Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Clinical Pharmacokinetics of Semaglutide: A Systematic Review

Xi-Ding Yang[1,2], Yong-Yu Yang[1,3]

[1]Department of Pharmacy, The Second Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China; [2]Phase I Clinical Trial Center, The Second Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China; [3]Hunan Provincial Engineering Research Central of Translational Medical and Innovative Drug, The Second Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China

Correspondence: Yong-Yu Yang, Department of Pharmacy, The Second Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China, Email yongyuyang@csu.edu.cn

Purpose: The aim of this review was to provide all the pharmacokinetic data for semaglutide in humans concerning its pharmacokinetics after subcutaneously and oral applications in healthy and diseased populations, to provide recommendations for clinical use.

Methodology: The PubMed and Embase databases were searched to screen studies associated with the pharmacokinetics of semaglutide. The pharmacokinetic parameters included area under the curve plasma concentrations (AUC), maximal plasma concentration (C_{max}), time to C_{max}, half-life ($t_{1/2}$), and clearance. The systematic literature search retrieved 17 articles including data on pharmacokinetic profiles after subcutaneously and oral applications of semaglutide, and at least one of the above pharmacokinetic parameter was reported in all included studies.

Results: Semaglutide has a predictable pharmacokinetic profile with a long $t_{1/2}$ that allows for once-weekly subcutaneous administration. The AUC and C_{max} of both oral and subcutaneous semaglutide increased with dose. Food and various dosing conditions including water volume and dosing schedules can affect the oral semaglutide exposure. There are limited drug–drug interactions and no dosing adjustments in patients with upper gastrointestinal disease, renal impairment or hepatic impairment. Body weight may affect semaglutide exposure, but further studies are needed to confirm this.

Conclusion: This review encompasses all the pharmacokinetic data for subcutaneous and oral semaglutide in both healthy and diseased participants. The existing pharmacokinetic data can assist in developing and evaluating pharmacokinetic models of semaglutide and will help clinicians predict semaglutide dosages. In addition, it can also help optimize future clinical trials.

Keywords: Pharmacokinetics, semaglutide, curve plasma concentrations, type 2 diabetes, obesity, glucagon-like peptide-1, drug–drug interaction

Introduction

Type 2 diabetes (T2D) and obesity are major public health burdens with an important economic impact and their incidences have increased in the past decades.[1,2] It is estimated that approximately 537 million adults around the world affected with diabetes in 2021,[3] and this number is expected to increase to over 700 million by 2045.[4] T2D is the most prevalent type of diabetes, accounting for about 90% of the population suffering from diabetes.[5,6] Patients with T2D are at high risk for long-term macrovascular and microvascular complications including cardiovascular diseases.[7] The treatment of T2D has greatly improved recent years, but it is necessary to explore new therapeutic strategies. Obesity as a major global health problem is an important risk factor for T2D. Obesity is also associated with various other chronic diseases including hypertension and cardiovascular disease.[8] According to the World Health Organization, more than 1 billion individuals worldwide are overweight, and about 300 million of whom are clinically obese.[9] Obesity is also associated with many comorbidities, so new efficacy treatment strategies for obesity are urgently needed too.

Since 2005, there have been several glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs), including lixisenatide, exenatide, albiglutide, dulaglutide and liraglutide, recommended for the treatment of T2D approved by the US Food and Drug Administration (FDA).[10–15] Liraglutide was also introduced for the treatment of obesity.[16] GLP-1RAs

Received: 26 March 2024
Accepted: 18 June 2024
Published: 25 June 2024

are a class of recognized hypoglycemic agents, which can induce insulin secretion and suppress glucagon secretion via the stimulation of GLP-1 receptors.[17–19] Semaglutide is a human GLP-1 analog, studied for the management of T2D and obesity. To improve glycemic control, semaglutide induces glucose-mediated insulin secretion stimulation, decreases glucagon secretion, and decreases hepatic glucose output. To promote weight loss, semaglutide delays gastric emptying, increases satiety, decreases appetite and energy intake.[20] Semaglutide demonstrated promising efficacy in glycemic control and weight loss compared with placebo and active comparators such as insulin glargine, sitagliptin, dulaglutide and exenatide sustained-release.[21–26] In addition, semaglutide significantly improved cardiovascular outcomes.[27] It was approved for the treatment of T2D by FDA in 2017 (Ozempic) and 2019 (Oral semaglutide, Rybelsus), and for obesity management by FDA in 2021 (Wegovy).

Semaglutide is currently the only GLP-1RA that is available in both a subcutaneously injectable and oral formulation. Semaglutide is structurally 94% homologous to native human GLP-1, with specific modifications at positions 8, 26, and 34 to prolong its half-life ($t_{1/2}$). It is allowed for once-weekly subcutaneously administration due to the long $t_{1/2}$.[20] The prolonged exposure of semaglutide is primarily due to slow elimination and, to a lesser extent, delayed absorption,[28] which is consistent with the observation that the large majority of semaglutide molecules are bound to albumin.[29] The metabolism of semaglutide is not confined to specific organs. It is metabolised across tissues through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty di-acid side chain, and that degradation metabolites are excreted via urine and faeces.[28] Semaglutide is administered subcutaneously once-weekly at doses of 0.5 and 1.0 mg, with an initial dose of 0.25 mg/week for the first 4 weeks. Oral semaglutide tablets (Rybelsus) is a modified form of semaglutide with the addition of a carrier sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC).[30,31] Due to the degradation of peptide-based drugs by proteolytic enzymes, the low permeability of intestinal epithelium, and the low pH of the gastrointestinal tract, oral administration of semaglutide is challenging. The absorption enhancer SNAC can temporarily open the tight junctions between the epithelium, promoting the transport and entry of semaglutide into the systemic circulation. Oral semaglutide is administered once-daily at doses of 7 and 14 mg, with an initial dose of 3 mg once-daily for the first 30 days.

In recent years, a variety of studies have been conducted on the pharmacokinetics of semaglutide, including pharmacokinetics in healthy, pharmacokinetics in diseased, and the effects of drug–drug interactions and drug–food interactions on the pharmacokinetics of semaglutide in humans. To date, there is no systematic review that encompasses all the clinical pharmacokinetic parameters of both subcutaneous and oral semaglutide. In this review, we summarized and presented all the pharmacokinetic data for semaglutide in humans concerning its pharmacokinetics after subcutaneously and oral applications in healthy and diseased populations, to provide evidence-based recommendations for clinical use.

Methods

The current systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[32] A systematic literature search was performed for screening the articles related to the pharmacokinetics of semaglutide in PubMed and Embase databases in August 2023. The adopted strategy included following search algorithm: semaglutide AND (pharmacokinetic OR pharmacokinetics OR bioavailability). In addition, a manual snowball search was conducted in the reference lists of all the included studies.

The review included studies written in English investigating pharmacokinetic profiles after subcutaneously and oral applications of semaglutide in healthy or patients had T2D, obesity, hepatic impairment, renal impairment, or upper gastrointestinal disease. Moreover, all the articles containing food interactions, dosing condition interactions and drug interactions with semaglutide were also included to observe the change of semaglutide pharmacokinetics. The pharmacokinetic parameters included area under the curve plasma concentrations (AUC), maximal plasma concentration (C_{max}), time to C_{max} (T_{max}), $t_{1/2}$, and clearance (CL). Only those studies in which at least one of the above pharmacokinetic parameter was reported were included. Studies which did not fulfill these criteria were excluded from this review. Letters to the editor, commentaries and conference abstracts were also excluded. The relevant data were then extracted from the selected studies including the author's name, year, study population, number of subjects, age of participants, administration route, dose, frequency, and available pharmacokinetic parameters of semaglutide.

