Frequency of GLP-1 receptor agonists use in diabetic patients diagnosed with delayed gastric emptying and their demographic profile

M Ammar Kalas ,[1] The Q Dang,[1] Gian Galura,[2] Luis Alvarado,[3] Alok Kumar Dwivedi ,[3] Abhizith Deoker,[1] Richard McCallum[2]

[1]Internal Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, Texas, USA
[2]Gastroenterology, Texas Tech University Health Sciences Center El Paso, El Paso, Texas, USA
[3]Division of Biostatistics and Epidemiology, Texas Tech University Health Sciences Center El Paso, El Paso, Texas, USA

Correspondence to
Dr M Ammar Kalas, Internal Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, Texas, USA; mkalas@ttuhsc.edu

Accepted 24 August 2022

To cite: Kalas MA, Dang TQ, Galura G, *et al*. *J Investig Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jim-2022-002480

ABSTRACT

Advances in the management of diabetes mellitus have come a long way in the 21st century. One of the most important developments in diabetes management has been the discovery of glucagon-like peptide-1 (GLP-1) receptor agonists. The most common side effects of GLP-1 receptor (GLP-1R) agonists are nausea and vomiting which have been attributed to delayed gastric emptying. While the effects of GLP-1R agonists on gastric emptying have prompted further research in this field, there are limited studies evaluating their effects on patients with pre-existing gastroparesis. Additionally, the frequency of GLP-1R agonist use among patients with gastroparesis has not been assessed in the past and this study aims to identify that percentage along with evaluating for possible iatrogenic gastroparesis. A retrospective review of all the gastric emptying studies performed at one academic medical center between January 2019 and January 2021 was performed. We found that although patients on GLP-1R agonists were more likely to have delayed gastric emptying, we could not establish a statistical significance. This could be due to the small sample size in the study. However, GLP-1R agonists use was associated with delayed gastric emptying in patients with diabetes for <10 years. Moreover, a significant proportion (24%) of patients with diabetes with delayed gastric emptying were on a GLP-1R agonist. Recently, semaglutide (GLP-1R agonist) gained Food and Drug Administration approval as a weight loss medication in both patients with and without diabetes. This should prompt further research to evaluate the safety profile of these medications in patients with and without pre-existing gastroparesis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Glucagon-like peptide-1 (GLP-1) receptor agonists are growing in popularity and are known to exert their effects partly through their effect on the gastrointestinal tract.
⇒ The primary effect on the gastrointestinal tract is through decreasing gastric motility and hence resulting in weight loss and improved diabetic control.
⇒ Studies evaluating GLP-1 receptor (GLP-1R) agonists effects on gastric emptying study (GES) have been conflicting with some studies showing delayed gastric emptying and other showing no change in gastric emptying.

WHAT THIS STUDY ADDS

⇒ Our study looks into the association of this drug class and gastroparesis and assesses the frequency of this medication use in those with gastroparesis.
⇒ Our study showed that, overall, GLP-1R agonists were not statistically associated with delayed gastric emptying; however, GLP-1R agonists use in patients with diabetes for <10 years was statistically associated with increased risk of delayed GES in our study.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Prospective studies with GES prior to initiation, during, and after GLP-1R agonist use would help better characterize the effects on these medications.
⇒ A few studies suggested possible increased effect of GLP-1R agonists on those with normal gastric emptying.
⇒ This is of particular relevance with the recent approval of semaglutide for weight loss in patients with obesity without diabetes whose gastric emptying is likely normal and hence better weight loss results could be expected as well as the possibility of accompanying gastroparesis symptoms.

