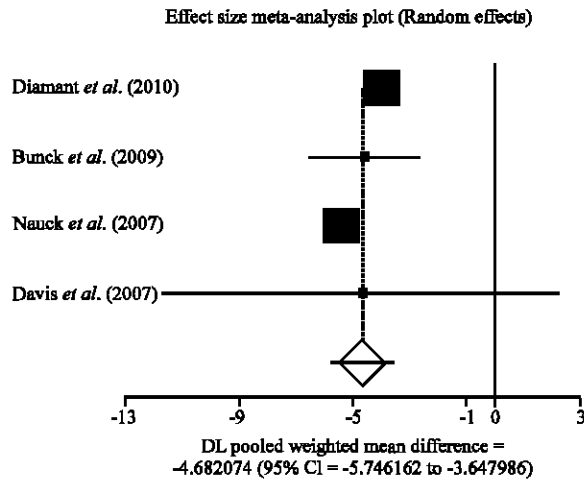


Fig. 2: Individual and pooled effect size for weighted mean difference for the outcome of “Δ BW” in the studies considering exenatide comparing to insulin therapy

**Efficacy**

**Efficacy of exenatide in Fasting Plasma Glucose (FPG) in comparison to insulin:** The summary effect size for weighted mean difference of mean variation of FPG (ΔFPG) for all included data for exenatide in comparison to insulin in three trials (Diamant *et al.*, 2010; Bunck *et al.*, 2009; Nauck *et al.*, 2007) was 0.558361 with 95% CI = -0.185313 to 1.302035 (p = 0.1411). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p = 0.0242) and could not be combined, thus the random effects for individual and summary of effect size for weighted mean difference was applied. Regression of normalized effect vs. precision for all included studies for Δ FPG among exenatide vs. insulin therapy could not be calculated because of too few strata.

**Efficacy of exenatide in Body Weight (BW) in comparison to insulin:** The summary effect size for weighted mean difference of mean variation of BW (Δ BW) for all included data for exenatide in comparison to insulin in four trials (Diamant *et al.*, 2010; Bunck *et al.*, 2009; Nauck *et al.*, 2007; Davis *et al.*, 2007) was -4.682074 with 95% CI = -5.746162 to -3.617986 (p<0.0001, Fig. 2). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p = 0.0066) and could not be combined, thus the random effects for individual and summary of effect size for weighted mean difference was applied. Regression of normalized effect vs. precision for all included studies for Δ BW among exenatide vs. insulin therapy was 0.037132 (95% CI = -9.196063 to 9.270326, p = 0.9878) and Kendall’s test on standardized effect vs. variance indicated tau = -0.333333, p = 0.3333.

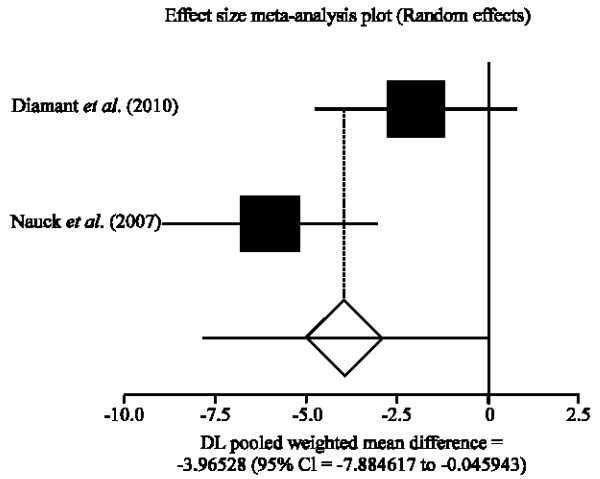


Fig. 3: Individual and pooled effect size for weighted mean difference for the outcome of “Δ Systolic BP” in the studies considering exenatide comparing to insulin therapy

**Efficacy of exenatide in hemoglobin A1C (HbA1C) in comparison to insulin:** The summary effect size for weighted mean difference of mean variation of HbA1C (Δ HbA1C) for all included data for exenatide in comparison to insulin in five trials (Diamant *et al.*, 2010; Bunck *et al.*, 2009; Nauck *et al.*, 2007; Davis *et al.*, 2007; Heine *et al.*, 2005) was -0.118171 with 95% CI = -0.25776 to 0.021418 (p = 0.0971). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p<0.0001) and could not be combined, thus the random effects for individual and summary of effect size for weighted mean difference was applied. Regression of normalized effect vs. precision for all included studies for Δ AC1 among exenatide vs. insulin therapy was 2.050726 (95% CI = -4.779041 to 8.880493, p = 0.4098) and Kendall’s test on standardized effect vs. variance indicated tau = -0.2, p = 0.4833.

