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# Glucagon-Like Peptide-1 Receptor Agonist Effects on Gastric Motility: A Systematic Review

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## ABSTRACT

***Objective:*** *Glucagon-like peptide-1 receptors agonists (GLP-1 RAs) are adjunctive treatment for patients with diabetes. The mechanism of action is to increase insulin and decrease glucagon secretion along with delay of gastric emptying which has superior effect toward post-prandial blood glucose level. However, the GLP-1RAs effect on gastric emptying (GE) on patients with compromised gastric motility, especially in diabetes patients, is not well-documented. The aim of this systematic review is to determine the effects of GLP-1 RAs on gastric motility in healthy subjects, diabetic type 1 and type 2 patients and to identify the specific conditions that could alter these effects.*

***Research design and methods:*** *A search was conducted for studies of patients received GLP-1 RAs with control group and included gastric motility measurement as an outcome. We included studies published up to January, 2017 using PubMed, Scopus, Web of Sciences, and Clinicaltrial.gov databases. The studies were classified by studied subjects and method of GE measurement.*

***Results:*** *Nineteen studies were included in the review, with 4 studies in healthy, 2 in obese, 5 in diabetes type 1 and 8 in diabetes type 2 subjects. Fifteen studies showed significantly dose-responded decrease of gastric motility and we found this decrease in all three groups of studied patients. Studies that did not demonstrate delay in gastric motility include study with specific condition including relatively low dose of GLP-1 RA, hypoglycemic stage and concomitant high-fat diet.*

***Conclusions:*** *GLP-1 RAs has potential effect to decrease gastric motility in non-diabetes and diabetes patients. This effect correlates with its known effect to decrease post-prandial blood glucose level.*

## Keywords

GLP-1 receptor agonist, Gastric motility, Gastric emptying, Scintigraphy, Acetaminophen absorption.

## Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are GLP-1 analogs, resistant to degradation by dipeptidyl-peptidase-4 (DDP-4), which results in longer half-life [1]. The first drug, exenatide, was approved for adjunctive therapy of diabetes since 2005. This subcutaneous antidiabetic drug class is promising drug in diabetic care as its mechanism to increase insulin and decrease glucagon release with low risk of hypoglycemia [2]. Besides this effect on endocrine pancreas, it also delays gastric emptying (GE) which superiorly improves postprandial glucose level [3,4]. The GLP-1 has several pathways that slow GE classified as peripheral and central regulations. GLP-1 is a hormone secreted mainly from

intestinal L-cell after food intake and absorbed into blood stream [5]. The GLP-1 receptors are located in various organs, particularly pancreas, gastrointestinal tract and hypothalamus [6,7]. Although, stomach has GLP-1 receptors in parietal and smooth muscle cells, the effect of delay in GE by GLP-1 is also proposed to be mediated via vagal innervation [7,8]. The vagal pathway is supported by study from Plamboeck *et al.* which GLP-1 infusion had no effect on patients who underwent vagotomy [9]. GLP-1 also activates GLP-1 receptor in intestine and portal vein which send signal to central nervous system through intestinal vagal afferent, and consequently causes increase of satiety, and also send the signal back to stomach to slow GE [10].

In patients with diabetes, autonomic neuropathy with gastroparesis resulted in delayed GE is well-documented [11]. Diabetic patients have decreased level of GLP-1 due to their enhanced clearance [3]. The decrease in GLP-1 consequently causes an increase in post-prandial blood glucose which results in acceleration of GE. Thus, the effect of GLP-1 RAs in the diabetic patients is altered and complex.

Addressing the effects of GLP-1 RAs effect on GE is essential to improve diabetes patient care with this alternative potential and safe drug, The aim of this systematic review is to determine the effects of GLP-1 RAs on gastric motility in healthy subjects, diabetic type 1 and type 2 patients and to identify the specific conditions that could alter these effects.

## Method

### Data Sources and Searches

We performed a systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines (**Checklist S1**) [12]. Two authors (NW and MA) independently searched four databases including PubMed, Scopus, Web of Sciences, and Clinicaltrial.gov from inception of the databases through January, 2017 (search strategy described in **Supplementary data 1**). There was no language restriction. We also excluded non-human studies and review publication type. In addition, the title and abstract of the reference lists of the included studies were screened.

