

## Review

# The Effects of Exenatide on Serum CRP Levels in Patients with Type 2 Diabetes: A Systematic Review of Randomized Controlled Trials

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## Abstract

**Introduction:** There is a well-established link between type 2 diabetes and cardiovascular events risk. C-reactive protein is a biomarker of vascular inflammation used in the management of cardiovascular diseases. Exenatide, part of the glucagon-like peptide-1 receptor agonists, is used in type 2 diabetes treatment and has shown a decrease in cardiovascular risk factors. The objective of this systematic review is to evaluate the potential effect of exenatide on the C-reactive protein levels in patients with type 2 diabetes. **Material and Methods:** Medical databases, including PubMed®, Embase®, and Cochrane, were searched for randomized controlled trials based on the PICOS (P-Population, I-Interventions, C-Comparative interventions, O-Outcomes and S-Study design) framework. **Results:** 7 randomized controlled trials were included. Exenatide twice per day was used in all. Statistically significant decrease of serum C-reactive protein levels was reported in 4 randomized controlled trials in the exenatide twice per day group between baseline and end of the study. In 4 randomized controlled trials, exenatide twice per day decreased C-reactive protein levels more than metformin, sulfonylureas, and insulin glargine. **Conclusions:** Exenatide decreases serum C-reactive protein levels; therefore, it may decrease the inflammatory state associated with atherosclerosis, reducing the risk of cardiovascular diseases.

**Keywords:** Inflammation, Biomarkers, Glucagon-Like Peptide 1.

## Introduction

Since 1980, the global age-standardized prevalence of diabetes in the adult population has nearly doubled, from 4.7% to 8.5% [1]. The most common type of diabetes is Type 2 Diabetes (T2D) and represents around 90% of all cases [2]. It is a heterogeneous disease characterized by high blood glucose because of a progressive loss of beta-cell insulin secretion often associated with insulin resistance [3].

In patients with T2D, treatment with glucagon-like peptide-1 receptor agonists (GLP-1RAs) improves glyce-mic control, as a result of multiple mechanisms includ-ing glucose-dependent insulinotropic and glucagonos-tatic effects, decreased food intake and delayed gastric emptying [4].

In 2005, the U.S. Food and Drug Administration (FDA) approved exenatide twice a day (EXBID). It was the first GLP-1RA used in the treatment of T2D. The exenatide once weekly (EXQW) was approved later



and compared to EXBID demonstrated superior glycemic control, with fewer side effects, in particular, nausea [5].

Since 1979, from the Framingham cohort, a link between the presence of diabetes and subsequent cardiovascular events has been observed [6]. A meta-analysis conducted by The Emerging Risk Factors Collaboration highlighted that independently from other conventional risk factors, diabetes confers about a two-fold excess risk for a wide range of vascular diseases [7].

Vascular inflammation, associated with atherosclerosis, is one of the most common pathophysiological changes that characterize cardiovascular diseases (CVDs). To assist the detection of CVDs and to monitor their evolution, prognosis, and therapy implementation, inflammatory biomarkers are used. C-reactive protein (CRP) is an acute-phase protein whose serum concentration rises as a response of pro-inflammatory cytokines. CRP is a biomarker of the inflammatory process and has an essential role in atherosclerosis [8].

The long-term prospective cardiovascular outcomes trials (CVOTs) for new antidiabetic drugs were conducted after the release of FDA's recommendation for the pharmaceutical industry to demonstrate that treatment with antidiabetic therapies for T2D will not dramatically increase the cardiovascular risk [9]. As the results from the CVOTs for new antidiabetic drugs were published, several representatives of the GLP-1 RA group, besides demonstrating non-inferiority, highlighted the superiority in terms of their cardiovascular outcomes [10-14]. EXQW had CVOT with the highest number of patients. It proved, as intended, that the treatment with EXQW in patients with T2D with or without previous CVD does not significantly lead to differences between the incidence of major adverse cardiovascular events compared to placebo [15].

The aim of this systematic review of randomized controlled trials (RCTs) is to evaluate the potential effect of EXBID or EXQW on serum CRP levels in patients with T2D.