**Efficacy of exenatide in systolic Blood Pressure (BP) in comparison to insulin:** The summary effect size for weighted mean difference of mean variation of systolic BP (Δsystolic BP) for all included data for exenatide in comparison to insulin in two trials (Diamant *et al.*, 2010; Nauck *et al.*, 2007) was -3.96528 (95% CI = -7.884617 to -0.045943) a significant result (p = 0.0474, Fig. 3). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (p = 0.0532) and could be combined but because of too few included studies, the random effects for individual and summary of effect size for weighted mean difference was applied. Regression of normalized effect vs. precision for all included studies for Δ systolic BP among exenatide vs. insulin therapy could not be calculated because of too few strata.

Table 1: Different adverse events of all types of exenatide comparing to insulin

Adverse events	RR combined meta analysis	CI	p-value for RR	p-value for heterogeneity	Publication bias
Nasopharyngitis	0.89	0.66-1.21	0.4582	0.6078	NA
Headache	1.14	0.78-1.66	0.4985	0.7079	NA
Nausea	10.29	3.70-28.65	<0.0001	0.0319	No
Diarrhea	2.68	1.65-4.34	<0.0001	0.4881	NA
Vomiting	4.48	2.75-7.28	<0.0001	0.9761	NA
Hypoglycemia	0.52	0.40-0.69	<0.0001	0.0568	No
Injection site reaction	5.25	2.22-12.39	0.0002	0.8778	NA

NA: Not Applicable

**Efficacy of exenatide in diastolic BP in comparison to insulin:**

The summary effect size for weighted mean difference of mean variation of diastolic BP ( $\Delta$  diastolic BP) for all included data for exenatide in comparison to insulin in two trials (Diamant *et al.*, 2010; Nauck *et al.*, 2007) was -1.674989 (95% CI = -4.594861 to 1.244883) a nonsignificant result ( $p = 0.2609$ ). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ( $p = 0.0808$ ) and could be combined but because of too few included studies, the random effects for individual and summary of effect size for weighted mean difference was applied. Regression of normalized effect vs. precision for all included studies for  $\Delta$  diastolic BP among exenatide vs. insulin therapy could not be calculated because of too few strata.

**Tolerability****Nasopharyngitis due to exenatide comparing to insulin:**

The summary RR for nasopharyngitis of exenatide in three trials (Diamant *et al.*, 2010; Nauck *et al.*, 2007; Heine *et al.*, 2005) was 0.89 with a 95% CI of 0.66 to 1.21 and a non significant RR ( $p = 0.4582$ ) (Table 1). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ( $p = 0.6078$ ) and could be combined but because of too few included studies, the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for nasopharyngitis among exenatide vs. insulin therapy could not be calculated because of too few strata.

**Headache due to exenatide comparing to insulin:**

The summary RR for headache of exenatide 5  $\mu$ g bid in three trials (Diamant *et al.*, 2010; Nauck *et al.*, 2007; Heine *et al.*, 2005) was 1.14 with a 95% CI of 0.78 to 1.66, a nonsignificant RR ( $p = 0.4985$ ). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ( $p = 0.7079$ ) and could be combined but because of too few included studies the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for headache among exenatide vs. insulin therapy could not be calculated because of too few strata.