Results

Literature Search Results

The complete literature search and detail on the inclusion and exclusion criteria are described in Figure 1. The database searches yielded a total of 547 articles, 61 of which were duplicates. The remaining 486 articles were further screened according to the inclusion and exclusion criteria (Figure 1). A total of 17 articles fulfilled the eligibility criteria were finally included and 469 were excluded on the basis of animal, title, abstract, full-text access, and full-text reading.

Characteristics of Included Studies

The characteristics of the included studies are mentioned in Table 1, including the author's name, year, study population, number of subjects, age of participants, administration route, dose, and frequency. The review included eight studies administered semaglutide by subcutaneous injection in doses ranging from 0.5 to 2.4 mg, nine studies administered semaglutide by oral route in doses ranging from 2 to 40 mg. Eight studies included healthy volunteers. Eight studies included diseased participants with T2D, obesity, hepatic impairment, renal impairment, or upper gastrointestinal disease. One study included both healthy volunteers and diseased participants with T2D. Two studies were related to drug–drug interactions, 2 were related to drug–food interactions, and 3 were relevant to drug-dosing condition interactions of semaglutide.

Quality of Included Studies

Critical Appraisal Skills Programme (CASP) scoring system was employed for quality assessment of the 17 included articles.[48,49] CASP scoring consists of 11 redesigned questions that evaluate the validity of the article, where a score of >6 indicates high quality, 4–6 moderate, and <4 means low quality. A total of 15 articles were of high quality, and 2 articles were of moderate quality. The summary of quality assessment is presented in Supplementary Table S1.

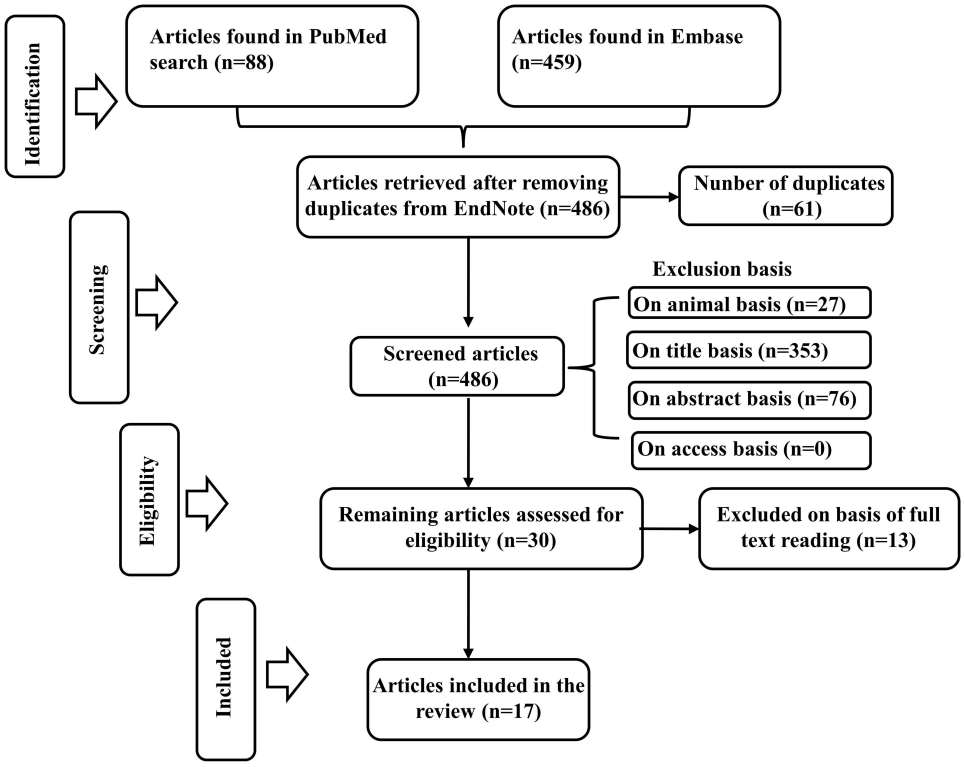

Figure 1 PRISMA flow chart diagram.

Table 1 Characteristics of Included Studies

No.	Study	Population (Ethnicity)	No. of Subjects	Age (Years)	Dosage Form	Dose	Frequency
Subcutaneous Injections							
1	Jensen et al (2017)[28]	Healthy (NA)	7	48–64	Subcutaneous injection	0.5 mg	Once
2	Ikushima et al (2018)[33]	Healthy (Japanese)	8	34.1 (23–44)	Subcutaneous injection	0.25 mg (4 weeks) 0.5 mg (9 weeks)	Once-weekly
		Healthy (Japanese)	8	39.1 (29–47)	Subcutaneous injection	0.25 mg (4 weeks) 0.5 mg (4 weeks) 1.0 mg (5 weeks)	Once-weekly
		Healthy (Japanese)	6	41.4 (27–51)	Subcutaneous injection	Placebo (13 weeks)	Once-weekly
		Healthy (Caucasian)	8	33.4 (26–52)	Subcutaneous injection	0.25 mg (4 weeks) 0.5 mg (9 weeks)	Once-weekly
		Healthy (Caucasian)	8	35.0 (25–51)	Subcutaneous injection	0.25 mg (4 weeks) 0.5 mg (4 weeks) 1.0 mg (5 weeks)	Once-weekly
		Healthy (Caucasian)	6	36.5 (26–49)	Subcutaneous injection	Placebo (13 weeks)	Once-weekly
3	Shi et al (2021)[34]	Healthy (Chinese)	12	33.6 (23–44)	Subcutaneous injection	0.25 mg (4 weeks)→ 0.5 mg (9 weeks)	Once-weekly
		Healthy (Chinese)	12	33.3 (22–44)	Subcutaneous injection	0.25 mg (4 weeks)→ 0.5 mg (4 weeks)→ 1.0 mg (5 weeks)	Once-weekly
		Healthy (Chinese)	12	33.3 (27–52)	Subcutaneous injection	Placebo (13 weeks)	Once-weekly
4	Kapitza et al (2015)[35]	Postmenopausal women with T2D (NA)	43	62.2±6	Subcutaneous injection	0.25 mg (4 weeks)→ 0.5 mg (4 weeks)→ 1.0 mg (5 weeks)	Once-weekly
5	Blundell et al (2017)[36]	Subjects with obesity	30	42 (21–70)	Subcutaneous injection	0.25 mg (4 weeks)→ 0.5 mg (4 weeks)→ 1.0 mg (5 weeks)	Once-weekly

6	Marbury et al (2017)[37]	Healthy (NA)	14	54.6±9.1	Subcutaneous injection	0.5 mg	Once
		Mild RI (NA)	11	62.9±8.0	Subcutaneous injection	0.5 mg	Once
		Moderate RI (NA)	11	66.5±6.6	Subcutaneous injection	0.5 mg	Once
		Severe RI (NA)	10	62.8±9.1	Subcutaneous injection	0.5 mg	Once
		ESRD (NA)	10	48.2±7.2	Subcutaneous injection	0.5 mg	Once
7	Jensen et al (2018)[29]	Normal hepatic function (NA)	19	52 (34–67)	Subcutaneous injection	0.5 mg	Once
		Mild HI (NA)	8	52 (34–64)	Subcutaneous injection	0.5 mg	Once
		Moderate HI (NA)	10	56 (35–67)	Subcutaneous injection	0.5 mg	Once
		Severe HI (NA)	7	55 (45–61)	Subcutaneous injection	0.5 mg	Once
8	Enebo et al (2021)[38]	Overweight participants who are otherwise healthy (Hispanic or Latino or other)	96	40.6±9.2	Subcutaneous injection	Cagrilintide (0.16–4.5 mg) + semaglutide 2.4 mg	Once-weekly
Oral administration							
9	Granhall et al (2019)[39]	Healthy (White/Black or African American/ Asian/ Other)	135	30.1±8.0	Tab. (Oral administration)	2–20 mg Placebo	Once
		Healthy (White/Black or African American/ Other)	84	44.7±11.6	Tab. (Oral administration)	20 or 40 mg Placebo (10 weeks)	Once-daily
		Type 2 diabetic (White/Black or African American)	23	54.5±8.3	Tab. (Oral administration)	40 mg Placebo (10 weeks)	Once-daily
10	Bækdal et al (2021a)[40]	Healthy (NA)	26	38±11	Tab. (Oral administration)	10 mg with 50 mL water 10 mg with 240 mL water	Twice (2-period crossover trial)
11	Bækdal et al (2021b)[41]	Healthy (White/Black or African American/ Other)	78	55.1±13.9	Tab. (Oral administration) Food-effect trial: fasting/fed/ reference	Semaglutide 5 mg (5 days) → 10 mg (5 days)	Once-daily
		Healthy (White/Black or African American/ Other)	158	40.5±9.7	Tab. (Oral administration) Dosing conditions trial: with 50 or 120 mL water, and 15–120 min post-dose fast	10 mg (10 days)	Once-daily

(*Continued*)

https://doi.org/10.2147/DDDT.S470826

Table 1 (Continued).