## Material and Methods

We conducted a preliminary literature search, which included a broad approach to databases to find previously published reviews that analyzed the population and the targeted intervention.

We found systematic reviews and meta-analyses evaluating the same outcome, but the articles had been

published more than 3 years ago and included, alongside EXBID or EXQW, other GLP-1 RAs. The current systematic review only assessed the effect of exenatide treatment in T2D patients on serum CRP concentration in RCT.

Previously published guidelines for systematic reviews were searched and used for writing this review [16, 17]. We based this review on a specific framework, PICOS; P (Population-patients diagnosed with T2D), I (Interventions-EXBID or EXQW), C (Comparative interventions-placebo or/and control group), O (Outcomes-CRP or hs-CRP) and S (Study design- RCT).

We included English written studies that were published from January 2005 until December 2019 inclusive. The studies were searched in the following databases: PubMed<sup>®</sup>, Embase<sup>®</sup>, MEDLINE<sup>®</sup>, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CCTR) and <https://www.clinicaltrials.gov> for published and unpublished studies. The last search was on the 31st of January 2020.

For our search an association of relevant MeSH terms was used. In case of PubMed<sup>®</sup> we used ((“exenatide”[MeSH Terms] OR “exenatide”[All Fields]) AND (“diabetes mellitus, type 2”[MeSH Terms] OR “type 2 diabetes mellitus”[All Fields] OR “type 2 diabetes”[All Fields])) AND (“c-reactive protein”[MeSH Terms] OR (“c-reactive”[All Fields] AND “protein”[All Fields]) OR “c-reactive protein”[All Fields] OR “c reactive protein”[All Fields]) AND (Clinical Trial[ptyp] AND “humans”[MeSH Terms]).

Using the sites [www.clinicaltrials.gov](http://www.clinicaltrials.gov), or [www.clinicalstudyresults.org](http://www.clinicalstudyresults.org) we retrieved, if available and relevant, results of unpublished trials. Two reviewers (BA, AC) retrieved and screened the full text of the studies that meet the inclusion criteria.

The following exclusion criteria were: studies that did not have a randomized-controlled design, patients diagnosed with Type 1 Diabetes, patients without T2D, patients younger than 18 years, studies in which there was no sufficient information on CRP in every group in the beginning or at the follow-up (means and standard deviations (SD)).

Two researchers (BA and AC) assessed the risk of bias in the included RCTs following Cochrane criteria [18] independently. The following items were used for the assessment of each study: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and other sources of bias [18]. Unclear issues were discussed with a third party (BC) and resolved by consensus.

## Results

In our search, we identified 127 records, as seen in Figure 1. After we checked for duplicates and excluded the studies that did not match the inclusion criteria, we analyzed seven RCTs.

Of the reviewed RCTs, three were multi-center, one included patients from 14 countries, one compared the EXBID treatment with a surgical procedure, and one included patients diagnosed with T2D and non-alcoholic fatty liver disease. EXBID was compared to placebo in 2 RCTs. The sample size ranged between 11 and