**Nausea due to exenatide comparing to insulin:**

The summary RR for nausea of exenatide in four trials (Diamant *et al.*, 2010; Nauck *et al.*, 2007; Davis *et al.*, 2007; Heine *et al.*, 2005) was 10.29 with a 95% CI of 3.7 to 28.65, a significant RR ( $p < 0.0001$ ). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous ( $p = 0.0319$ ) and could not be combined, thus the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for nausea among exenatide vs. insulin therapy was 1.414029 (95% CI = -4.245881 to 7.073938,  $p = 0.3949$ ) and Kendall's test on standardized effect vs. variance indicated  $\tau = 1$ ,  $p = 0.0833$ .

**Diarrhea due to exenatide comparing to insulin:**

The summary RR for diarrhea of exenatide in three trials (Diamant *et al.*, 2010; Nauck *et al.*, 2007; Heine *et al.*, 2005) was 2.68 with a 95% CI of 1.65 to 4.34 and a significant RR ( $p < 0.0001$ ). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ( $p = 0.4881$ ) and could be combined but because of too few included studies, the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for diarrhea among exenatide vs. insulin therapy could not be calculated because of too few strata.

**Vomiting due to exenatide comparing to insulin:**

The summary RR for vomiting of exenatide in three trials (Diamant *et al.*, 2010; Nauck *et al.*, 2007; Heine *et al.*, 2005) was 4.48 with a 95% CI of 2.75 to 7.28, a significant RR ( $p < 0.0001$ ). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ( $p = 0.9761$ ) and could be combined but because of too few included studies the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for vomiting among exenatide vs. insulin therapy could not be calculated because of too few strata.

**Hypoglycemia due to exenatide comparing to insulin:**

The summary RR for hypoglycemia of exenatide in five trials

(Diamant *et al.*, 2010; Bunck *et al.*, 2009; Nauck *et al.*, 2007; Davis *et al.*, 2007; Heine *et al.*, 2005) was 0.52 with a 95% CI of 0.4 to 0.69 and a significant RR ( $p < 0.0001$ ). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ( $p = 0.0568$ ) and could be combined, thus the fixed effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for hypoglycemia among exenatide vs. placebo therapy was 0.260533 (95% CI = -5.321606 to 5.842671,  $p = 0.8913$ ) and Kendall's test on standardized effect vs. variance indicated  $\tau = -0.2$ ,  $p = 0.4833$ .

**Injection site reaction due to exenatide comparing to insulin:** The summary RR for Injection site reaction of exenatide in two trials (Diamant *et al.*, 2010; Heine *et al.*, 2005) was 5.25 with a 95% CI of 2.22 to 12.39 and a significant RR ( $p = 0.0002$ ). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ( $p = 0.8778$ ) and could be combined but because of too few included studies the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for injection site reaction among exenatide vs. insulin therapy could not be calculated because of too few strata.

## DISCUSSION

The safety and efficacy of exenatide were investigated in several clinical trials. Most of them have been conducted as placebo-controlled trials while some others are controlled trials that compared exenatide with insulin or other hypoglycemic agents. Therefore, we analyzed these trials in two separate articles. The first meta-analysis was performed on placebo-controlled clinical trials and the second meta-analysis was done on the data extracted from clinical trials compared exenatide with insulin. To prevent bias, in cases which studies showed heterogeneity, the random effects method for individual and summary of RR was applied.

Considering the goal of tight glucose control in diabetes, treatment protocols provide a guide into adding second line hypoglycemic agents as well as insulin to the drug regimen (Kajbaf *et al.*, 2007). As sometimes these regimens are not efficient several approaches such as trying on newer drugs are considered (Ansari *et al.*, 2008; Mojtahedzadeh *et al.*, 2008).

In the terms of clinical efficacy, our former meta-analysis showed that exenatide significantly lowers FPG and HbA1C in comparison with placebo (submitted for publication). Compared with insulin, although the results of some clinical trials more emphasize on the greater FPG reduction by insulin versus exenatide (Diamant *et al.*,

2010; Bunck *et al.*, 2009; Heine *et al.*, 2005), our results show that there is no significant difference between insulin and exenatide in decreasing FPG. In our study, the Cochrane Q test showed heterogeneity and thus random effect could not be calculated because of too few trials.

