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EXPERT REVIEW

Therapeutic Potential of Semaglutide, a Newer GLP-1 Receptor Agonist, in Abating Obesity, Non-Alcoholic Steatohepatitis and Neurodegenerative diseases: A Narrative Review

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Abstract

Introduction Semaglutide, a peptidic GLP-1 receptor agonist, has been clinically approved for treatment of type 2 diabetes mellitus and is available in subcutaneous and oral dosage form. Diabetes, insulin resistance, and obesity are responsible for the pathological manifestations of non-alcoholic steatohepatitis (NASH). Similarly, insulin resistance in brain is also responsible for neurodegeneration and impaired cognitive functions.

Background Observations from phase-3 clinical trials like SUSTAIN and PIONEER indicated anti-obesity potential of semaglutide, which was established in STEP trials. Various pre-clinical and phase-2 studies have indicated the therapeutic potential of semaglutide in non-alcoholic steatohepatitis and neurodegenerative disorders like Parkinson's and Alzheimer's disease.

Discussion Significant weight reduction ability of semaglutide has been demonstrated in various phase-3 clinical trials, for which recently semaglutide became the first long-acting GLP-1 receptor agonist to be approved by the United States Food and Drug Administration for management of obesity. Various pre-clinical and clinical studies have revealed the hepatoprotective effect of semaglutide in NASH and neuroprotective effect in Parkinson's and Alzheimer's disease.

Conclusion Many GLP-1 receptor agonists have shown hepatoprotective and neuroprotective activity in animal and human trials. As semaglutide is an already clinically approved drug, successful human trials would hasten its inclusion into therapeutic treatment of NASH and neurodegenerative diseases. Semaglutide improves insulin resistance, insulin signalling pathway, and reduce body weight which are responsible for prevention or progression of NASH and neurodegenerative diseases.

KEY WORDS GLP-1 receptor agonist · metabolic diseases · neurodegenerative diseases · obesity · semaglutide

INTRODUCTION

Glucagon Like Peptide-1 (GLP-1), secreted from nutrient responsive enteroendocrine cells or L cells of intestine, is a prominent incretin hormone responsible for glucoregulatory effect in human body. GLP-1 augments glucose-dependent insulin secretion, improves β-cell functioning and glucose tolerance, inhibits glucagon secretion, and offers protection from glucolipotoxicity, apoptosis (1, 2). GLP-1 plays a vital role in ameliorating insulin resistance and production of VLDL (Very Low-Density Lipoprotein) via an intrinsic gut-liver signalling pathway (3). Although expression of GLP-1 receptors in hepatocytes remained a subject of debate among researchers, an insulin-independent direct action on liver has been suggested (4). GLP-1 plays an important role in digestion by delaying gastric emptying and suppress appetite centre in hypothalamus (5). GLP-1 is expressed in different parts of the brain and affects satiety centre, water intake, stress reaction, neurogenesis, neurodegeneration, thermogenesis, and energy homeostasis (6). Therefore, GLP-1 receptor agonists have been found to improve cognitive impairment and neurological deficit associated with diabetes or obesity (7). It suggests the potential of GLP-1 receptor agonists which can be deployed for treatment of diabetes, obesity, Non-alcoholic

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Steatohepatitis (NASH) and neurodegenerative diseases like Parkinson's and Alzheimer's.

Researchers focused on developing GLP-1 receptor agonists which needs less frequent dosing (weekly-once) to improve patient adherence and to reduce the treatment burden. Only three GLP-1 receptor agonists- exenatide extended release, semaglutide and dulaglutide are currently approved for weekly-once dosing (8). Semaglutide ($C_{187}H_{291}N_{45}O_{59}$) is a longer-acting GLP-1 receptor agonist with 94% structural similarity to the native GLP-1 (9). Semaglutide can be safely administered to adults and geriatric patients with renal, hepatic or cardiovascular (CV) disorders. It is available as Ozempic® (subcutaneous injection, weekly-once dosing; available in 0.5, 1.0 mg strength) and Rybelsus® (oral tablets, once-daily dosing; available in 3, 7, 14 mg strength), both approved by USFDA, Health Canada, European Medicines Agency, Japanese Health ministry for use in treatment of type 2 diabetes. Semaglutide has been found to reduce hyperglycaemia, body weight, steatosis, and improves cognitive ability in neurodegenerative diseases (Fig. 1). The status of semaglutide in treatment of type 2 diabetes has been well documented (10); hence this narrative review will discuss the therapeutic potential of semaglutide in three different sections- management of obesity, NASH and neurodegenerative diseases.