INTRODUCTION

Gastroparesis (GP) is a disorder with a wide variety of symptoms ranging from mild abdominal bloating to severe abdominal pain with intractable nausea, vomiting, and intolerance of oral intake. It is defined as delayed gastric emptying evidenced by an objective gastric emptying assessment tool in the absence of mechanical obstruction. The gold standard modality for assessment of gastric emptying is scintigraphy. Other modalities have been

assessed and used, such as breath tests using 13-C-octanoate or spirulina and wireless motility capsule.[1]

Etiologies are variable and include metabolic diseases with diabetes mellitus (DM) as the leading cause, systemic diseases such as Parkinson's disease or scleroderma, medication induced such as opioids and glucagon-like peptide-1 (GLP-1) receptor agonists, postsurgical causes (postvagotomy), or idiopathic which is the most common cause of GP.

GLP-1 receptor (GLP-1R) agonists have surged in popularity owing to their convenient weekly dosing and favorable weight loss side effect.[2] This medication class acts through binding to incretin receptors and results in glucose-induced insulin release and attenuation of gastric emptying. In addition, GLP-1R agonists have favorable cardiovascular outcomes due to improved glycemic control, blood pressure improvement, and weight loss.[3]

This study aims to assess the frequency of GLP-1R agonist use in patients with GP, and the association between GLP-1R agonist use and GP.

MATERIALS AND METHODS

A retrospective chart review was performed at the Texas Tech University Health Sciences Center El Paso of all adult (>18 years of age) patients who underwent a gastric emptying study (GES) from January 2019 to January 2021. Patients with history of illicit drug use or opioids use were excluded to eliminate any possible confounding effect. The final number of patients included in our study was 384. A manual chart review was done and the following data were obtained: age, gender, reason for the GES, medical history such as hypertension and diabetes, surgical history, social history such as history of smoking and alcohol intake, GES findings, procedure dates, and which GLP-1R agonists have been used.

Delayed gastric emptying was defined as >10% retention of radioactive isotope in the stomach at 4 hours as per the current guidelines. The hemoglobin A1C (HbA1C) cut-off of 8% was used as this is generally the threshold used by clinicians for diabetes control. In addition, patients glucose levels were checked prior to the GES and if it was >275 mg/dL, then the study was rescheduled.[4]

Statistical analysis

Categorical variables were summarized using frequencies and percentages while quantitative variables were summarized using mean and SD.

Variables were compared across GES status at 4 hours using a χ^2 test, Fisher's exact test, and an unpaired t-test. The same procedure was applied when comparing across GLP-1R agonist distribution. A univariate and multivariable relative risk regression was conducted to determine the association between GLP-1R agonists and GES along with variables of interest. The same relationship was further investigated in specific subpopulations. Relative risk (RR), 95% CI, and p values were used to describe the analysis. Missing data were accounted for and not included in the analysis. P values were considered significant at 5% level of significance. All data analysis and data management was conducted using Stata V.15.1.

RESULTS

The characteristics of the 384 patients included in the study are depicted in table 1. Average age at diagnosis was 52 years of age with no significant difference among patients with or without delayed GES. The duration of GLP-1R agonist use in years was unremarkable between patients with diabetes with or without delayed GES. The duration of DM prior to the GES was expectedly longer in patients with delayed GES likely due to diabetic GP. Interestingly, the HbA1C was similar in both groups. Moreover, despite the majority of patients being females, there was no statistical significance between the two sexes which could be attributed to the smaller sample size. The majority of patients were of hispanic ethnicity (81.7%), however there was no statistical significance regarding the GES results based on ethnicity. Smoking and alcohol use were not associated with delayed gastric emptying in our study.

We found that overall, 23.6% of our patients with diabetes were on a GLP-1R agonist. Moreover, of the patients with diabetes with delayed gastric emptying, 24% were on a GLP-1R agonist.

Table 2 illustrates the relation between GES and GLP-1R agonists administration. Our study showed no relation between GES and GLP-1R agonist use.

Moreover, analysis of the association of GLP-1R agonist use and GES within specific populations was performed to explore the effects of GLP-1R agonists on specific subpopulations (table 3). Patient demographics such as age and sex did not show any association between the two variables mentioned above. Furthermore, diabetic control with a set HbA1C target of 8% also did not show an association between GLP-1R agonists and GES. Interestingly, patients with DM for <10 years had an increased risk of delayed GES with GLP-1R agonists use. Patients with diabetes for >10 years duration are more likely to have a component of GP due to prolonged glycemic toxicity and neuronal dysfunction.