No.	Study	Population (Ethnicity)	No. of Subjects	Age (Years)	Dosage Form	Dose	Frequency
12	Hauge et al (2021)[42]	Healthy (NA)	45	36±8	Tab. (Oral administration)	Semaglutide 14 mg (5 days); Semaglutide 14 mg + five placebo tablets (5 days)	Once-daily
13	van Hout et al (2023)[43]	Healthy (Hispanic or Latino or Other)	156	40±12	Tab. (Oral administration)	3 mg (5 days) → 7 mg (5 days)	Once-daily
14	Bækdal et al (2018a)[44]	Normal hepatic function (NA)	24	49±11	Tab. (Oral administration)	5 mg (5 days) → 10 mg (5 days)	Once-daily
		Mild HI (NA)	12	52±10	Tab. (Oral administration)	5 mg (5 days) → 10 mg (5 days)	Once-daily
		Moderate HI (NA)	12	54±10	Tab. (Oral administration)	5 mg (5 days) → 10 mg (5 days)	Once-daily
		Severe HI (NA)	8	52±8	Tab. (Oral administration)	5 mg (5 days) → 10 mg (5 days)	Once-daily
15	Granhall et al (2018)[45]	Normal renal function (NA)	24	52±8	Tab. (Oral administration)	5 mg (5 days) → 10 mg (5 days)	Once-daily
		Mild RI (NA)	12	57±13	Tab. (Oral administration)	5 mg (5 days) → 10 mg (5 days)	Once-daily
		Moderate RI (NA)	12	59±11	Tab. (Oral administration)	5 mg (5 days) → 10 mg (5 days)	Once-daily
		Severe RI (NA)	12	57±12	Tab. (Oral administration)	5 mg (5 days) → 10 mg (5 days)	Once-daily
		ESRD (NA)	11	54±13	Tab. (Oral administration)	5 mg (5 days) → 10 mg (5 days)	Once-daily
16	Meier et al (2022)[46]	Type 2 diabetic with upper gastrointestinal disease (All White)	36	62±8	Tab. (Oral administration)	3 mg (5 days) → 7 mg (5 days)	Once-daily
		Type 2 diabetic without upper gastrointestinal disease (18 White and 1 Black or African American)	19	58±12	Tab. (Oral administration)	3 mg (5 days) → 7 mg (5 days)	Once-daily
17	Bækdal et al (2018b)[47]	Healthy (NA)	28	52±13	Tab. (Oral administration)	5 mg (5 days) → 10 mg (5 days)	Once-daily
			26	59±7	Tab. + gastro-resistant capsules (Oral administration)	semaglutide 5 mg + omeprazole 40 mg (5 days) → semaglutide 10 mg + omeprazole 40 mg (5 days)	Once-daily

Abbreviation: NA, not available.

Subcutaneous Route of Semaglutide

Eight pharmacokinetic studies of semaglutide administered subcutaneously including single dose pharmacokinetic study and steady-state pharmacokinetic study after multiple administrations. We summarized the above pharmacokinetic studies of semaglutide in healthy and diseased participants. Among all the included studies, eight subcutaneous studies were conducted in different populations, of which three studies were conducted in healthy participants, five in diseased participants. Four studied the single-dose pharmacokinetics and five studied the steady-state pharmacokinetics of semaglutide (One studied both single-dose and steady-state pharmacokinetics). In addition, one of these studies evaluated the effect of drug–drug interactions on the pharmacokinetics of subcutaneous semaglutide. AUC, C_{max}, and T_{max} were the main pharmacokinetic parameters mentioned in all studies whereas parameters like $t_{1/2}$ and CL/F were present in some studies, as mentioned in Table 2.

Studies in Healthy Participants

Out of a total of 17 studies, three subcutaneous studies were conducted in healthy individuals. Subcutaneous administration of one-time semaglutide 0.25 mg or 0.5 mg reached C_{max} in 42 h and 56 h, respectively.[28,34] A dose-dependent increase in AUC, and C_{max} was found in included single-dose studies. Steady-state pharmacokinetics of semaglutide was investigated in different healthy population including Caucasian, Japanese, and Chinese. The $AUC_{0-168,\ SS}$ and $C_{max,SS}$ of semaglutide were similar between Caucasian and Japanese.[33] Exposure in Chinese subjects was slightly higher than that observed in Caucasian and Japanese, however, after adjusting for differences in body weight, exposure in Chinese was similar to exposure seen in Caucasian and Japanese.[34] The exposure of semaglutide 1.0 mg appeared to be approximately double that of semaglutide 0.5 mg, while clearance and distribution appeared similar for both doses in all included steady-state pharmacokinetic studies. T_{max} in steady-state pharmacokinetic studies was similar among the groups (range 30–36 h). $T_{1/2}$ value of semaglutide in all three subcutaneous studies was in the range of 145–168 h (approximately 1 week). The other parameters are shown in Table 2.

Studies in Diseased Participants

Among eight included subcutaneous studies, two steady-state pharmacokinetics of semaglutide 1.0 mg was respectively studied in postmenopausal women with T2D[35] and obese subjects.[36] Exposure of semaglutide in both postmenopausal women with T2D and obese subjects was obviously lower than that in healthy subjects.[35,36] The mean $AUC_{0-168h,\ ss}$ and $C_{max,\ ss}$ were respectively 4602 nmol·h /L and 33.8 nmol/L in postmenopausal women with T2D, 4467 nmol·h /L and 32.0 nmol/L in obese subjects, while mean $AUC_{0-168h,\ ss}$ and $C_{max,\ ss}$ value in healthy subjects were in the range of 7449–7961 nmol·h /L and 50.6–55.9 nmol/L, respectively. This is most likely due to differences in body weight of the subjects. The average body weight of the included postmenopausal women with T2D was 101.3 kg,[35] while the weight of the healthy subjects was within the normal range. Pharmacokinetics in people with hepatic impairment[29] and renal impairment[37] after a single, subcutaneous dose of 0.5 mg semaglutide were also conducted. Semaglutide exposure did not appear to be affected by hepatic and renal impairment, suggesting that dose adjustment may not be warranted for patients with hepatic or renal impairment. The t_{max} varied across the hepatic impairment (range 53.6–77.8 h) and renal impairment groups (range 24–51 h); mean $t_{1/2}$ in all hepatic impairment groups was comparable; mean $t_{1/2}$ was longer in subjects with severe renal impairment (221 h) and those with end-stage renal disease (ESRD) (243 h) than in subjects with mild and moderate renal impairment or normal renal function.