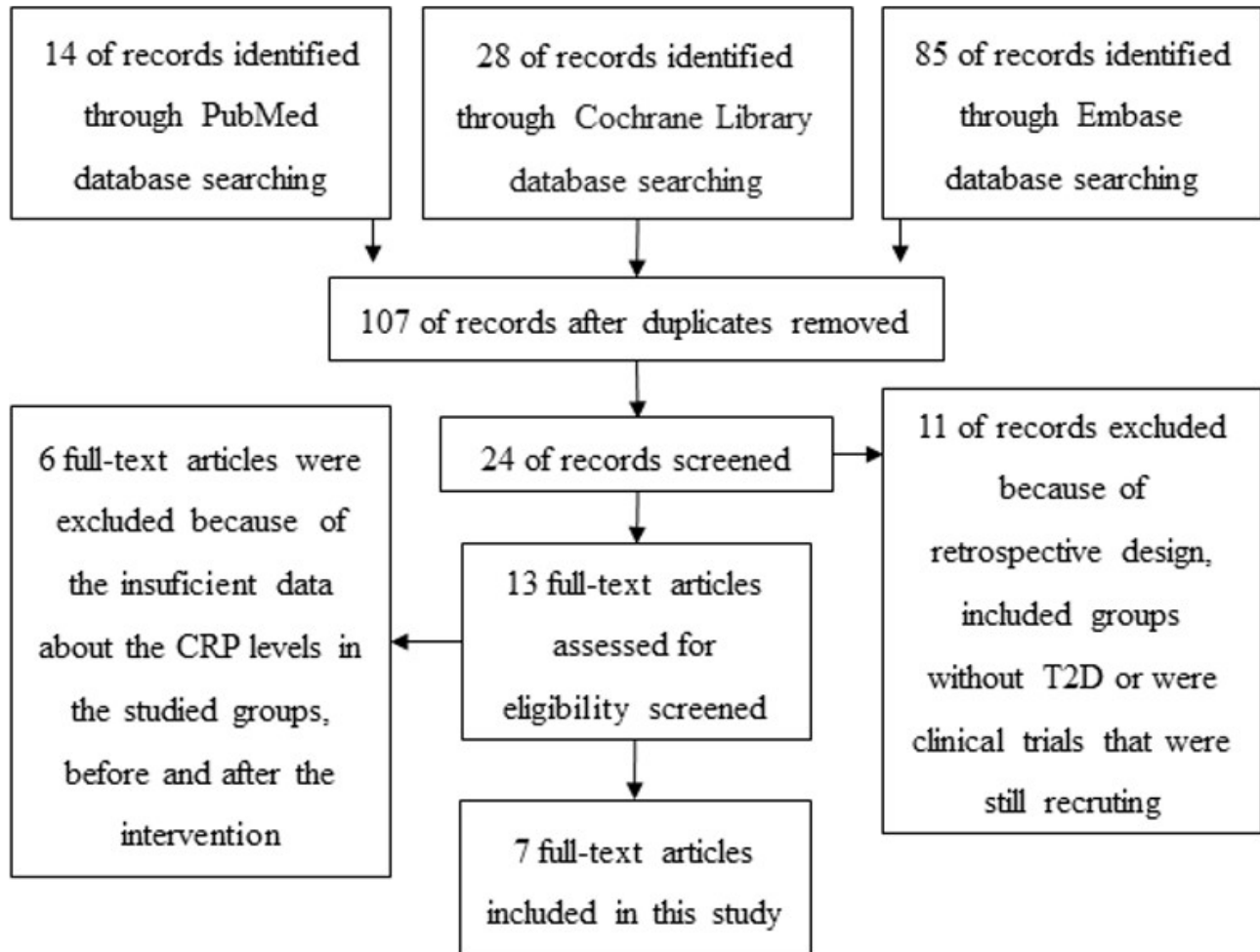


Figure 1: Selection of the articles included in the study.

Table 1: Baseline characteristics of the included studies.

Study	Location	Duration of study	Study design	Number of participants (Male/Female)	Mean age of participants (years)	Mean duration of Diabetes
Derosa et al. [19]	Italy (Multi-center)	52 weeks	Randomized single-blinded controlled study	Exenatide 63 (30/33) Glibenclamide 65 (33/32)	Exenatide (57 ± 2) Glibenclamide (56 ± 6)	-
Wu et al. [20]	China (Nanjing)	16 weeks	Randomized double-blinded controlled study	Exenatide 12 (6/6) Placebo 11 (3/8)	Exenatide (57 ± 10) Placebo (54 ± 9.5)	Exenatide (7.3 ± 4.4) Placebo (5.0 ± 2.5)