Furthermore, there was no association between the type of GLP-1R agonist used and GES at different doses (table 4).

DISCUSSION

GLP-1 is a gastrointestinally released peptide that is a part of the 'glucagon hormone family' and is secreted primarily from the intestinal L cells through neuroendocrine stimulation rather than direct stimulation of the gastrointestinal tract and is inactivated by dipeptidyl peptidase IV. Its effects are exhibited biochemically through G-protein coupled receptors and lead to increased glucose-dependent insulin release, glucagon suppression, pyloric sphincter contraction and decreased antro-duodenal motility.

GLP-1R agonists mechanism on gastrointestinal motility have been poorly understood. Studies have suggested the effects to be due to GLP-1R agonists effects centrally. GLP-1R agonists can cross the blood-brain barrier.[5] Centrally located GLP-1 receptors are found at a high concentration in the dorsal motor nucleus of the vagal nerve. In addition, GLP-1 immunoreactive soma were found in the brainstem, specifically in the nucleus tractus solitarii. A prospective animal-based study was done by Holmes *et al*, which aimed to evaluate the effects of GLP-1 on gastrointestinal motility and the specific pathways involved. This study is unique

Table 1 Patients' characteristics and gastric emptying results

Factor	Value	GE		P value
		Delayed GE	Normal GE	
N	384	151	233	
Age at time of GES, mean (SD)	52.2 (15.9)	52.2 (14.9)	52.2 (16.5)	0.970
Duration of GLP-1R agonist use in years, mean (SD)	1.0 (1.02)	1.23 (1.34)	0.86 (0.60)	0.260
Duration of DM, median (IQR)	8.0 (5.0, 14.0)	10.0 (5.0, 19.0)	8.0 (4.0, 10.0)	0.033
HbA1C, median (IQR)	8.1 (6.8, 9.7)	8.1 (6.9, 9.7)	8.1 (6.7, 9.7)	0.960
Gender				0.071
Male	97 (25.26%)	46 (30.46%)	51 (21.89%)	
Female	287 (74.74%)	105 (69.54%)	182 (78.11%)	
Ethnicity				0.500
Non-Hispanic	70 (18.23%)	30 (19.87%)	40 (17.17%)	
Hispanic	314 (81.77%)	121 (80.13%)	193 (82.83%)	
GES results				---
Delayed GE	151 (39.32%)	---	---	
Normal GE	233 (60.68%)	---	---	
GLP-1R agonist use				0.130
No	332 (86.68%)	126 (83.44%)	206 (88.79%)	
Yes	51 (13.32%)	25 (16.56%)	26 (11.21%)	
DM (Y/N)				<0.001
N	157 (42.55%)	45 (30.20%)	112 (50.91%)	
Y	212 (57.45%)	104 (69.80%)	108 (49.09%)	
Smoking hx				0.430
No	299 (79.95%)	116 (77.85%)	183 (81.33%)	
Yes	75 (20.05%)	33 (22.15%)	42 (18.67%)	
Alcohol use				0.630
No	356 (95.19%)	143 (95.97%)	213 (94.67%)	
Yes	18 (4.81%)	6 (4.03%)	12 (5.33%)	

DM, diabetes mellitus; GE, gastric emptying; GES, gastric emptying study; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; HbA1C, hemoglobin A1C; hx, history; N, no; Y, yes.

as it evaluated the effects of GLP-1 in vitro and in vivo. In vitro, GLP-1 resulted in depolarisation of vagal neurons which was abolished after washout. In vivo (rats), GLP-1 induced decrease in gastric motility which was vagally mediated as vagotomy resulted in loss of GLP-1 effects on gastric motility. In addition, the authors found that the specific mechanism involved in the slowing of gastric emptying was through the non-adrenergic non-cholinergic postganglionic vagal inhibition of the stomach as bethanechol infusion which acts through parasympathetic cholinergic excitatory pathway, did not negate the effects of GLP-1 on gastric tone.[6]

These effects combined lead to better glycemic control through decreased gastric emptying leading to early satiety, subsequent weight loss which increases insulin sensitivity and improvement in postprandial and fasting glucose levels. Hence, this effect was noted and was used through the development of medications targeting GLP-1 receptors, the GLP-1R agonists.