OBESITY

Excess accumulation of body fat or a body mass index (BMI) of ≥ 30 indicates obesity, which is a life-style disorder caused by more calorie intake, reduced physical activity, endocrinological conditions, genetic factors and certain medications (11). Central obesity is often accompanied with metabolic syndrome characterized by hyperglycemia, hypertension and dyslipidemia. (12)

Pathogenesis

White adipose tissue is composed of mature fat cells or adipocytes which stores excess energy obtained from food as triglycerides and also hosts various immune cells like fibroblasts, macrophages, and lymphocytes. Adipose tissue dysfunction in obesity leads to imbalance in the distribution and activity of immune cells causing local as well as systemic inflammation (13). In obesity, radical changes occur in immune cell composition of adipose tissue which activates inflammatory signaling pathways with increased expression of inflammatory receptors (14). Visceral fat in obesity is linked to the display of inflammatory markers and development of insulin resistance (15). Research suggests that obesity with metabolic syndrome is linked to increased deaths among patients with type 2 diabetes and cardiovascular diseases. Homeostatic and hedonic pathway are two important systems for regulating food and energy intake in humans. Homeostatic system, controlled by hypothalamus and brain stem, stimulates food intake in case of low energy stores (16). Hedonic pathway represents reward or motivational aspects of food intake and thus stimulates intake of food during relative energy deficiency. In addition, it also stimulates intake of highly palatable foods during periods of low energy demand (17). Altered sympathetic nervous system activity contributes to obesity; overeating increases sympathetic nervous system activity (18), whereas fasting