Derosa et al. [21]	Italy (Multi-center)	12 months	Randomized double-blinded controlled study	Exenatide 86 (43/43) Placebo 85 (41/44)	Exenatide (57.3 ± 7.7) Placebo (56.7 ± 7.3)	Exenatide (7.6 ± 2.8#) Placebo (7.8 ± 3.1#)
Fan et al. [22]	China (Beijing)	12 weeks	Randomized controlled study	Exenatide 49 (28/21) Metformin 68 (38/30)	Exenatide (51.02 ± 10.1) Metformin (54.68 ± 12.14)	-
Liang et al. [23]	China (Chonhqing)	12 months	Randomized controlled study	Exenatide 34 (24/10) RYGB 31 (22/9) Usual care 36 (24/12)	Exenatide (50.94 ± 5.89) RYGB (50.81 ± 5.44) Usual care (51.75 ± 6.70)	Exenatide (7.17 ± 1.80) RYGB (7.39 ± 1.69) Usual care (7.24 ± 1.61)
Gurkan et al. [24]	Turkey (Kocaeli)	26 weeks	Randomized controlled study	Exenatide 17 (5/12) Insulin glargine 17 (10/7)	Exenatide (52.18 ± 7.26) Insulin glargine (53.12 ± 6.99)	Exenatide (6.88 ± 3.23) Insulin glargine (7.59 ± 4.26)
Simo et al. [25]	14 countries (Multi-center)	36 months	Randomized controlled study	Exenatide 511 (56/44†) Glimepiride 508 (52/44†)	Exenatide (56 ± 10) Glimepiride (57 ± 9)	Exenatide (5.8 ± 4.8) Glimepiride (5.5 ± 4.3)

Note: s.d: #months; † percentage (%); RYGB=Laparoscopic Roux-en-Y Gastric Bypass.

Table 2: Pre- and post- treatment changes in hs-CRP in the included studies.

Study	Background therapy	Intervention	Baseline hs-CRP (mg/L)	End point hs-CRP (mg/L)
Derosa et al. [19]	Metformin, (before inclusion in the study) specific diet and physical exercise (after inclusion in the study)	Exenatide two times a day versus glibenclamide three times a day	Exenatide (2.1 ± 0.8) Glibenclamide (2.0 ± 0.7)	Exenatide (1.5 ± 0.3**†) Glibenclamide (1.8 ± 0.5)
Wu et al. [20]	Metformin and/or a sulfonylurea (before inclusion in the study)	Exenatide two times a day versus placebo	Exenatide (0.4 ± 0.5) Placebo (0.6 ± 0.4)	Exenatide (0.2 ± 0.3#) Placebo (1.4 ± 1.6)
Derosa et al. [21]	Metformin (given 8 ± 2 months before inclusion in the study), specific energy diet and physical exercise	Exenatide two times a day versus placebo	Exenatide (2.0 ± 0.8) Placebo (2.0 ± 0.8)	Exenatide (1.4 ± 0.2*) Placebo (1.6 ± 0.4)
Fan et al. [22]	-	Exenatide two times a day versus metformin two times a day	Exenatide (3.14 ± 0.58) Metformin (3.16 ± 0.68)	Exenatide (2.18 ± 0.34†) Metformin (2.69 ± 0.53)
Liang et al. [23]	Hypoglycemic medication, insulin (were continued during study for usual care group and exenatide + usual care group), diet and physical exercise. Pharmacological treatment was discontinued within 14 days after RYGB	Usual care and exenatide two times a day versus RYGB versus usual care	Exenatide (3.14 ± 1.14) RYGB (3.24 ± 0.95) Usual care (2.91 ± 1.55)	Exenatide (3.86 ± 0.57*) RYGB (1.52 ± 0.32*) Usual care (3.86 ± 1.34)

Gurkan et al. [24]	Metformin (at least two months before inclusion in the study and maintained during intervention)	Exenatide two times a day versus insulin glargine once daily	Exenatide (0.87 ± 0.89) Insulin glargine (0.49 ± 0.42)	Exenatide (0.52 ± 0.47*) Insulin glargine (0.44 ± 0.47)
Simo et al. [25]	Metformin (before inclusion in the study and maintained during intervention)	Exenatide two times a day versus glimepiride two times a day	Exenatide (4.8 ± 7.7) Glimepiride (4.2 ± 5.1)	Exenatide (-1.74 ± 6.56††) Glimepiride (-0.2 ± 4.01)

Note: #p<0.05 compared to placebo; \*p<0.05 compared to baseline; \*\*p<0.01 compared to baseline; †p<0.05 compared to glibenclamide/metformin; ††p<0.004 compared to glimepiride; RYGB=Laparoscopic Roux-en-Y Gastric Bypass; hs-CRP= high sensitive C-reactive protein.