In our study, we found that the HbA1C was similar in both groups (delayed and normal GE), which suggests that the duration of DM has a greater correlation with GP rather than HbA1C levels.[7 8]

In addition, we did not find any association between GLP-1R agonists use and GP which is consistent with the literature where one explanation is tachyphylaxis. Another hypothesis is that the effect of GLP-1R agonists on gastric emptying is more pronounced in the first hour of GES rather than towards GES completion.[9 10]

Moreover, patients with DM for <10 years had a higher risk of delayed GES with GLP-1R agonists use compared with those with DM for >10 years. This was also an observation found in the literature as studies showed that GLP-1R agonists are more likely to delay gastric emptying in patients with a normal baseline GES rather than if GP is

Table 2 GLP-1R agonist administration and GES results

Factor	GLP-1R agonist administered		P value
	No	Yes	
N	332	51	
GES results			0.17
Delayed GE	126 (37.95%)	25 (49.02%)	
Normal GE	206 (62.05%)	26 (50.98%)	
Univariate model: GES outcome (delayed)			
Variables	**RR**	**95% CI**	**P value**
GLP-1R agonist use	1.298	0.84 to 1.98	0.242

GE, gastric emptying; GES, gastric emptying study; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; RR, relative risk.

Table 3 Relative risk model interpreting the association of GLP-1R agonist and GES within specific populations

	GLP-1R agonist—no		GLP-1R agonist—yes				
	GES normal	GES delayed	GES normal	GES delayed			
Variables	n1	n2	n3	n4	RR	95% CI	P value
GLP-1							
Male	47	38	4	8	1.49	0.69 to 3.19	0.304
Female	159	88	22	17	1.22	0.73 to 2.05	0.446
DM—yes	83	79	25	25	1.03	0.65 to 1.61	0.913
DM—no	111	45	1	0	–	–	–
Age ≤50 years	81	62	8	5	0.88	0.35 to 2.21	0.797
Age >50 years	125	64	18	20	1.56	0.94 to 2.56	0.085
Smoking—yes	37	23	5	10	1.74	0.83 to 3.65	0.144
Smoking—no	162	101	21	15	1.08	0.63 to 1.86	0.768
HbA1C <8%	35	41	7	7	0.93	0.42 to 2.06	0.853
HbA1C ≥8%	37	36	15	16	1.05	0.58 to 1.89	0.880
Duration of DM <10 years	43	25	5	13	1.96	1.01 to 3.84	0.048
Duration of DM ≥10 years	22	35	9	10	0.86	0.42 to 1.73	0.667

DM, diabetes mellitus; GES, gastric emptying study; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; HbA1C, hemoglobin A1C; RR, relative risk.

present, which is usually in patient with longer duration of diabetes.[11 12]

Diabetes prevalence has been on the rise globally primarily due to the obesity pandemic and has a worldwide prevalence of approximately 9.3%, of which 95% are type II diabetics.[2 3]

GP is a potential long-term complication of DM type I or type II and its incidence correlates with the number of years the patient has been diabetic. GP was found to be more prevalent in patients with DM for >10 years.[13]

The mechanism of GP in patients with diabetes is heterogenous, however several mechanisms have been proposed in the literature. The Gastroparesis Clinical Research Consortium proposed dysfunction of the 'pacemaker' cells of the gut (interstitial cells of cajal), pyloric sphincter dysfunction, neurotransmission defects, specifically that of neuronal nitric oxide synthase and immune dysfunction with cellular inflammation as possible mechanisms of GP.[14]