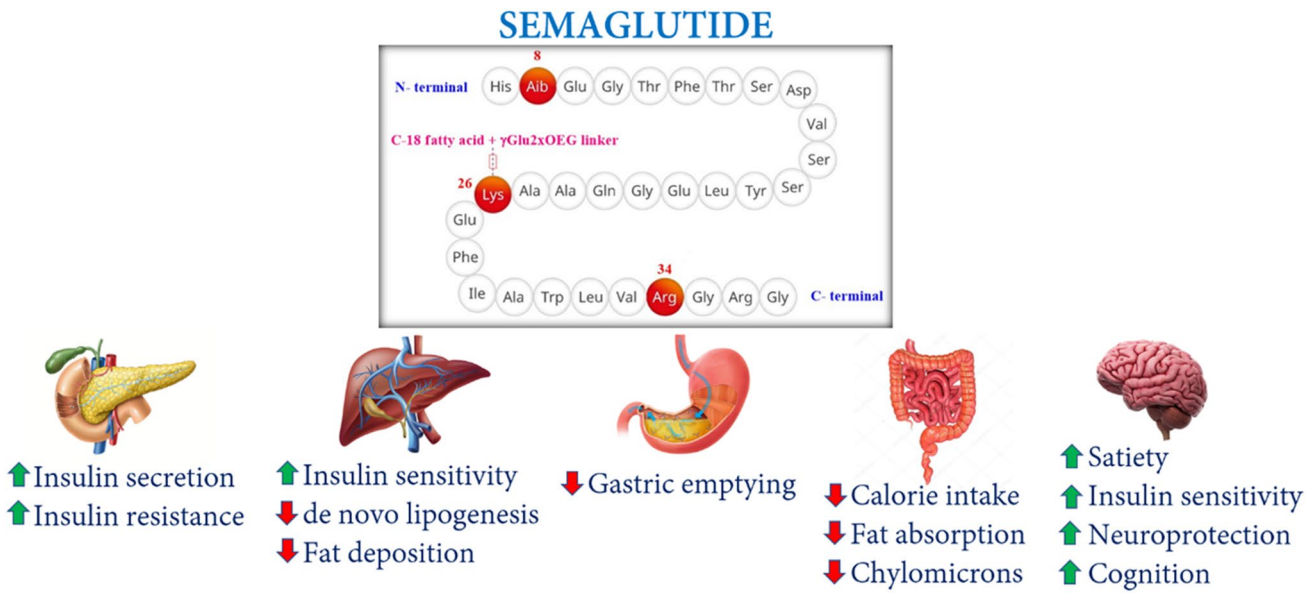

Fig. 1 Mechanism of semaglutide for management of obesity, NASH, and neurodegenerative diseases.

reduces this activity (19). Reduced serotonin signaling in hypothalamus causes overeating by impairing the negative feedback on food intake and thus contributes to obesity (20). Similarly, decrease in dopamine signaling causes overeating of palatable foods (21). In response to food intake, secretion of ghrelin or hunger hormone is suppressed, but this regulation is hampered in obesity. (22) In obesity, food consumption is associated with reduced activity of anorexigenic hormones like GLP-1, Peptide YY (PYY) and cholecystokinin (CCK). Leptin counterbalance the effect of ghrelin and also helps in synthesizing anorexigenic peptides. But in obese individuals, leptin signaling is impaired leading to overconsumption of food (23). Development of insulin resistance in brain impairs the insulin mediated response to food intake and metabolism in obesity. (24) Disturbance in circadian rhythm and altered timing of food intake causes gain in body weight (25); hence the night-shift workers are more prone to develop obesity (26). Apart from these factors, childhood-onset obesity is also caused by genetic predisposition (monogenic or polygenic mutations). (27)

GLP-1 is an intestinal incretin hormone which shows anorectic property centrally as well as peripherally by enhancing satiation and delayed gastric emptying (28). Various GLP-1 receptor agonists like exenatide, liraglutide, lixisenatide, dulaglutide and semaglutide have shown to reduce the body weight by reducing energy intake (29). Tirzepatide is a newer dual agonist of GLP-1 and GIP (gastric inhibitory peptide) which has shown promising anti-obesity effect. (30)

Anti-obesity Mechanism of Semaglutide

Semaglutide has exhibited significant weight loss in comparison to liraglutide and exenatide in various clinical studies (31). The weight loss has been attributed to reduced energy intake because semaglutide doesn't affect energy expenditure and that too without raising the resting metabolic rate. It also improves the hedonic feature of food intake, i.e., less cravings for food due to enhanced satiation, less likeness for high fat foods (31, 32). Although a gut to brain communication is involved in mediating reduced appetite and energy intake of semaglutide, but the exact mechanism is still unclear (33, 34). It has been proposed that semaglutide's effect on suppressed appetite might be facilitated through hypothalamus by a central mechanism similar to that of liraglutide (34). Another plausible explanation involves a peripheral mechanism similar to native GLP-1 which causes delay in gastric motility. It also activates gastro-mechano receptors which in turn suppresses the satiation centre situated in brainstem by relaying signals through vagus nerve (35, 36).

Clinical Trials for Anti-obesity Effect of Semaglutide

Semaglutide has exhibited significant weight reducing property in various phase-3 SUSTAIN and PIONEER trials (presented in Table I and Table II respectively) over dulaglutide and liraglutide (31). These results encouraged the researchers to carry out trials on weekly-once s.c. semaglutide for better management of obesity.

Phase-1 Studies

NCT02079870: A cross over trial study on 30 obese subjects investigated the mechanism of semaglutide by studying energy intake, appetite sensation, gastric emptying, and postprandial glucose as well as triglyceride metabolism. Participants received weekly-once s.c. semaglutide (initially 0.25, then 0.5 and finally 1.0 mg with dose escalation) or placebo for 12-weeks, followed by a washout period of 5 to 7 weeks, and finally another 12-weeks treatment period. Semaglutide has shown about 24% drop in net calorie consumption with 5 kg weight reduction. Therefore, lower energy intake, enhanced satiation, less food craving, reduced body fat and weight loss are the plausible mechanism for the anorexic effect of semaglutide (32).