511 patients. In two studies, we could not identify the diabetes duration. In one RCT, the gender distribution was presented as percentages. The studies varied in duration from 12 weeks to 36 months (Table 1).

We did not find RCTs that assessed the effects of treatment with EXQW on CRP and were eligible for inclusion.

CRP was significantly reduced in all studies, but in 4 RCTs, it was compared to baseline, in 3 RCTs was compared to the control group, and in 1 RCT was compared to placebo (Table 2).

There were some concerns regarding the risk of bias due to deviation from the intended interventions for 4 RCTs, but overall the risk-of-bias was low according to Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).

## Discussion

The findings in this systematic review are based on previous reports which highlighted the role of exenatide in decreasing serum CRP concentrations.

In the most recent RCT investigating the effect of EXBID versus Glimepiride in patients with T2D, serum hs-CRP levels were significantly reduced in the EXBID group (-1.74 ± 6.56 vs. -0.2 ± 4.01 mg/L, p=0.004) after 36 months of treatment [25].

EXBID was compared to another sulfonylurea, Glibenclamide, in a multi-centric RCT published by Derosa et al. in 2010. In this RCT, the decrease in hs-CRP after 52 weeks of treatment was statistically significant in the EXBID group (1.5 ± 0.3 mg/L) compared to the baseline value (1.9 ± 0.6 mg/L, p<0.001) and Glibenclamide group (1.8 ± 0.5 mg/L, p<0.05) [19]. The same author published in 2012 a multi-centric RCT in which the patients were given, after 8 ± 2 months of Metformin pre-treatment, EXBID, or placebo for 12 months. The

difference in serum hs-CRP levels was statistically significant only in the EXBID + Metformin group after 12 months of treatment compared to baseline (2.0 ± 0.8 compared to 1.4 ± 0.2 mg/L, p<0.05). After 12 months of treatment, the differences between the EXBID + Metformin group and placebo + Metformin group were not statistically significant, nor were the differences between baseline and 12 months for the Placebo + Metformin group, concerning the serum hs-CRP levels [21].

Another EXBID vs. placebo RCT was published by Wu et al. in 2011. The study had the most reduced number of patients included in each group (12 treated with EXBID vs. 11 with placebo) and lasted for 16 weeks, compared to the other RCTs. The only statistically significant decrease of serum hs-CRP level was reported between the EXBID group and the Placebo group at 16 weeks of treatment (0.2 ± 0.3 vs. 1.4 ± 1.6 mg/L, p<0.05) [20].

Gurkan et al. reported a statistically significant decrease in serum hs-CRP only in the EXBID group between pre- and post-treatment parameters (0.87 ± 0.89 vs. 0.52 ± 0.47 mg/L, p<0.017), at 26 weeks of treatment. The comparator group was treated with Insulin glargine, and there was no statistically significant difference in the reduction of serum hs-CRP between groups or in the Insulin glargine group between baseline and week 26 of treatment [24].

In a 12 weeks study in which EXBID was compared to Metformin in patients diagnosed with concomitant T2D and non-alcoholic fatty liver disease, serum hs-CRP levels were markedly reduced in the EXBID group vs. Metformin group (2.18 ± 0.34 vs. 2.69 ± 0.53 mg/L, p<0.05) [22].

In another study, the EXBID group was compared to a usual care group and a surgical procedure group to assess the effect of laparoscopic Roux-en-Y gastric bypass surgery on T2D patients with hypertension. In the EXBID group, the reduction in serum hs-CRP levels af-

ter 12 months of treatment was statistically significant compared with pre-treatment values ( $3.14 \pm 1.14$  vs.  $3.86 \pm 0.57$  mg/L,  $p < 0.05$ ) [23].

We did not manage to include RCTs that evaluated the effect of EXQW treatment on CRP. During the screening phase of our study, we found papers that included groups of patients treated with EXQW, but the studies did not meet the inclusion criteria: the patients from the studies were not diagnosed with T2D [26-28]; the analysis was done retrospectively, on a subgroup of patients or the formulation of exenatide was not clearly stated [29-31].