Currently, there are no studies evaluating the prevalence of GLP-1R agonist use among diabetics. Endocrinology guidelines have shifted their focus towards GLP-1R agonists and sodium-glucose co-transporter 2 (SGLT-2) inhibitors and recommend earlier initiation of these medications, especially in those with cardiovascular disease.[15]

Due to the pharmacological properties of GLP-1R agonists, much debate has risen regarding the effects of GLP-1R agonists on gastric emptying. Several studies have attempted to study this association and conflicting findings were reported. A prospective study by Little *et al* evaluated the use of high-dose and low-dose intravenous GLP-1 in healthy patients without diabetes and demonstrated delayed gastric emptying in 50% of the participants at both low and high doses.[16] A similar prospective study by Meier *et al* evaluated the effects of IV GLP-1 on GES in type II diabetics with a baseline normal gastric emptying. Gastric emptying was found to be delayed after GLP-1 administration in a dose-dependent manner. It is important to note that the study used breath $^{13}CO_2$ excretion rates to evaluate gastric emptying.[17] The aforementioned studies evaluated the effects of short-term GLP-1 use and do not look into

Table 4 Differences among different GLP-1R agonists and doses on GE

		GE		
Factor	Value	Delayed GE	Normal GE	P value
Dulaglutide				1.000
Dulaglutide 0.75 mg/week	17 (42.50%)	8 (42.11%)	9 (42.86%)	
Dulaglutide 1.5 mg/week	23 (57.50%)	11 (57.89%)	12 (57.14%)	
Liraglutide				1.000
Liraglutide 1.2 mg/day	4 (57.14%)	2 (50.00%)	2 (66.67%)	
Liraglutide 1.8 mg/day	3 (42.86%)	2 (50.00%)	1 (33.33%)	
Semaglutide				0.330
Semaglutide 0.75 mg/week	1 (33.33%)	0 (0.00%)	1 (100.00%)	
Semaglutide 1 mg/week	2 (66.67%)	2 (100.00%)	0 (0.00%)	
Dulaglutide versus liraglutide				0.700
Dulaglutide	40 (85.11%)	19 (82.61%)	21 (87.50%)	
Liraglutide	7 (14.89%)	4 (17.39%)	3 (12.50%)	

GE, gastric emptying; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor.

the potential resolution of GP after continued use, which is a theory that was proposed in other studies. A prospective study by van Can *et al* divided patients into groups receiving daily liraglutide at different doses for a total of 5 weeks. The study found that early gastric emptying (at 1 hour) between liraglutide versus placebo was significantly delayed. However, at 5 hours, there was no difference in GES between all groups.[9] In addition, a prospective study by Nauck *et al* showed that GLP-1-induced delayed gastric emptying was related to the duration of GLP-1 administration and that tachyphylaxis occurs with continued use, leading to attenuation of the effects on gastric emptying.[10] Moreover, studies have evaluated whether the duration of GLP-1 dose administration had similar impacts on gastric emptying. A randomized double-blinded clinical trial by Umapathysivam *et al* evaluated the impact of prolonged GLP-1 infusion and intermittent GLP-1 administration on gastric emptying. The study demonstrated that both groups had delayed gastric emptying compared with placebo, however, patients in the prolonged infusion group had waning effects on gastric emptying even though GES remained delayed.[18] This study also demonstrates the possibility of tachyphylaxis and the potential that long-acting GLP-1R agonists are more likely to exhibit similar effects due to a longer half-life. It is important to note that all the aforementioned studies were carried out on participants with normal gastric emptying at baseline.