The cross-over design was the primary limitation of this study. Patients who received semaglutide likely recovered the weight during wash-out period but may not have reached the pre-treatment level. This could be a reason for slight weigh gain in placebo group (32).

NCT03842202: This trial assessed the effect of semaglutide on energy intake, appetite and gastric emptying in 72 subjects with obesity, who received weekly-once s.c. semaglutide (2.4 mg) or placebo for 20 weeks. Reduced energy intake, better appetite control, less food cravings were responsible for the weight reduction (9.9%) exhibited by semaglutide. Delayed gastric emptying (assessed indirectly through paracetamol absorption) was not found to be associated with semaglutide (37).

Indirect measurement of paracetamol absorption has several limitations for predicting gastric emptying. However, the limitations were mitigated by providing paracetamol with semi-solid food, measurement of post-dose paracetamol concentration and time to reach the peak concentration (37).

NCT03600480: This phase-1b trial assessed the safety, efficacy of cagrilintide (amylin analogue) in combination with semaglutide on 96 obese subjects (without lifestyle modification). They received a combined therapy of weekly-once s.c. cagrilintide (0·16/0·30/0·60/1·2/2·4/4·5 mg) and weekly-once s.c. 2.4 mg semaglutide or placebo for 20-weeks. Superior weight reduction was achieved in combination therapy with good safety profile over placebo (38).

The weight reduction data is not solely due to semaglutide treatment, because this study evaluated the safety,

Table I Weight Reduction Property of Weekly-once s.c. Semaglutide in SUSTAIN Trials

SUSTAIN	Clinical trial identification number	Population	Duration (weeks)	Background medication	Semaglutide trial dose & Comparator	Weight loss (kg)	
1	NCT02054897	388	30	None	0.5 mg 1.0 mg Placebo	-3.73 -4.53 -0.98	
2	NCT01930188	1231	56	Metformin and/or Pioglitazone/Rosiglitazone	0.5 mg 1.0 mg Sitagliptin (100 mg)	-4.3 -6.1 -1.9	
3	NCT01885208	813	56	Metformin and/or Thiazolidinediones and/or Sulfonylurea	1.0 mg Exenatide ER (2.0 mg)	-5.6 -1.9	
4	NCT02128932	1089	30	Metformin alone or with Sulfonylurea	0.5 mg 1.0 mg Insulin glargine	-3.47 -5.17 +1.15	
5	NCT02305381	397	30	Basal insulin alone or with Metformin	0.5 mg 1.0 mg Placebo	-3.7 -6.4 -1.4	
6	NCT01720446	3297 (83% with CV and/or CKD)	104	None	0.5 mg 1.0 mg Placebo (0.5 mg) Placebo (1.0 mg)	-3.6 -4.9 -0.7 -0.5	
7	NCT02648204	1201	40	Metformin	0.5 mg 1.0 mg Dulaglutide (0.75 mg) Dulaglutide (1.5 mg)	-4.6 -6.5 -2.3 -3.0	
8	NCT03136484	788	52	Metformin	1.0 mg Canagliflozin (300 mg)	-5.3 -4.2	
9	NCT03086330	302	30	SGLT-2 inhibitor alone or with Sulfonylurea/Metformin	1.0 mg Placebo	-4.7 -0.9	
10	NCT03191396	577	30	Metformin and Sulfonylurea/SGLT-2 inhibitor	1.0 mg Liraglutide (1.2 mg)	-5.8 -1.9	
11	NCT03689374	2275	52	Metformin alone or with Sulfonylurea/Meglitinide/DPP-4 inhibitor/α-glucosidase inhibitor	1.0 mg Insulin aspart (4 IU)	- -	
Japan-sitagliptin	NCT02254291	308	30	None	0.5 mg 1.0 mg Sitagliptin (100 mg)	-2.2 -3.9 0.0	
Japan	NCT02207374	601	56	None	0.5 mg 1.0 mg OAD monotherapy	-1.4 -3.2 +0.4	
China-MRCT	NCT03061214	868	30	Metformin	0.5 mg 1.0 mg Sitagliptin (100 mg)	-2.9 -4.2 -0.4	
FORTE	NCT03989232	961	40	Metformin alone or with Sulfonylurea	1.0 mg 2.0 mg Placebo	Trial product estimand -6.0 kg -6.9 kg -	Treatment policy estimand -5.6 kg -6.4 kg -