The main limitation of our study was that we included only RCTs written in English, increasing the chance of selection bias. Another limitation was the heterogeneity of the trial periods, some being calculated in weeks [19, 20, 22, 24], other in months [21, 23, 25]. Also, the duration of diabetes before the inclusion in the trial was different, and several studies from this systematic review had small sample sizes [20, 24].

The potential benefit of exenatide on inflammatory markers that are linked to T2D is complex and needs further investigation.

## Conclusion

Hs-CRP is an essential biomarker of inflammatory diseases such as CVD and T2D.

Our findings confirmed the association between exenatide and reduced serum CRP levels. Exenatide may, therefore, decrease the inflammatory state associated with atherosclerosis, reducing the risk of CVDs.

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## Conflict of Interest

Cornelia Bala declared speaker and consultancy fees from: Astra Zeneca, Eli Lilly, NovoNordisk, Sanofi, Boehringer Ingelheim, Servier.

## References

1. World Health Organization. Global Report on Diabetes. [online] Available at: [https://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257\\_eng.pdf?sequence=1&fbclid=IwAR2pWZUCkpOdXDgDDeUqE0KnJFzmn4oUiVG17GU75Q3Rh9wm\\_lHcyzFaa0](https://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf?sequence=1&fbclid=IwAR2pWZUCkpOdXDgDDeUqE0KnJFzmn4oUiVG17GU75Q3Rh9wm_lHcyzFaa0) [Accessed 10th Jan 2020]
2. International Diabetes Federation. Type 2 Diabetes. [online] Available at: [https://idf.org/aboutdiabetes/type-2-diabetes.html?fbclid=IwAR1\\_7w-cuCKdLntyXicEaTjvi5X\\_3YFKY084WWg-c0WHv0zj\]4z0vSXckVME](https://idf.org/aboutdiabetes/type-2-diabetes.html?fbclid=IwAR1_7w-cuCKdLntyXicEaTjvi5X_3YFKY084WWg-c0WHv0zj]4z0vSXckVME) [Accessed 10th Jan 2020]
3. American Diabetes Association. Standards of Medical Care in Diabetes—2020. *Diabetes Care* 43(1):S1-S212, 2020 [online] Available at: [https://care.diabetesjournals.org/content/43/Supplement\\_1/S1?fbclid=IwAR2CM5kZiU6UGLYt5Vdyy439-vGKT-8jVQE4mX8CXuZBuEiPt9lAw34\\_vwuU](https://care.diabetesjournals.org/content/43/Supplement_1/S1?fbclid=IwAR2CM5kZiU6UGLYt5Vdyy439-vGKT-8jVQE4mX8CXuZBuEiPt9lAw34_vwuU) [Accessed 10th Jan 2020]
4. Knop F, Brønden A, Vilsbøll T. Exenatide: pharmacokinetics, clinical use, and future directions. *Expert Opin Pharmacother* 18(6): 555-571, 2017
5. Blevins T, Pullman J, Malloy J et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab* 96(5): 1301-1310, 2011.
6. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 241(19): 2035-2038, 1979.
7. Sarwar N, Gao P, Kondapally SR et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 375(9733): 2215-2222, 2010.
8. Castro AR, Silva SO, Soares SC. The use of high sensitivity C-Reactive Protein in cardiovascular disease detection. *J Pharm Pharm Sci* 21: 496-503, 2018.
9. FDA. Guidance for Industry Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes [online]. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diabetes-mellitus-evaluating-cardiovascular-risk-new-antidiabetic-therapies-treat-type-2-diabetes> [Accessed 10th Jan 2020]
10. Sheahan KH, Wahlberg EA, Gilbert MP. An overview of GLP-1 agonists and recent cardiovascular outcomes trials. *Postgrad Med J* 96(1133): 156-161, 2020.
11. Marso SP, Daniels GH, Brown-Frandsen K et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 375(4): 311-322, 2016.
12. Marso SP, Bain SC, Consoli A et al. Semaglutide and cardiovascular outcomes in patients with Type 2 Diabetes. *N Engl J Med* 375(19): 1834-1844, 2016.
13. Hernandez AF, Green JB, Janmohamed S et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 392(10157): 1519-1529, 2018.
14. Gerstein HC, Colhoun HM, Dagenais GR et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomized placebo-controlled trial. *Lancet* 394(10193): 121-130, 2019.