### Inclusion Criteria

We included studies that met all of the following criteria: (i) randomized controlled trial (RCT) studies, (ii) comparing patients receiving any GLP-1 receptor agonist and placebo (iii) measuring GE as primary or secondary outcome. We did not limit sample size or subject condition such as healthy or diabetes mellitus patients. The quality of RCTs were assessed by Jadad scale including randomization (2 points), blinding (2 points), and patients' attrition (1 point) [13]. The study is classified as adequate quality if the score is ≥3 out of 5. Two authors (NW and MA) independently assigned the study quality.

### Data Extraction

Data were extracted from full-text articles independently by two review authors (NW and MA) using standardized form. Disagreements were identified and discussed with the third author (BS). The extracted information included author name, country where study was conducted, publication year, study methodology (study design, method of randomization, inclusion and exclusion criteria, primary and secondary endpoint, and dropout rate), patients' baseline characteristics, and study interventions (GLP-1RA type, dose, and exposure time). The outcomes of each study were extracted and converted into SI unit. The studies were classified by subjects as non-diabetes, diabetes type 1, and diabetes type.

The protocol for this study was registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42017055339).

## Results

### Study characteristics

A total of 333 articles were included from the databases (Figure 1). After title and abstract screening, 57 potentially related articles were assessed. Thirty-eight studies were excluded due to following reasons: 6 had no full paper, 4 were the conference abstract of other included studies, 23 were not relevant to gastric motility measurement or GLP-1RA, 4 did measurement of gastrointestinal tract but not stomach, 1 was pediatric patients study, 1 was IBS patients study, 1 had no control group, and 2 contained inadequate data for analysis. A total of 19 studies were included to explore the methods that used for gastric motility measurement in this review.

Of the 19 studies, there were 4, 2, 5, and 8 studies of healthy, obese, diabetes type 1 and diabetes type 2 subjects, respectively. Regarding methods of measurement, 3, 14, and 1 study used scintigraphy, acetaminophen absorption test, and [13] C breath test, respectively, with 1 study using both acetaminophen absorption and [13] C breath test [14]. The studies' characteristics are provided in Table 1A, 1B, and 1C.

### Methods of GE measurement (scintigraphy and acetaminophen absorption test)

GE measurements are varied by both methods and parameters. Of the three included studies with scintigraphy, one study measured gastric volume by liquid meal, one studies measured proportion of gastric content emptied after mixed meal, and the other study measured $\log_e$ of $T_{50}$ with calculation of least-square geometric mean. The 14 studies with acetaminophen absorption assessed plasma acetaminophen concentration with varied duration from 120 to 480 minutes. The most common duration used is 240 minutes (n=7), followed by 300 minutes (n=4). Mixed meals were used in 8 studies while liquid meals were used in other 6 studies. Most studies used mainly AUC of acetaminophen at 0 to total duration as parameter to compare treatment groups and controls (n=10) and 3 studies used ratio of the AUC. There was only one study that applied solely time to peak acetaminophen concentration ($t_{max}$) and maximal acetaminophen concentration ($C_{max}$) as a determinant [15].