Limited studies are available evaluating the use of GLP-1R agonists in patients with pre-existing GP. A study conducted in Germany by Beti *et al* is one of the few studies evaluating the effect of GLP-1R agonists on patients with diabetes with and without pre-existing diabetic GP. In the study, 75% of the participants with normal gastric emptying prior to GLP-1R agonist developed delayed gastric emptying, fulfilling GP diagnosis. In contrast, 30% of participants with pre-existing diabetic GP had worsening GP while the remaining 70% had no change or minimal improvement after GLP-1R agonist initiation. This study however did not use gastric scintigraphy to evaluate gastric emptying but rather used the breath $^{13}CO_2$ excretion rates.[11] Furthermore, a study by Linnejberg *et al* evaluated the effects of exenatide on gastric emptying in type 2 diabetics. The study showed a dose-dependent delay in gastric emptying in the exenatide groups. Moreover, patients with slower baseline GES had less change in GES following exenatide administration.[12] This can be explained in part due to the mechanism of GLP-1R agonists effect on gastric emptying. Although not fully understood, GLP-1 is thought to mediate its effects on gastric emptying through the autonomic nervous system (vagal nerve), hence, in patients with diabetic GP, autonomic dysfunction has already occurred rendering the effects of GLP-1 on the autonomic nervous system to be diminished.[19] This theory aligns with and could explain the findings of the study by Beti *et al*.[11] Due to the effects of GLP-1R agonists on gastric emptying, pharmaceutical companies and researchers are looking into a possible alternative with similar outcomes and without the possibility of delayed gastric emptying. Glucose-dependent insulinotropic polypeptide (GIP) is another incretin that results in glucose-dependent insulin release. A novel dual GIP and GLP-1R agonist—tirzepatide has been studied as part of a randomized double-blinded clinical trial to compare the effects of tirzepatide with a traditional GLP-1R agonist on gastric emptying. The study showed similar effects on gastric emptying in both groups. In addition, the effect on gastric emptying was attenuated following multiple doses of either of the medications studied, likely secondary to the possibility of tachyphylaxis which has been observed in prior studies.[20] Semaglutide is a GLP-1R agonist which has been recently approved by the Food and Drug Administration for weight loss in individuals with and without diabetes. This was brought about after a double-blinded clinical trial showed a 14.9% change in body weight in participants on semaglutide vs 2.9% in those on placebo. The most reported side effects were nausea and vomiting; however, these were found to be transient and resolved with continued use which suggests the possibility of tachyphylaxis. The study excluded patients with diabetes and no GES was performed before or during the study to assess for possible iatrogenic GP or the presence of tachyphylaxis.[21]

CONCLUSION

This study evaluates the effect and the association between GLP-1R agonists and GP. Overall, there was no statistically significant association between GLP-1R agonist use and GP, which is consistent with the current literature. However, GLP-1R agonist use was associated with delayed GES in patients with diabetes for <10 years. We observed that the duration of DM is a stronger predictor of delayed GES compared with HbA1C levels. Our study was limited inherently by its retrospective design. Given the approval of GLP-1R agonists in patients without diabetes for weight loss, its effects on GES should be evaluated prospectively with baseline GES for accurate assessment. This is of the utmost importance, as patients without diabetes with normal baseline GES could be more susceptible to GLP-1R agonist-induced delayed GES (iatrogenic GP).

Acknowledgements The authors would like to thank the Department of Nuclear Medicine, Texas Tech University Health Sciences Center El Paso.

Contributors Concept and design of the work: MAK, TQD, GG, AD, RMcC. Analysis: LA, AKD. Drafting the paper: MAK, TQD, GG, LA. Revising the paper: MAK, RMcC, AD. Guarantor: RMcC.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests RMcC is the editor in chief of the *Journal of Investigative Medicine* and is a coauthor on this manuscript. AKD is an Editorial Board member.

Patient consent for publication Not applicable.