Weight reduction activity of weekly once s.c. semaglutide (0.5, 1.0, and 2.0 mg)

Table II Weight Reduction Property of Daily-Once Oral Semaglutide in PIONEER Trials

PIONEER	Clinical trial identification number	Population	Duration (weeks)	Background medication	Semaglutide trial dose & Comparator	Trial product estimand	Treatment policy estimand
						Weight loss	Weight loss
1	NCT02906930	703	26	None	3 mg 7 mg 14 mg Placebo	-0.2 -1.0 -2.6 -1.5	-0.1 -0.9 -2.3 -1.4
2	NCT02863328	822	52	Metformin	14 mg Empagliflozin (25 mg)	-4.7 -3.8	-3.8 -3.6
3	NCT02607865	1864	78	Metformin with/without Sulfonylurea	3 mg 7 mg 14 mg Sitagliptin (100 mg)	-1.8 -2.7 -3.5 -1.1	-1.8 -2.7 -3.2 -1.0
4	NCT02863419	711	52	Metformin with/without SGLT-2 inhibitor	14 mg Liraglutide (s.c. 1.8 mg) Placebo	-5.0 -3.1 -1.2	-4.3 -3.0 -1.0
5	NCT02827708	324 (with moderate renal impairment)	26	Metformin/Sulfonylurea, or both, or Basal insulin with/without Metformin	14 mg Placebo	-3.7 -1.1	-3.4 -0.9
6	NCT02692716	3183 (84.7% with CV or CKD)	Event-driven; Median time = 69 weeks	None	14 mg Placebo	-4.2 kg -0.8 kg	
7	NCT02849080	504	52	One/two amongst Metformin, Sulfonylureas, SGLT-2 inhibitors, or Thiazolidinediones	14 mg Sitagliptin (100 mg)	-2.9 -0.8	-2.6 -0.7
8	NCT03021187	731	52	Insulin with/without Metformin	3 mg 7 mg 14 mg Placebo	-1.0 -2.9 -4.3 +0.6	-0.8 -2.0 -3.7 +0.5
9	NCT03018028	243	52	None	3 mg 7 mg 14 mg Placebo Liraglutide (s.c. 0.9 mg)	0.0 -0.6 -2.8 -1.0 +0.4	-0.3 -0.8 -2.6 -0.6 0.0
10	NCT03015220	458	52	Sulfonylurea/glinide/thia zolidinedione/α-glucosidase inhibitor/SGLT-2 inhibitor monotherapy	3 mg 7 mg 14 mg Dulaglutide (s.c. 0.75 mg)	+0.1 -1.0 -1.9 +1.1	0.0 -0.9 -1.6 +1.0
11	NCT04109547	664	26	None	3 mg 7 mg 14 mg Placebo	- - - -	- - - -

Table II (continued)

PIONEER	Clinical trial identification number	Population	Duration (weeks)	Background medication	Semaglutide trial dose & Comparator	Trial product estimand	Treatment policy estimand
						Weight loss	Weight loss
12	NCT04017832	1444	26	Metformin	3 mg	-	-
					7 mg	-	-
					14 mg	-	-
					Placebo	-	-
					Sitagliptin (100 mg)	-	-
TEENS	NCT04596631	132 (aged 10–17 years)	52	Metformin and/or basal insulin	Semaglutide (maximum tolerated dose)	-	-
					Placebo		

Weight reduction activity of once-daily oral semaglutide (3, 7, and 14 mg)

tolerability of cagrilintide in combination with semaglutide. Short study duration and only 4 weeks of treatment with final target dose limits the evaluation accuracy. Exclusion of persons with BMI more than 40 kg/m (2) and high cardiovascular risk is also a major limitation, because severe obese persons are often associated with cardiovascular diseases. Inclusion of persons of either sex with non-childbearing potential is also another limitation. However, it was decided to include persons with childbearing potential in future trials (38).