Drug–Drug Interactions

Only one study reported the effect of other drug on pharmacokinetic parameters of subcutaneous semaglutide.[38] Ninety-six overweight participants who were otherwise healthy were randomly assigned to cagrilintide (0.16–4.5 mg) or placebo, in combination with subcutaneous semaglutide 2.4 mg. Semaglutide exposure and elimination were similar across treatment groups. $AUC_{0-168\ h}$ ranged from 12,757 to 15305 nmol·h /L, and C_{max} ranged from 96.4 to 120 nmol/L. Semaglutide 2.4 mg had a $t_{1/2}$ of 145–165 h, with a median t_{max} of 12–24 h. Cagrilintide dose did not affect semaglutide exposure and elimination.[38]

https://doi.org/10.2147/DDDT.S470826 DovePress

Table 2 Studies of Semaglutide with Subcutaneous Route

No.	Study	Plasma Pharmacokinetic Parameters						
		Population	Administered Dose And Dosage Form	AUC (nmol h /L)	C_{max} (nmol/L)	$T_{1/2}$ (h)	T_{max} (h)	CL/F (L/h)
1	Jensen et al (2017)[28]	Healthy (NA)	Single dose 0.5 mg	$AUC_{0\text{-}inf}$: 3123.4±12.0	10.9±18.2	168.3±6.3	56	0.039±12.021
2	Ikushima et al (2018)[33]	Healthy (Japanese)	Steady-state 0.5 mg	$AUC_{0\text{-}168h}$: 3583±17.8	25.1±17.8	145±8.0	30 (12–72)	0.034±17.8
		Healthy (Japanese)	Steady-state 1.0 mg	$AUC_{0\text{-}168h}$: 7449±12.2	51.6±11.1	163±10.9	36 (18–96)	0.033±12.2
		Healthy (Caucasian)	Steady-state 0.5 mg	$AUC_{0\text{-}168h}$: 3371±2.4	23.7±7.5	159±9.0	36 (24–72)	0.036±2.4
		Healthy (Caucasian)	Steady-state 1.0 mg	$AUC_{0\text{-}168h}$: 7490±17.9	50.6±17.5	167±13.2	30 (24–72)	0.032±17.9
3	Shi et al (2021)[34]	Healthy (Chinese)	Single dose 0.25 mg	$AUC_{0\text{-}168h}$: 918	6.9	NA	36 (24–96)	NA
			Steady-state 0.5 mg	$AUC_{0\text{-}168h}$: 4000	28.8	156	36 (30–42)	0.030
		Healthy (Chinese)	Single dose 0.25 mg	$AUC_{0\text{-}168h}$: 937	7.0	NA	42 (24–120)	NA
			Steady-state 1.0 mg	$AUC_{0\text{-}168h}$: 7961	55.9	159	30 (12–96)	0.031
4	Kapitza et al (2015)[35]	Postmenopausal women with T2D	Steady-state 1.0 mg	$AUC_{0\text{–}168h}$: 4602	33.8	165	36 (12.0–167.2)	NA
5	Blundell et al (2017)[36]	Obese subjects	Steady-state 1.0 mg	$AUC_{0\text{-}168h}$: 4467	32.0	NA	33.2	NA
6	Marbury et al (2017)[37]	Normal	Single dose 0.5 mg	$AUC_{0\text{-}inf}$: 2600±27	10.3±35	183±15	24 (8–66)	0.047±27
		Mild RI	Single dose 0.5 mg	$AUC_{0\text{-}inf}$: 2615±19	9.8±22	169±14	35 (14–96)	CL/F:0.046±19 L/h
		Moderate RI	Single dose 0.5 mg	$AUC_{0\text{-}inf}$: 2999±20	9.0±44	201±14	24 (14–96)	CL/F:0.041±20 L/h
		Severe RI	Single dose 0.5 mg	$AUC_{0\text{-}inf}$: 3179±22	9.8±37	221±26	41 (16–96)	CL/F:0.038±22 L/h
		ESRD	Single dose 0.5 mg	$AUC_{0\text{-}inf}$: 2567±18	7.4±22	243±19	51 (28–72)	CL/F:0.047±18 L/h
7	Jensen et al (2018)[29]	Normal hepatic function	Single dose 0.5 mg	$AUC_{0\text{-}inf}$: 3026 $AUC_{0\text{-}last}$: 2731	9.5	150	65.8 (30.0–167.5)	NA
		Mild HI	Single dose 0.5 mg	$AUC_{0\text{-}inf}$: 2872 $AUC_{0\text{-}last}$: 2621	9.3	155	65.9 (54.4–119.8)	NA
		Moderate HI	Single dose 0.5 mg	$AUC_{0\text{-}inf}$: 3080 $AUC_{0\text{-}last}$: 2807	9.7	151	77.8 (23.8–144.1)	NA
		Severe HI	Single dose 0.5 mg	$AUC_{0\text{-}inf}$: 2937 $AUC_{0\text{-}last}$: 2539	10.9	163	53.6 (29.9–144.9)	NA
8	Enebo et al (2021)[38]	Overweight participants who are otherwise healthy	Steady-state 2.4 mg + cagrilintide (0.16–4.5 mg)	$AUC_{0\text{–}168h}$: 12,757–15,305	96.4–120	145–165	12–24	NA

Abbreviation: NA, not available.

Oral Route of Semaglutide

The degradation of peptide-based drugs by proteolytic enzymes, the low permeability of intestinal epithelium and its mucus layer and the low pH of the gastrointestinal tract, are the major barriers preventing the oral administration of GLP-1RAs. An oral option would overcome the potential fear of injection among patients. These challenges cannot be addressed by increasing the administered dose, as this could lead to a parallel increase in the incidence of adverse reactions. Semaglutide is the first developed oral GLP-1RA by combining it with the absorption enhancer SNAC, which is a small-chain fatty acid that facilitates the absorption of semaglutide by acting transcellularly on the gastric mucosa through local pH elevation.[30,31] Among all the included studies, nine oral studies were conducted in different populations, of which six studies were conducted in healthy participants, four in diseased participants (one in both healthy and diseased participants). Two studied the single-dose pharmacokinetics and eight studied the steady-state pharmacokinetics of semaglutide (One studied both single-dose and steady-state pharmacokinetics). In addition, four of these studies evaluated the effect of food and various dosing conditions and one evaluated drug–drug interactions on the pharmacokinetics of oral semaglutide. Table 3 provides pharmacokinetic Results from oral studies.

Studies in Healthy Participants

In a single-dose trial, 135 healthy subjects received oral semaglutide (2–20 mg) or placebo with 50 mL water while fasting, a high proportion of subjects with oral semaglutide treatment had no measurable semaglutide concentration in plasma (64 of 112 subjects).[39] In another single-dose, 2-period crossover trial, 26 healthy subjects received 10 mg oral semaglutide with 50 or 240 mL water while fasting, semaglutide plasma concentrations were measurable. However, C_{max} and AUC values were not provided.[40] These findings may be explained by the low bioavailability of oral semaglutide after a single dose. Nevertheless, therapeutic plasma concentrations of semaglutide are obtained at steady state in subjects treated with once-daily oral semaglutide. In a 10-week, once-daily, multiple-dose trial, semaglutide exposure at steady state was about two fold higher with oral semaglutide 40 mg versus 20 mg in healthy subjects. The $t_{1/2,\ ss}$ was comparable between two dose groups, with geometric means of 153 and 161 h in healthy subjects receiving 20 and 40 mg respectively, which is similar to semaglutide administered subcutaneously, suggesting that the elimination phase of oral semaglutide is comparable with that observed with subcutaneous administration.[39]

Drug–Food Interactions

Oral semaglutide is absorbed in the stomach, and its absorption is affected by the presence of food. Effect of food and other substances on the pharmacokinetics of oral semaglutide was conducted in healthy participants. In a food-effect trial, limited or no measurable semaglutide plasma concentration at steady-state was observed in the fed group, while all subjects in the fasting group had measurable semaglutide concentrations. $AUC_{0–24\ h}$ and C_{max} at steady-state for the fasting appeared approximately 40% greater than reference group. Median t_{max} was longer for the fasting (1.75 h) versus reference groups (1.00 h), while no obvious difference was seen for $t_{1/2}$ (160 h and 152 h, respectively) between the fasting and reference groups.[41] Besides the usual food, the consequence of other substances in the stomach on oral semaglutide pharmacokinetics should also be considered. At steady-state, semaglutide $AUC_{0\text{-}24h}$ was decreased by 34% (544 VS 360 nmol·h /L) and C_{max} was decreased by 32% (27.7 VS 18.8 nmol/L) when oral semaglutide was co-administered with five oral placebo tablets compared to oral semaglutide alone.[42] These results support dosing of oral semaglutide in the fasting state. Food and other substances in the stomach can reduce the semaglutide exposure.