Diamant *et al.* (2010) found greater reduction in HbA1C and BW by exenatide usage compared to insulin glargine (Diamant *et al.*, 2010), as well as other investigations which reported similar reduction in HbA1C by exenatide and insulin (Bunck *et al.*, 2009; Nauck *et al.*, 2007). Our meta-analysis resulted in no significant difference between exenatide and insulin in decreasing HbA1C. In a meta-analysis on all randomized clinical trials, similar results in HbA1C by comparing glucagon-like peptide-1 (GLP-1) receptor agonists and insulin was reported (Monami *et al.*, 2009). Also, no difference in decreasing HbA1C and FPG comparing exenatide with insulin glargine or biphasic as part was found (Amori *et al.*, 2007).

Regarding the importance of weight reduction in treatment of type 2 diabetes investigations into finding the best treatment modalities are continuing (Hasani-Ranjbar *et al.*, 2009). Our former meta-analysis resulted in significant weight reduction with exenatide in comparison to placebo especially at the dose of 10  $\mu\text{g}$  bid for more than 16 weeks (submitted for publication). A progressive weight reduction by exenatide vs. progressive increase by insulin was observed (Diamant *et al.*, 2010) which is supported by other similar studies (Bunck *et al.*, 2009; Nauck *et al.*, 2007; Davis *et al.*, 2007; Heine *et al.*, 2005). In comparison with insulin, our analysis showed that exenatide significantly decreases body weight however because of heterogeneity the random effect did not show significance. The result of our study is in agreement with the results of the meta-analysis done by Monami *et al.* (2009), however the meta-analysis of Amori *et al.* (2007) showed more pronounced weight reduction by exenatide vs. insulin.

Comparing with placebo, exenatide showed significant reduction in both systolic and diastolic BP (submitted for publication). Nauck *et al.* (2007) reported significant reduction in systolic and diastolic BP by exenatide compared with insulin (Nauck *et al.*, 2007) whereas, Diamant *et al.* (2010) found significant decrease in systolic BP only. The results of this meta-analysis show that exenatide has substantial effect on systolic BP in comparison with insulin while its effect on diastolic BP was not significant. The random effect could not be used because of too few trials.

In the terms of tolerability, Diamant *et al.* (2010) reported that nasopharyngitis and headache are more common with insulin while, Nauck *et al.* (2007) reported more nasopharyngitis with exenatide and more headaches

with insulin in contrast to the study of Heine *et al.* (2005). Comparing exenatide with placebo, no significant difference in incidence of nasopharyngitis and headache was found (submitted for publication). Gastrointestinal disorders (nausea, diarrhea, vomiting) are more frequently associated with exenatide (Diamant *et al.*, 2010; Nauck *et al.*, 2007; Heine *et al.*, 2005). In our meta-analysis, the risk of nasopharyngitis and headache with exenatide was not differing from insulin, while the risk of nausea, diarrhea and vomiting due to exenatide was significantly higher than insulin. These results were confirmed by Amori *et al.* (2007) in a meta-analysis.

Hypoglycemia was profoundly reported with insulin (Diamant *et al.*, 2010; Bunck *et al.*, 2009; Heine *et al.*, 2005) while the rate of hypoglycemia was similar in both exenatide and insulin in two trials (Nauck *et al.*, 2007; Davis *et al.*, 2007). In our study, exenatide in comparison with insulin significantly caused less hypoglycemic and injection site reactions which is in accordance with meta-analysis of Monami *et al.* (2009). Instead, Amori *et al.* (2007) reported similar risk of hypoglycemia between exenatide and insulin.

In spite of several clinical trials which determined better efficacy of exenatide compared with insulin, the net result of this meta-analysis confirms no superiority of exenatide over insulin. In fact, the main issue which is focusing in most clinical trials in diabetes is BW which its reduction is essential in the treatment of diabetes type 2. This analysis showed that exenatide not only does not differ in decreasing BW from insulin but also its impact on glycemic control is not in favor; also its gastrointestinal side effects is a major concern that may decrease patients compliance.

Lack of enough trials comparing the safety and efficacy of exenatide with insulin and the other hypoglycemic agents limits our understanding about the possible superiority of exenatide. Therefore, further clinical trials on exenatide with active comparators are highly recommended.

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