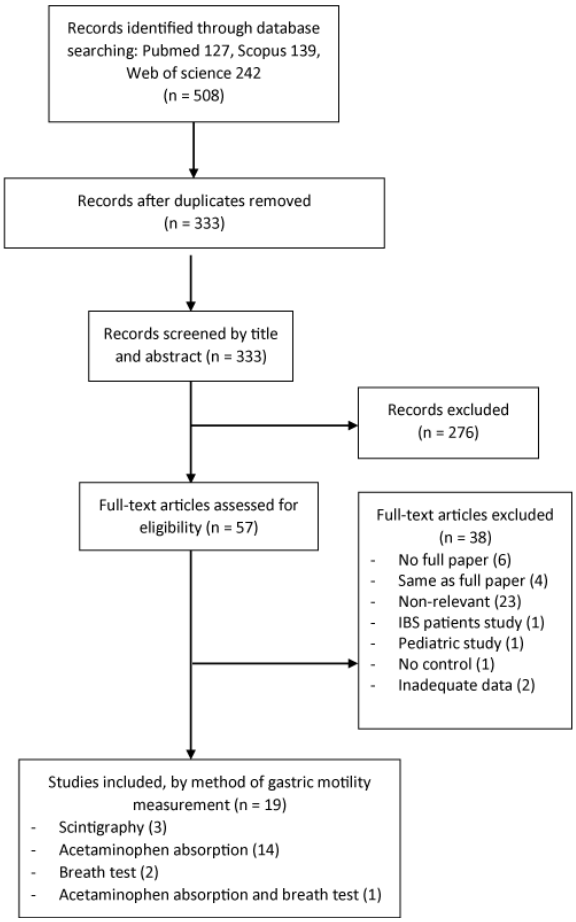


**Figure 1**. Search methodology and selection process.

## Studies quality

Twelve of nineteen studies had adequate quality whereas five studies had inadequate quality by Jadad score (Table S2). We presented studies with both adequate and inadequate quality. However, we included all the studies regardless of quality. As all the inadequate quality studies are due to blinding and the gastric motility measurement is an objective measurement which is less likely to be affected by blinding.

## Gastric emptying

Most studies found statistically significant decrease of GE of treatment groups compared to controls. Of the five studies that assigned several different doses in treatment arms [16-20], three studies showed dose-dependent response [16,18,20].

## Gastric emptying in non-diabetes subjects

Of the six studies of non-diabetic patients, there were significant decreased GE in five studies [15,16,21-23] and significantly decreased initial GE in one study [19]. In scintigraphy method, Yoon *et al.* found that exenatide significantly increased post-prandial but not fasting gastric volume compared to control, reflecting on delayed emptying of stomach content. With different method of scintigraphy, Acosta *et al.* found that exenatide significantly decreased solid emptied from stomach in the first 1 hour after meal. However, in this study, volume to fullness and maximum tolerated volume were not different between groups.

In acetaminophen absorption method, Beck *et al.* assigned 4 different doses of lixisenatide to healthy subjects and found dose-dependent relationship with $AUC_{Act}$ 0-240 min, $AUC_{Act}$ 0-60 min, $t_{max}$, and $C_{max}$ confirming the dose dependency of the GLP-1 RA on GE. Study from Van Can et al. Of 5-week liraglutide in obese subjects found an initial delayed of GE ($AUC_{Act}$ 0-60 min) in 3 mg dose, but not in 1.8 mg dose or total GE ($AUC_{Act}$ 0-300 min) of both doses.

## Gastric emptying in diabetes type 1 patients

Of the five studies in diabetes type 1 patient, there were significant decreased GE in four studies [24-27] and no significant different GE from placebo in 1 study [28]. All studies used acetaminophen absorption to measured GE. Patients in 2 studies had no residual insulin secretion, 1 study had residual insulin secretion, and 2 studies had mixed patients' status. Most studies of single dose and long-term treatment from 3 weeks to 6 months also found that GLP-1 RA significantly delayed GE.

However, a study from Frandsen *et al.* of liraglutide effects during insulin-induced hypoglycemia found no difference of GE, in both $AUC_{Act}$ 0-240 min and $t_{max}$, between treatment and control group.

### Gastric emptying in diabetes type 2 patients

Of the eight studies of diabetes type 2 patients, there were significant decreased GE in six studies [17,18,20,29,30] and no significant deferent GE from placebo in two studies [14,31]. One study that used scintigraphy method from Linnebjerg *et al.* explored 2 doses of exenatide and found significantly decreased $\log_e$ of $T_{50}$ in both solid and liquid meals.

In studies that used acetaminophen absorption method, three studies found that GLP-1 RA significantly decreases GE compared to control whereas others three studies founded no difference between the two groups. Study from Hermansen *et al.* which studied effect of liraglutide with high-fat diet (65% energy from fat) found ratio of $AUC_{Act}$ 0-60 min and ratio of $C_{max}$ of treatment and control group were approximate to 1. Flint et al. found no decreased GE with low dose of 0.6 mg/day of liraglutide per day while Degn*et al.* also demonstrated that liraglutide at a dose of 6 µg/kg/day did not decrease GE.

## Discussion

GLP-1 RAs significantly decreased GE in healthy and obese subjects, as well as in patients with type 2 and type 1 diabetes in most studies with a dose-dependent response. This was proposed to be one of the mechanisms that decrease blood glucose level, particularly postprandial glucose. Due to heterogeneity among the studies, the meta-analysis could not be conducted.