Drug-Dosing Conditions Interactions

Effect of water volume and dosing schedules on the pharmacokinetics of oral semaglutide were also conducted in healthy participants. Bækdal et al published two studies mentioned effect of water volume on oral semaglutide pharmacokinetics in 2021, one is a single-dose study and another is a multiple-dose study. In the single-dose study, subjects received 10 mg oral semaglutide with 50 or 240 mL water while fasting, $AUC_{0\text{-}24h}$ and C_{max} were approximately 70% higher when dosed with 50 versus 240 mL water. Median t_{max} was 1.5 hours for both water volumes with a range of 0.5–3.0 hours for 50 mL and a range of 0.5–4.0 hours for 240 mL.[40] Their other multiple-dose study with the once-daily oral semaglutide 10 mg for 10 days found that steady-state exposure of semaglutide was comparable when the oral semaglutide tablet was

Table 3 Studies of Semaglutide with Oral Route

No.	Study	Plasma Pharmacokinetic Parameters					
		Population	**Administered Dose**	**AUC (nmol ħ /L)**	**C_{max} (nmol/L)**	**$T_{1/2}$ (h)**	**T_{max} (h)**
1	Granhall et al (2019)[39]	Healthy	Single dose 2–20 mg	NA	NA	NA	NA
		Healthy	Steady-state 20 mg	NA	NA	153	NA
		Healthy	Steady-state 40 mg	NA	NA	161	NA
		Type 2 diabetic	Steady-state 40 mg	NA	NA	158	NA
2	Bækdal et al (2021a)[40]	Healthy	Single dose 10 mg	NA	NA	NA	1.5
3	Bækdal et al (2021b)[41] Food-effect trial:	Fasting: healthy	Steady-state 10 mg	~40% greater for the fasting VS reference	~40% greater for the fasting VS reference	160	1.75 (0.50–6.02)
		Reference: healthy	Steady-state 10 mg			152	1.00 (0.50–4.00)
	Dosing conditions trial: Water volume	Healthy	Steady-state 10 mg	Comparable with 50 or 120 mL water	Comparable with 50 or 120 mL water	Comparable with 50 or 120 mL	Comparable with 50 or 120 mL
	Dosing conditions trial: post-dose fasting period	Healthy	Steady-state 10 mg	increased significantly with longer post-dose fasting	increased significantly with longer post-dose fasting	Comparable	t_{max} increased with longer post-dose fasting (median range 0.5–2.3 h).
4	Hauge et al (2021)[42]	Healthy	Steady-state 14 mg	$AUC_{0–24\ h}$: 544	27.7	NA	1.0 (0.0–11.9)
			Steady-state 14 mg + five placebo tablets	$AUC_{0–24\ h}$: 360	18.8	NA	1.0 (0.0–3.0)
5	van Hout et al (2023)[43]	Healthy	Steady-state 7 mg	NA	NA	NA	0.8–1.0
6	Bækdal (2018a)[44]	Normal	Steady-state 10 mg	$AUC_{0\text{-}24h}$: 250.3±64	13.3±62.3	156.4 ±12.1	1.0 (0.5–4.0)
		Mild HI	Steady-state 10 mg	$AUC_{0\text{-}24h}$: 221.9±78.3	11.8±82.4	142.1 ±7.6	1.0 (0.5–3.0)
		Moderate HI	Steady-state 10 mg	$AUC_{0\text{-}24h}$: 204.2±71.4	10.5±73.5	146.7 ±13.9	1.0 (1.0–3.0)
		Severe HI	Steady-state 10 mg	$AUC_{0\text{-}24h}$: 227.8±41.6	12.0±41.4	153.7 ±12.5	1.5 (1.0–3.0)

7	Granhall et al (2018)[45]	Normal renal function	Steady-state 10 mg	$AUC_{0\text{-}24h}$: 283.7±53.3	14.9±53.2	151.7 ±9.1	1.0 (0.5–4.0)
		Mild RI	Steady-state 10 mg	$AUC_{0\text{-}24h}$: 378.2±78.9	20.2±75.9	159.3 ±12.0	1.0 (0.5–2.5)
		Moderate RI	Steady-state 10 mg	$AUC_{0\text{-}24h}$: 298.5 ±107.3	16.6±102.0	162.8 ±11.2	1.0 (0.5–4.0)
		Severe RI	Steady-state 10 mg	$AUC_{0\text{-}24h}$: 163.5±65.6	8.6±62.9	164.9 ±8.9	1.5 (0.5–4.0)
		ESRD	Steady-state 10 mg	$AUC_{0\text{-}24h}$: 287.7 ±128.7	15.7±128.3	152.8 ±49.0	1.0 (0.5–2.0)
8	Meier et al (2022)[46]	Type 2 diabetic with upper gastrointestinal disease	Steady-state 7 mg	143.95	7.72	141	1.0 (0.0–6.0)
		Type 2 diabetic without upper gastrointestinal disease	Steady-state 7 mg	122.05	6.63	142	1.0 (0.5–6.0)
9	Bækdal et al (2018b)[47]	Healthy	Steady-state 10 mg	$AUC_{0–24\ h}$: 290	15.2	150	1.0 (0.2–4.0)
			Steady-state 10 mg + omeprazole 40 mg	$AUC_{0–24\ h}$: 328	17.6	156	1.0 (1.0–6.0)

Abbreviation: NA, not available.

https://doi.org/10.2147/DDDT.S470826

administered with 50 or 120 mL water. Water volume had no apparent effect on t_{max} and $t_{1/2}$.[41] These results support dosing of oral semaglutide with up to 120 mL water.

Two randomised trials in healthy subjects evaluated the effect of various dosing schedules (including different pre-dose and/or post-dose fasting times) on the steady-state pharmacokinetics of oral semaglutide. In different pre-dose fasting times groups (2, 4, 6 h or overnight pre-dose fast followed by a 30 min post-dose fast), shorter pre-dose fasting times in the 2, 4 and 6 h treatment groups resulted in significantly lower semaglutide exposure and C_{max} compared with an overnight pre-dose fast. The median t_{max} appeared to be similar across the treatment groups (ranged from 0.8–1.0 h).[43] This trial supports dosing of oral semaglutide in the fasting state in accordance with the prescribing information. In different post-dose fasting times groups (15, 30, 60, or 120 min) after overnight pre-dose fasting, semaglutide $AUC_{0–24h}$ and C_{max} increased with longer post-dose fasting periods, particularly from 15 to 30 min. The median t_{max} increased with longer post-dose fasting times. Post-dose fasting time had no apparent effect on *t*1/2.[41] If the post-dose fasting time continues to extend, will the pharmacokinetics of semaglutide be more affected? An overnight post-dose fasting trial was conducted and found that semaglutide AUC $_{0–24h}$ and C_{max} at steady state were similar for the 30 min and overnight post-dose fasting treatment groups.[43] Administration of oral semaglutide at least 30 min post-dose fasting results in clinically relevant semaglutide exposure.