Phase-2 Study

NCT02453711: A dose-ranging study was conducted on 957 obese subjects to explore the effectiveness of semaglutide in obesity management. Participants received daily-once s.c. semaglutide (initially 0.05, or 0.1 or 0.2 or 0.3 or 0.4 mg with incremental escalation) or daily-once 3.0 mg s.c. liraglutide (initially 0.6 mg, then dose escalation of 0.6 mg every week) or placebo for 52-weeks. Superior weight reduction of 6.0–13.8% and 11.4–16.3% were exhibited by the semaglutide with slow escalation (4-week period) and fast escalation (2-week period) respectively over liraglutide and placebo (39).

Unmasking of participants and site staffs to the assigned dose might have incorporated biasness in reporting adverse effects or treatment discontinuation. As the participants were not evaluated for the source of body weight loss and estimation of energy balance, it was difficult to determine whether the participants strictly adhered to the diet and exercise activity recommendations (39).

Phase-3 Studies

STEP (Semaglutide Treatment Effect in People with obesity) trials: All the trials were randomised, parallel-group and placebo-controlled (presented in Table III). Except for STEP-3 trial, the net energy expenditure for all trials was determined by: estimated basal metabolic rate x physical activity level value (1.3) (40).

STEP-1 (NCT03548935): This trial investigated the effectiveness of weekly-once s.c. 2.4 mg semaglutide on 1961 obese subjects, who received semaglutide (0.25 mg dose followed by 0.5 mg, 1.0 mg, 1.7 mg, 2.4 mg with dose escalation) or placebo for 68-weeks. A significant weight loss of 14.9% was achieved with semaglutide treated group over 2.4% with placebo. Apart from the gastrointestinal side effects, semaglutide was found to be safe and well-tolerated. A sub-population study demonstrated that semaglutide treatment causes reduction in fat mass as proved by whole body DXA scanning (40, 41).

Majority of the participants were women and belongs to White ethnicity. Persons with type 2 diabetes were excluded, but obesity and type 2 diabetes frequently co-occur in many patients. The DXA scanning was performed on a sub-population only which limits the accuracy of this data (41).

STEP-2 (NCT03552757): This trial explored the effectiveness of weekly-once s.c. 2.4 mg semaglutide on 1210 obese, type 2 diabetic subjects who received 1.0 mg semaglutide (initially 0.25, then 0.5, 1 mg) or 2.4 mg semaglutide (initially 0.25, then 0.5, 1.0, 1.7, 2.4 mg) or placebo for 68-weeks. A significant decrease of 9.6% in body weight was exhibited by the 2.4 mg semaglutide treated group over 3.4% with placebo (40, 42).

Patients on insulin therapy were excluded from this study. But weight loss effects due to add-on insulin therapy could have been studied as observed in SUSTAIN 5 (42).

STEP-3 (NCT03611582): Effectiveness of weekly-once 2.4 mg s.c. semaglutide was investigated on 611 obese subjects who received 2.4 mg semaglutide (initially 0.25, then 0.5, 1.0, 1.7, finally 2.4 mg) or placebo for 68-weeks. A

Table III Weight Reduction Property of Weekly-once s.c. Semaglutide in STEP Trials