Ethics approval The Texas Tech University Health Sciences Center El Paso (IRB Study ID number: E21110IRB) exempted this study due to its retrospective nature. Patient data were anonymized. No risk to patients involved.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iDs
M Ammar Kalas http://orcid.org/0000-0002-6230-9172
Alok Kumar Dwivedi http://orcid.org/0000-0003-4574-1761

REFERENCES

1 Camilleri M, Parkman HP, Shafi MA, *et al*. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013;108:18–37.
2 Gupta V. Glucagon-Like peptide-1 analogues: an overview. *Indian J Endocrinol Metab* 2013;17:413–21.

3 Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. *Ther Adv Endocrinol Metab* 2021;12:2042018821997320.
4 Abell TL, Camilleri M, Donohoe K, *et al*. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. *Am J Gastroenterol* 2008;103:753–63.
5 Kastin AJ, Akerstrom V, Pan W. Interactions of glucagon-like peptide-1 (GLP-1) with the blood-brain barrier. *J Mol Neurosci* 2002;18:07–13.
6 Holmes GM, Browning KN, Tong M, *et al*. Vagally mediated effects of glucagon-like peptide 1: in vitro and in vivo gastric actions. *J Physiol* 2009;587:4749–59.
7 Hyett B, Martinez FJ, Gill BM, *et al*. Delayed radionucleotide gastric emptying studies predict morbidity in diabetics with symptoms of gastroparesis. *Gastroenterology* 2009;137:445–52.
8 Chang J, Russo A, Bound M, *et al*. A 25-year longitudinal evaluation of gastric emptying in diabetes. *Diabetes Care* 2012;35:2594–6.
9 van Can J, Sloth B, Jensen CB, *et al*. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. *Int J Obes* 2014;38:784–93.
10 Nauck MA, Kemmeries G, Holst JJ, *et al*. Rapid tachyphylaxis of the glucagon-like peptide 1-induced deceleration of gastric emptying in humans. *Diabetes* 2011;60:1561–5.
11 Beti C, Stratmann B, Bokman G, *et al*. Exenatide delays gastric emptying in patients with type 2 diabetes mellitus but not in those with gastroparetic conditions. *Horm Metab Res* 2019;51:267–73.
12 Linnebjerg H, Park S, Kothare PA, *et al*. Effect of exenatide on gastric emptying and relationship to postprandial glycemia in type 2 diabetes. *Regul Pept* 2008;151:123–9.
13 Shen S, Xu J, Lamm V, *et al*. Diabetic gastroparesis and nondiabetic gastroparesis. *Gastrointest Endosc Clin N Am* 2019;29:15–25.
14 Marathe CS, Rayner CK, Jones KL, *et al*. Relationships between gastric emptying, postprandial glycemia, and incretin hormones. *Diabetes Care* 2013;36:1396–405.
15 American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2021. *Diabetes Care* 2021;44:S111–24.
16 Little TJ, Pilichiewicz AN, Russo A, *et al*. Effects of intravenous glucagon-like peptide-1 on gastric emptying and intragastric distribution in healthy subjects: relationships with postprandial glycemic and insulinemic responses. *J Clin Endocrinol Metab* 2006;91:1916–23.
17 Meier JJ, Gallwitz B, Salmen S, *et al*. Normalization of glucose concentrations and deceleration of gastric emptying after solid meals during intravenous glucagon-like peptide 1 in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2003;88:2719–25.
18 Umapathysivam MM, Lee MY, Jones KL, *et al*. Comparative effects of prolonged and intermittent stimulation of the glucagon-like peptide 1 receptor on gastric emptying and glycemia. *Diabetes* 2014;63:785–90.
19 Delgado-Aros S, Vella A, Camilleri M, *et al*. Effects of glucagon-like peptide-1 and feeding on gastric volumes in diabetes mellitus with cardio-vagal dysfunction. *Neurogastroenterol Motil* 2003;15:435–43.
20 Urva S, Coskun T, Loghin C, *et al*. The novel dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide transiently delays gastric emptying similarly to selective long-acting GLP-1 receptor agonists. *Diabetes Obes Metab* 2020;22:1886–91.
21 Wilding JPH, Batterham RL, Calanna S, *et al*. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021;384:989–1002.