Drug–Drug Interactions

Only one study reported the effect of other drug on pharmacokinetic parameters of oral semaglutide.[47] A randomized study investigated the effect of omeprazole (40 mg once-daily) on the pharmacokinetics of oral semaglutide in 54 healthy subjects. Exposure of semaglutide appeared to be slightly non-statistically significant increased when oral semaglutide was administered with omeprazole versus oral semaglutide alone. $T_{1/2}$ and t_{max} for semaglutide were similar in subjects treated with oral semaglutide alone or with omeprazole.[47]

Studies in Diseased Participants

The effect of hepatic impairment on oral semaglutide pharmacokinetics was studied in 56 patients with varying degrees of hepatic function categorized as having normal hepatic function, and mild, moderate and severe hepatic impairment received once-daily oral semaglutide (5 mg for 5 days followed by 10 mg for 5 days).[44] $AUC_{0–24h}$ and C_{max} at steady state appeared similar across the four hepatic function groups, indicating that hepatic impairment does not affect oral semaglutide exposure. The $t_{1/2}$ and t_{max} of semaglutide were also similar across all groups.[44] The effect of renal impairment on oral semaglutide pharmacokinetics was studied in 71 patients with normal renal function, and mild, moderate, severe renal impairment, and ESRD, received once-daily oral semaglutide (5 mg for 5 days followed by 10 mg for 5 days).[45] Semaglutide exposure did not vary in a consistent pattern across the 5 renal function groups. $T_{1/2}$ and t_{max} were similar in subjects with different renal function. Further, haemodialysis did not affect the pharmacokinetics of oral semaglutide.[45] Based on the two above trials, hepatic impairment and renal impairment should not affect dose recommendations for oral semaglutide, which is similar to semaglutide administered subcutaneously.

Considering that oral semaglutide is primarily absorbed in the stomach, the effect of upper gastrointestinal disease on oral semaglutide pharmacokinetics was studied in 55 type 2 diabetes with or without upper GI disease received once-daily oral semaglutide (3 mg for 5 days followed by 7 mg for 5 days).[46] Semaglutide exposure ($AUC_{0–24h}$ and C_{max} after the tenth dose) was not significantly different between patients with and without upper gastrointestinal disease, hence no dose adjustment is required. Similarly, there was no apparent effect of upper gastrointestinal disease on $t_{1/2}$ and t_{max} of oral semaglutide.[46] Upper gastrointestinal disease, renal impairment and hepatic impairment did not affect oral semaglutide pharmacokinetic profile.

Discussion

The studies investigating pharmacokinetics of semaglutide administered subcutaneously demonstrated T_{max} values ranged from 30 h to 56 h in healthy subjects, and from 24 h to 77.8 h in diseased participants. Studies administering oral semaglutide demonstrated T_{max} values ranged from 0.8 h to 1.75 h in healthy subjects, and from 1.0 h to 1.75 h in diseased participants. These indicate that oral absorption of semaglutide is significantly faster than subcutaneous

administration. A $t_{1/2}$ of approximately 1 week was observed following both oral and subcutaneous administrations, demonstrating that the elimination phase was similar, irrespective of the route of administration. AUC and C_{max} are similar following the same dose of subcutaneous semaglutide in healthy subjects with different races.[28,33,34] Although the absorption enhancer SNAC can promote the transport and entry of oral semaglutide into the systemic circulation, semaglutide exposure remains relatively low compared to subcutaneous injection. Bioavailability was 0.8% when oral semaglutide was dosed using the recommended dosing conditions.[50] Oral absorption is significantly faster and bioavailability is lower, so the variability is greater.[51] The exposure from consecutive doses was overlapped and day-to-day variability in oral absorption was reduced by the once-daily dosing and long $t_{1/2}$, resulting in stable steady-state concentrations of oral semaglutide. Combined with the clinically relevant effects of once-daily oral semaglutide were observed in improving glycemic control and weight loss in multiple-dose trials,[39,52] hence oral semaglutide dosed once-daily with higher dose levels compared to subcutaneous injection.

Renal impairment and hepatic impairment did not affect oral and subcutaneous semaglutide pharmacokinetic profile.[29,37,44,45] Oral semaglutide exposure also did not appear to be affected by upper gastrointestinal disease.[46] Exposure of semaglutide in both postmenopausal women with T2D and obese subjects was obviously lower than that in healthy subjects.[35,36] This is most likely due to differences in body weight of the subjects, which were consistent with those predicted based on population pharmacokinetic models.[50,53,54] In population pharmacokinetic models using data from trials with oral or subcutaneous administration of semaglutide, body weight had an effect on semaglutide pharmacokinetics, which did not warrant dose adjustment.[50,53,54]

Unlike most oral medications that are absorbed in the intestines, oral administration of semaglutide is absorbed by the stomach, which is unique to this drug. The absorption enhancer SNAC can temporarily open the tight junctions between the epithelium, promote the transport and entry of semaglutide into the systemic circulation. Oral semaglutide is absorbed in the stomach and its absorption is affected by the presence of food and water. Drug–food interaction studies found that food and other substances in the stomach can reduce the oral semaglutide exposure.[41,42] Drug-dosing condition interaction studies have shown that fasting for at least 30 minutes after administration of oral semaglutide with up to 120 mL water results in clinically relevant semaglutide exposure.[41,43]

Drug–drug interaction studies found that cagrilintide dose did not affect subcutaneous semaglutide exposure and elimination.[38] Exposure of semaglutide appeared to be slightly non-statistically significant increased when oral semaglutide was administered with omeprazole versus oral semaglutide alone.[47] Semaglutide reduces gastric emptying and potentially alters the rate of absorption of orally co-administered drugs. With subcutaneous semaglutide treatment at steady state (1.0 mg), the pharmacokinetics of metformin, warfarin, atorvastatin and digoxin, and the bioavailability of the combined oral contraceptive, ethinylestradiol/levonorgestrel, were not affected to a clinically relevant degree with semaglutide co-administration.[35,55] Semaglutide affected population pharmacokinetic model parameters of paracetamol and atorvastatin in healthy subjects. However, these effects were considered not to be clinically relevant.[56] Oral semaglutide did not affect the pharmacokinetics of lisinopril, warfarin, digoxin and combined oral contraceptive, ethinylestradiol/levonorgestrel,[57–62] suggesting that co-administration with oral semaglutide requires no need for dose adjustment. Differences were observed in exposure of certain drugs when co-administered with oral semaglutide compared to administration alone, AUC of furosemide increased by 28%, and C_{max} decreased by 34%,[63] AUC of rosuvastatin increased by 41%, and C_{max} increased by 10%,[63] AUC of metformin increased by 32%,[57] a small increase in exposure of furosemide and rosuvastatin[59] and minor increases in AUC of Levothyroxine.[42] These observed changes were not considered clinically relevant due to the wide therapeutic index of the drugs. The findings supported that the cause of the increase is due to the delayed gastric emptying effects of semaglutide.

The strength of this study may be that it is a systematic review of all pharmacokinetic studies of both subcutaneous and oral semaglutide published up to August 2023. Several systematic reviews on subcutaneous semaglutide or oral semaglutide have recently been published, but their focus is primarily on efficacy and safety, rather than pharmacokinetics.[64–66] In addition, a few of population pharmacokinetic models were established using data from selected clinical pharmacological trials to identify clinically relevant covariates of exposure, but they included limited trial data.[50,53,54] The limitation of this review is that we only searched two databases, so it is possible that we missed one study, which may reduce the validity and subsequent reliability of the findings.