STEP	Objective	Exclusion criteria	Population	Duration (weeks)	Semaglutide trial dose	Weight loss (%)
1 (NCT03548935)	Efficacy of semaglutide in obese patients	Type 2 diabetic patients	1961	68	2.4 mg Placebo	-14.9 -2.4
2 (NCT03552757)	Efficacy of semaglutide in type 2 diabetic obese patients	Patients on insulin	1210	68	2.4 mg Placebo	-9.6 -3.4
3 (NCT03611582)	Efficacy of semaglutide along with intensive lifestyle program	Patients with HbA1c ≥ 6.5%	611	68	2.4 mg Placebo	-16.0 -5.7
4 (NCT03548987)	Efficacy of semaglutide in obese patients	Patients with HbA1c ≥ 6.5%	902	68	2.4 mg Placebo (switch-on)	-7.9 +6.9
5 (NCT03693430)	Efficacy of semaglutide in obese patients	Patients with HbA1c ≥ 6.5%	304	104	2.4 mg	-
6 (NCT03811574)	Efficacy of semaglutide 1.7 mg and 2.4 mg in obese patients	Type 2 diabetic patients with renal impairment	401	68	2.4 mg 1.7 mg Placebo	-13.2 -9.6 -2.1
7 (NCT04251156)	Efficacy of semaglutide in obese patients	Type 2 diabetic patients with renal impairment	375	44	2.4 mg	-
8 (NCT04074161)	Efficacy of semaglutide as compared to liraglutide in obese patients	Type 2 diabetic patients	338	68	2.4 mg Liraglutide 3.0 mg	-15.8 -6.4
TEENS NCT04102189	Efficacy of semaglutide in adolescents with obesity	Type 2 diabetic patients; Obesity of secondary origin (hypothalamic or endocrinal)	163	68	1.0 mg	-

Weight reduction activity of weekly-once semaglutide established by STEP (Semaglutide Treatment Effect in People with obesity) trials

significant decline in weight (16%) was exhibited by semaglutide over 5.7% with placebo (40, 43).

The relative benefit of behavioral therapy and low-calorie diet along with semaglutide therapy couldn't be ascertained because it couldn't identify the individual contribution towards weight reduction. This short duration study couldn't make sure that persons treated with semaglutide would sustain this reduced weight after 68 weeks of treatment. Participants with HbA1c greater than 6.5% were excluded from this study (43).

STEP-4 (NCT03548987): Effectiveness of semaglutide was assessed on 902 obese subjects who received weekly-once s.c. semaglutide (initially 0.25 mg, 0.5, 1.0, 1.7, finally 2.4 mg) for initial 20-weeks. During maintenance period, 803 subjects (who achieved 2.4 mg dose during run-in period) randomly received either semaglutide (2.4 mg) or placebo for 48 weeks. Participants who reached the target dose may be switched to the placebo group to study the withdrawal effect of semaglutide therapy. A significant weight loss of 7.9% was observed during the maintenance period, whereas a mean weight loss of 10.6% was exhibited by the 2.4 mg semaglutide during the 68-week long trial. Participants who switched on to placebo treatment gained weight of 6.9% (40, 44).

Inflexibility in run-in period might have resulted in participants with more tolerance and adherence towards semaglutide therapy. It may cause biased results as the trial setting clearly differs from normal clinical settings. Contribution of lifestyle intervention couldn't be assessed. The withdrawal design of the study may cause overestimation of weight loss in semaglutide treated population as compared to a normal participant. Participants with HbA1c greater than 6.5% were excluded from this study (44).

STEP-5 (NCT03693430): Long-term efficacy of weekly-once s.c. semaglutide is being investigated on 304 obese subjects (without type 2 diabetes but having at least one weight related co-morbidities like CV disorder/hypertension/dyslipidaemia/obstructive sleep apnoea). Participants will receive 2.4 mg s.c. semaglutide (initially 0.25, then 0.5, 1.0, 1.7, finally 2.4 mg) or placebo for 104-weeks. The results have not been published (40).

Participants with HbA1c greater than equal to 6.5% were excluded. Contribution of low-calorie diet and physical activity would be difficult to determine (45).