15. Holman RR, Bethel A, Mentz RJ *et al.* Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 377: 1228-1239, 2017.
16. Liberati A, Altman DG, Tetzlaff J *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 6(7): e1000100, 2009.
17. Charrois TL. Systematic reviews: what do you need to know to get started? *Can J Hosp Pharm* 68(2): 144-148, 2015.
18. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: *Cochrane Handbook for Systematic Reviews of Interventions*. Higgins J, Thomas J, Chandler J *et al.* (eds). [online] Available at: [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook) [Accessed 15th Febr 2020].
19. Derosa G, Maffioli P, Salvadeo SA *et al.* Exenatide versus glibenclamide in patients with diabetes. *Diabetes Technol Ther* 12(3): 233-240, 2010.
20. Wu JD, Xu XH, Zhu J *et al.* Effect of exenatide on inflammatory and oxidative stress markers in patients with type 2 diabetes mellitus. *Diabetes Technol Ther* 13(2): 143-148, 2011.
21. Derosa G, Franzetti IG, Querci F *et al.* Exenatide plus metformin compared with metformin alone on  $\beta$ -cell function in patients with Type 2 diabetes. *Diabetic Med* 29(12): 1515-1523, 2012.
22. Fan H, Pan Q, Xu Y, Yang X. Exenatide improves type 2 diabetes concomitant with non-alcoholic fatty liver disease. *Arq Bras Endocrinol Metab* 57(9): 702-708, 2013.
23. Liang Z, Wu Q, Chen B, Yu P *et al.* Effect of laparoscopic Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus with hypertension: A randomized controlled trial. *Diabetes Res Clin Pract* 101: 50-56, 2013.
24. Gurkan E, Tarkun I, Sahin T, Cetinarslan B, Canturk Z. Evaluation of exenatide versus insulin glargine for the impact on endothelial functions and cardiovascular risk markers. *Diabetes Res Clin Pract* 106:567-575, 2014.
25. Simo R, Guerci B, Schernthaner G *et al.* Long-term changes in cardiovascular risk markers during administration of exenatide twice daily or glimepiride: results from the European exenatide study. *Cardiovasc Diabetol* 14: 116, 2015.
26. Lundkvist P, Pereira MJ, Katsogiannis P *et al.* Dapagliflozin once daily plus exenatide once weekly in obese adults without diabetes: Sustained reductions in body weight, glycaemia and blood pressure over 1 year. *Diabetes Obes Metab* 19: 1276-1288, 2017.
27. Kelly AS, Bergenstal RM, Gonzalez-Campoy JM, Katz H, Bank AJ. Effects of Exenatide vs. Metformin on endothelial function in obese patients with pre-diabetes: a randomized trial. *Cardiovasc Diabetol* 11: 64, 2012.
28. Wang X, Chen J, Li L *et al.* New association of bone morphogenetic protein 4 concentrations with fat distribution in obesity and Exenatide intervention on it. *Lipids Health Dis* 16: 70, 2017.
29. Bunck MC, Diamant M, Eliasson B *et al.* Exenatide affects circulating cardiovascular risk biomarkers independently of changes in body composition. *Diabetes Care* 33(8): 1734-1737, 2010.
30. Varanasi A, Chaudhuri A, Dhindsa S *et al.* Durability of effects of exenatide treatment on glycemic control, body weight, systolic blood pressure, C-reactive protein, and triglyceride concentrations. *Endocr Pract* 17(2): 192-200, 2011.
31. Chiquette E, Toth PP, Ramirez G, Cobble M, Chilton R. Treatment with exenatide once weekly or twice daily for 30 weeks is associated with changes in several cardiovascular risk markers. *Vasc Health Risk Manag* 8: 621-629, 2012.