Conclusion

This review encompasses all the pharmacokinetic data for subcutaneous and oral semaglutide in both healthy and diseased participants. Semaglutide has a predictable pharmacokinetic profile with a long $t_{1/2}$ that allows for once-weekly subcutaneous administration. The AUC and C_{max} of oral and subcutaneous semaglutide were both increase with dose. Oral absorption of semaglutide is significantly faster than subcutaneous administration. The elimination phase of subcutaneous and oral semaglutide is similar. Bioavailability of oral semaglutide is very low. Food and various dosing conditions including water volume and dosing schedules can affect the oral semaglutide exposure. There are limited drug–drug interactions and no dosing adjustments in patients with upper gastrointestinal disease, renal impairment or hepatic impairment. It is possible that body weight may affect semaglutide exposure, but further studies are needed to confirm this. The existing pharmacokinetic data can assist in developing and evaluating pharmacokinetic models of semaglutide and will help clinicians predict semaglutide dosages. In addition, it can also help optimize future clinical trials.

Data Sharing Statement

All the data used for this publication are presented in the main article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study received funding from the National Natural Science Foundation (No. 81603171), Scientific Research Project of Hunan Provincial Health Commission (B202303107060 and D202303058890), and the Natural Science Foundation of Hunan Province (2022JJ30860 and 2022JJ30862).

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Ginsberg HN, MacCallum PR. The obesity, metabolic syndrome, and type 2 diabetes mellitus pandemic: part I. Increased cardiovascular disease risk and the importance of atherogenic dyslipidemia in persons with the metabolic syndrome and type 2 diabetes mellitus. *J Cardiometab Syndr*. 2009;4:113–119. doi:10.1111/j.1559-4572.2008.00044.x
2. Tilinca MC, Tiuca RA, Niculas C, et al. Future perspectives in diabesity treatment: semaglutide, a glucagon-like peptide 1 receptor agonist (Review). *Exp Ther Med*. 2021;22. doi:10.3892/etm.2021.10601
3. International Diabetes Federation (IDF). IDF diabetes atlas 10th edition. Available from: http://www.diabetesatlas.org/. Accessed June 19, 2024.
4. Sun H, Saeedi P, Karuranga S, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabet Res Clin Pract*. 2022;183:109119. doi:10.1016/j.diabres.2021.109119
5. Hasanzad M, Sarhangi N. A narrative review of current trends in liraglutide: insights into the unmet needs in management of type 2 diabetes and obesity. *J Diabetes Metab Disord*. 2020;19:1863–1872. doi:10.1007/s40200-020-00619-9
6. Yang YY, Qi JJ, Jiang SY, et al. Esculin ameliorates obesity-induced insulin resistance by improving adipose tissue remodeling and activating the IRS1/PI3K/AKT/GLUT4 pathway. *J Ethnopharmacol*. 2024;319:117251. doi:10.1016/j.jep.2023.117251
7. Li X, Shi S, Jing D, et al. Signal transduction mechanism of exosomes in diabetic complications (Review). *Exp Ther Med*. 2022;23:155. doi:10.3892/etm.2021.11078
8. Gadde KM, Martin CK, Berthoud HR, et al. Obesity: pathophysiology and management. *J Am Coll Cardiol*. 2018;71:69–84. doi:10.1016/j.jacc.2017.11.011
9. World health organization obesity and overweight: world health organization global strategy on diet, physical activity and health fact sheet; 2003. Available from: http://www.who.int. Accessed September 16, 2005.
10. Adlyxin (lixisenatide) [prescribing information]. Bridgewater: Sanofi-Aventis US LLC; 2016.
11. Bydureon (exenatide) [prescribing information]. Wilmington: AstraZeneca Pharmaceuticals LP; 2017.
12. Byetta (exenatide) [prescribing information]. Wilmington: AstraZeneca Pharmaceuticals; 2015.
13. Tanzeum (albiglutide) [prescribing information]. Wilmington: GlaxoSmithKline; 2017.
14. Victoza (liraglutide) [prescribing information]. Bagsvaerd: Novo Nordisk; 2017.
15. Trulicity (dulaglutide) [prescribing information]. Indianapolis: Eli Lily and Company; 2017.

16. Ladenheim EE. Liraglutide and obesity: a review of the data so far. *Drug Des Devel Ther*. 2015;9:1867–1875. doi:10.2147/dddt.s58459
17. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2012;8:728–742. doi:10.1038/nrendo.2012.140
18. Romera I, Cebrián-Cuenca A, Álvarez-Guisasola F, et al. A review of practical issues on the use of glucagon-like peptide-1 receptor agonists for the management of type 2 diabetes. *Diabetes Ther*. 2019;10:5–19. doi:10.1007/s13300-018-0535-9
19. Isaacs D, Prasad-Reddy L, Srivastava SB. Role of glucagon-like peptide 1 receptor agonists in management of obesity. *Am J Health Syst Pharm*. 2016;73:1493–1507. doi:10.2146/ajhp150990
20. Lau J, Bloch P, Schäffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem*. 2015;58:7370–7380. doi:10.1021/acs.jmedchem.5b00726
21. Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5:251–260. doi:10.1016/s2213-8587(17)30013-x
22. Ahrén B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol*. 2017;5:341–354. doi:10.1016/s2213-8587(17)30092-x
23. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label. *Randomized Clin Trial*. 2018;41:258–266. doi:10.2337/dc17-0417
24. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5:355–366. doi:10.1016/s2213-8587(17)30085-2
25. Rodbard HW, Lingvay I, Reed J, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. *J Clin Endocrinol Metab*. 2018;103:2291–2301. doi:10.1210/jc.2018-00070
26. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol*. 2018;6:275–286. doi:10.1016/s2213-8587(18)30024-x
27. Aroda VR, Ahmann A, Cariou B, et al. Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: insights from the SUSTAIN 1-7 trials. *Diabetes Metab*. 2019;45:409–418. doi:10.1016/j.diabet.2018.12.001
28. Jensen L, Helleberg H, Roffel A, et al. Absorption, metabolism and excretion of the GLP-1 analogue semaglutide in humans and nonclinical species. *Eur J Pharm Sci*. 2017;104:31–41. doi:10.1016/j.ejps.2017.03.020
29. Jensen L, Kupcova V, Arold G, et al. Pharmacokinetics and tolerability of semaglutide in people with hepatic impairment. *Diabetes Obesity Metab*. 2018;20:998–1005. doi:10.1111/dom.13186
30. Beglinger C, Poller B, Arbit E, et al. Pharmacokinetics and pharmacodynamic effects of oral GLP-1 and PYY3-36: a proof-of-concept study in healthy subjects. *Clin Pharmacol Ther*. 2008;84:468–474. doi:10.1038/clpt.2008.35
31. Andersen A, Knop FK, Vilsbøll T. A pharmacological and clinical overview of oral semaglutide for the treatment of type 2 diabetes. *Drugs*. 2021;81:1003–1030. doi:10.1007/s40265-021-01499-w
32. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
33. Ikushima I, Jensen L, Flint A, et al. A randomized trial investigating the pharmacokinetics, pharmacodynamics, and safety of subcutaneous semaglutide once-weekly in healthy male Japanese and caucasian subjects. *Adv Ther*. 2018;35:531–544. doi:10.1007/s12325-018-0677-1
34. Shi A, Xie P, Nielsen LL, et al. Pharmacokinetics, safety and tolerability of once-weekly subcutaneous semaglutide in healthy Chinese subjects: a double-blind, phase 1, randomized controlled trial. *Adv Ther*. 2021;38:550–561. doi:10.1007/s12325-020-01548-y
35. Kapitza C, Nosek L, Jensen L, et al. Semaglutide, a once-weekly human GLP-1 analog, does not reduce the bioavailability of the combined oral contraceptive, ethinylestradiol/levonorgestrel. *ACS Chem Biol*. 2015;55:497–504. doi:10.1002/jcph.443
36. Blundell J, Finlayson G, Axelsen M, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. *Diabetes Obes Metab*. 2017;19:1242–1251. doi:10.1111/dom.12932
37. Marbury TC, Flint A, Jacobsen JB, et al. Pharmacokinetics and tolerability of a single dose of semaglutide, a human glucagon-like peptide-1 analog, in subjects with and without renal impairment. *Clin Pharmacokinet*. 2017;56:1381–1390. doi:10.1007/s40262-017-0528-2
38. Enebo LB, Berthelsen KK, Kankam M, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2·4 mg for weight management: a randomised, controlled, phase 1b trial. *Lancet*. 2021;397:1736–1748. doi:10.1016/s0140-6736(21)00845-x
39. Granhall C, Donsmark M, Blicher TM, et al. Safety and pharmacokinetics of single and multiple ascending doses of the novel oral human GLP-1 analogue, oral semaglutide, in healthy subjects and subjects with type 2 diabetes. *Clin Pharmacokinet*. 2019;58:781–791. doi:10.1007/s40262-018-0728-4
40. Bækdal TA, Donsmark M, Hartoft-Nielsen ML, et al. Relationship between oral semaglutide tablet erosion and pharmacokinetics: a pharmacoscintigraphic study. *Clin Pharmacol Drug Dev*. 2021;10:453–462. doi:10.1002/cpdd.938
41. Bækdal TA, Breitschaft A, Donsmark M, et al. Effect of various dosing conditions on the pharmacokinetics of oral semaglutide, a human glucagon-like peptide-1 analogue in a tablet formulation. *Diabetes Ther*. 2021;12:1915–1927. doi:10.1007/s13300-021-01078-y
42. Hauge C, Breitschaft A, Hartoft-Nielsen ML, et al. Effect of oral semaglutide on the pharmacokinetics of thyroxine after dosing of levothyroxine and the influence of co-administered tablets on the pharmacokinetics of oral semaglutide in healthy subjects: an open-label, one-sequence crossover, single-center, multiple-dose, two-part trial. *Clin Pharmacokinet*. 2021;17:1139–1148. doi:10.1080/17425255.2021.1955856
43. van Hout M, Forte P, Jensen TB, et al. Effect of various dosing schedules on the pharmacokinetics of oral semaglutide: a randomised trial in healthy subjects. *Clin Pharmacokinet*. 2023;62:635–644. doi:10.1007/s40262-023-01223-9
44. Bækdal TA, Thomsen M, Kupčová V, et al. Pharmacokinetics, safety, and tolerability of oral semaglutide in subjects with hepatic impairment. *J Clin Pharmacol*. 2018;58:1314–1323. doi:10.1002/jcph.1131
45. Granhall C, Søndergaard FL, Thomsen M, et al. Pharmacokinetics, safety and tolerability of oral semaglutide in subjects with renal impairment. *Clin Pharmacokinet*. 2018;57:1571–1580. doi:10.1007/s40262-018-0649-2