According to the included studies, GLP-1 RAs delayed GE in most studies of both diabetes type 1 and type 2 patients. Several studies demonstrated that GLP-1 RAs did not significantly delayed GE including; the study from Frandsen *et al.* which measured GE during insulin-induced hypoglycemia in T1DM patients, and the study from Hermansen *et al.* which used high-fat mixed meal during the acetaminophen absorption test in T2DM patients. The data of GLP-1 RAs and gastric emptying time during hypoglycemia is limited. One previous study of GLP-1 infusion in healthy subjects during hypoglycemia showed delayed GE effect compared to controls, however, with lesser extent of GE change than in normoglycemic stage [32], possibly due to contribution of sympathetic activation during hypoglycemia which is known to decrease gastrointestinal motility. High fat diet is known to slow GE and increase endogenous GLP-1 level [33].

Thus, the effect of GLP-1 RA drug could be masked. Recently, the study from Umapathysivam *et al.* has demonstrated tachyphylaxis effects on GE of GLP-1 which can also responsible for not significantly changes of GE in the two studies with the duration of GLP-1 RA was 12 and 3 weeks, respectively. In this study, GE in intermittent GLP-1 administration was significantly delayed more than the continuous group and suggested that the short acting GLP-1 RA may be superior to long-acting GLP-1 RA [34].

We found dose-response relationship with the higher dose of GLP-1 RAs resulted in more delayed GE. From the included studies, doses of lixisenatide ≤ 2.5 µg [16] and liraglutide ≤ 0.6mg [17] tended to have no significant effects to GE in diabetic patients compared to the higher doses. No study demonstrates the plateau of the dose response, possibly because with higher dose, the gastrointestinal side effects such as nausea, vomiting and bloating will be prominent and not-well tolerated. Comparison between drugs and doses across studies is difficult in our review due to heterogeneity of inclusion and exclusion criteria, drug duration and method of measurement. The only studied that compared different drugs found that the gastric emptying time is significantly delayed in lixisenatide 20 µg than both liraglutide 1.2 and 1.8 mg [35].

In post-prandial state, delay in GE by GLP-1 plays important role to decrease plasma glucose which the effect is more prominent than the effect from insulin [36]. The post-prandial insulin level of the groups with GLP-1 RA in the included studies varied with significantly increased in 5 studies, significantly decreased in 3 studies and not different in 5 studies, compared to control group. Only one study analyzed the correlation of GE and post-prandial glucose levels and found linear correlation [37]. In the effects of GLP-1 RAs in reducing blood sugar, post-prandial glucose are proposed to be related to decreased of GE, while fasting plasma glucose is more related to insulinotropic properties of GLP-1.

Methods used to measure gastric motility can also interfere with the results. The gold standard method is scintigraphy which is used in only one of the included studies. Acetaminophen were the most common method used in our systematic review because this would also facilitate the measurement of other related outcomes such as GLP-1, insulin, and glucose level in the form of AUC curves. One systematic review had compare the different of this standard method and acetaminophen absorption and found a well correlation [38].

According to review, the AUC and $C_{max}$ of acetaminophen are considered an accurate estimation, whereas the $T_{max}$ is varied and inaccurate. However, this measurement method can be interfered by many factors such as food-drug interaction which resulted in non-correlation of GE measured by scintigraphy in one study [39].

There are several limitations in our study. First, there is heterogeneity of the included studies. Also, the data of direct comparison between different drugs is very limited. Thus, the comparisons between the studies and drugs should be applied cautiously.

In conclusion, GLP-1 RAs decrease GE dose-dependently and result in decrease in post-prandial glucose. GLP-1 RAs has systemic effect on fasting blood glucose (through other mechanism that increases insulin secretion and decreases glucagon release) whereas the postprandial glucose effect is through delayed GE. Clinically, this distinct character is important for the decision of medication choice, particularly for diabetic patients. Further studies to demonstrate the correlation of drugs level, GE and long-term effect in fasting plasma glucose is warranted.

## Contributions

BS is the guarantor. NC, MA, SS, and BA drafted the manuscript. All authors developed the paper selection criteria, bias assessment and data extraction criteria. NC and MA created the search strategy. BS provided expertise on GLP-1 RA. All authors reviewed and provided final approval of the manuscript.

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