46. Meier JJ, Granhall C, Hoevelmann U, et al. Effect of upper gastrointestinal disease on the pharmacokinetics of oral semaglutide in subjects with type 2 diabetes. *Diabetes Obesity Metab*. 2022;24:684–692. doi:10.1111/dom.14632
47. Bækdal TA, Breitschaft A, Navarria A, et al. A randomized study investigating the effect of omeprazole on the pharmacokinetics of oral semaglutide. *Expert Opin Drug Metab Toxicol*. 2018;14:869–877. doi:10.1080/17425255.2018.1488965
48. Al-Dirini RM, Thewlis D, Paul G. A comprehensive literature review of the pelvis and the lower extremity FE human models under quasi-static conditions. *Work*. 2012;41(Suppl 1):4218–4229. doi:10.3233/wor-2012-1039-4218
49. CASP(Critical Skills Appraisal Programme)[EB/OL]; 2012. Available from: https://casp-uk.net/casp-tools-checklists. Accessed June 19, 2024.
50. Overgaard RV, Navarria A, Ingwersen SH, et al. Clinical pharmacokinetics of oral semaglutide: analyses of data from clinical pharmacology trials. *Clin Pharmacokinet*. 2021;60:1335–1348. doi:10.1007/s40262-021-01025-x
51. Hellriegel ET, Bjornsson TD, Hauck WW. Interpatient variability in bioavailability is related to the extent of absorption: implications for bioavailability and bioequivalence studies. *Clin Pharmacol Ther*. 1996;60:601–607. doi:10.1016/s0009-9236(96)90208-8
52. Davies M, Pieber TR, Hartoft-Nielsen ML, et al. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial. *JAMA*. 2017;318:1460–1470. doi:10.1001/jama.2017.14752
53. Overgaard RV, Delff PH, Petri KCC, et al. Population pharmacokinetics of semaglutide for type 2 diabetes. *Diabetes Ther*. 2019;10:649–662. doi:10.1007/s13300-019-0581-y
54. Carlsson Petri KC, Ingwersen SH, Flint A, et al. Semaglutide s.c. Once-weekly in type 2 diabetes: a population pharmacokinetic analysis. *Diabetes Therapy*. 2018;9:1533–1547. doi:10.1007/s13300-018-0458-5
55. Hausner H, Derving Karsbøl J, Holst AG, et al. Effect of semaglutide on the pharmacokinetics of metformin, warfarin, atorvastatin and digoxin in healthy subjects. *Clin Pharmacokinet*. 2017;56:1391–1401. doi:10.1007/s40262-017-0532-6
56. Langeskov EK. Population pharmacokinetic of paracetamol and atorvastatin with co-administration of semaglutide. *Int J Mol Sci*. 2022;10:e00962. doi:10.1002/prp2.962
57. Bækdal TA, Borregaard J, Hansen CW, et al. Effect of oral semaglutide on the pharmacokinetics of lisinopril, warfarin, digoxin, and metformin in healthy subjects. *Clin Pharmacokinet*. 2019;58:1193–1203. doi:10.1007/s40262-019-00756-2
58. Borregaard J, Bækdal TA, Golor G, et al. A study of drug-drug interactions of oral semaglutide with lisinopril and warfarin. *Diabetes*. 2017;66:A321.
59. Jordy AB, Albayaty M, Breitschaft A, et al. Effect of oral semaglutide on the pharmacokinetics of levonorgestrel and ethinylestradiol in healthy postmenopausal women and furosemide and rosuvastatin in healthy subjects. *Pharmaceutics*. 2021;60:1171–1185. doi:10.1007/s40262-020-00976-x
60. Jordy AB, Breitschaft A, Christiansen E, et al. Oral semaglutide does not affect the bioavailability of the combined oral contraceptive ethinylestradiol/levonorgestrel. *Diabetes*. 2018;67:A304.
61. Jordy AB, Breitschaft A, Christiansen E, et al. Oral semaglutide does not affect the bioavailability of the combined oral contraceptive, ethinylestradiol/levonorgestrel. *Diabetologia*. 2018;61:S346. doi:10.1007/s00125-018-4693-0
62. Thomsen M, Bækdal TA, Golor G, et al. A study of drug-drug interactions of oral semaglutide with metformin and digoxin. *Diabetologia*. 2017;60:S363. doi:10.1007/s00125-017-4350-z
63. Bækdal TA, Albayaty M, Manigandan E, et al. A trial to investigate the effect of oral semaglutide on the pharmacokinetics of furosemide and rosuvastatin in healthy subjects. *Diabetologia*. 2018;61:S346–S347. doi:10.1007/s00125-018-4693-0
64. Lewis AL, McEntee N, Holland J, et al. Development and approval of rybelsus (oral semaglutide): ushering in a new era in peptide delivery. *Drug Deliv Transl Res*. 2022;12:1–6. doi:10.1007/s13346-021-01000-w
65. Moriwaki N, Akahori M, Sugii H. Development of Rybelsus, the world's first oral GLP-1 receptor agonist. *Drug Deliv Sys*. 2022;37:169–173. doi:10.2745/dds.37.169
66. Nauck MA, Gallwitz B, Seufert J. Semaglutide- pharmacodynamic and pharmacokinetic characteristics of a new long-acting GLP-1-receptor agonist. *Diabetol Stoffwechs*. 2017;12:135–140. doi:10.1055/s-0043-104866