STEP-6 (NCT03811574): Effectiveness of two different doses of weekly-once s.c. semaglutide was explored on 401 East Asian obese type 2 diabetic subjects, who received 2.4 mg s.c. semaglutide (initially 0.25, then 0.5,

1.0, 1.7 and finally 2.4 mg) or placebo or 1.7 mg semaglutide (initially 0.25 mg, then 0.5, 1.0, then 1.7 mg) or placebo. Various parameters like weight loss, change in BMI, FPG, HbA1c, number of adverse events have been studied. A significant decline in weight was exhibited by 2.4 mg semaglutide (13.2%) and 1.7 mg semaglutide (9.6%) over 2.1% with placebo (46).

Type 2 diabetic patients who were also diagnosed with renal impairment or with uncontrolled diabetic retinopathy were excluded from this study. The long-term effects of semaglutide for management of chronic obesity couldn't be studied in this study; whereas STEP-5 covers this aspect with a global population. Adherence to lifestyle intervention couldn't be assessed in this study (46).

STEP-7 (NCT04251156): This on-going trial is aimed at exploring the effectiveness of semaglutide on 375 Chinese obese subjects (with weight related co-morbidity or type 2 diabetes), who receive 2.4 mg s.c. semaglutide or placebo for 44-weeks (47).

Type 2 diabetic patients who were also diagnosed with renal impairment or with uncontrolled diabetic retinopathy were excluded from this study (47).

STEP-8 (NCT04074161): This trial has compared the effectiveness of weekly-once 2.4 mg s.c. semaglutide with daily-once 3.0 mg s.c. liraglutide and placebo on 338 obese subjects (48). Semaglutide was found to be more potent and has achieved a weight loss of 15.8% over 6.4% with liraglutide (49).

Participants with a history of type 1 or type 2 diabetes were excluded from this study. Difference in initial doses of semaglutide and liraglutide may be the reason for high discontinuation rate and relatively lower weight loss achieved by liraglutide. Further biasness was incorporated as the missing data were handled by imputation; however, number of such cases were low (49).

STEP-TEENS (NCT04102189): This on-going trial would explore the safety, efficacy of semaglutide (weekly-once 2.4 mg s.c.) on 163 obese adolescent subjects with or without type 2 diabetes (12–18 years). The results have not been published (50).

Participants with obesity due to secondary reasons (hypothalamic, endocrinal) and those with Type 2 diabetic patients along with unstable diabetic retinopathy were excluded from this study. Apart from this, small sample population is also a limitation of this study (50).

SELECT (NCT03574597): This event-driven, on-going trial is aimed at investigating the efficacy of semaglutide in reducing CV risks (CV death, non-fatal stroke or myocardial infarction) on 17,500 obese subjects (age $\geq$ 45 years) with CV history, who receive weekly-once 2.4 mg s.c. semaglutide (initially 0.24 mg, then 0.5, 1.0, 1.7, finally 2.4 mg) or placebo (51, 52).

Participants with myocardial infarction, stroke within 60 days prior to the screening, and those with type 1 or 2 diabetes were excluded from this study. Irrespective of the positive outcomes, it couldn't provide insight for persons suffering from obesity, CVD, and type 2 diabetes (52).

Semalgutide as An Anti-Obesity Drug

Remarkable weight loss with good safety profile in clinical studies has paved the way for developing semaglutide into a promising anti-obesity drug. Encouraging results from phase-3 STEP trials led to the submission of new drug application (NDA) with priority review voucher for weekly-once s.c. 2.4 mg semaglutide as anti-obesity drug to the USFDA by Novo Nordisk on 4th December, 2020 (53). A similar Marketing Authorization Application (MAA) has been filed with European Medicines Agency (EMA) on 18th December 2020 for introducing weekly-once s.c. 2.4 mg semaglutide for management of obesity (54). Although oral semaglutide didn't show superior efficacy over placebo in the CV outcome trial (PIONEER-6), Novo Nordisk has announced to initiate phase-3a studies on oral semaglutide for treatment of obesity (55). On 4th June, 2021 USFDA has approved weekly-once s.c. 2.4 mg semaglutide (under brand name Wegovy™) for management of obesity (56). EMA has also approved the use of s.c. semaglutide on 11th November, 2021 for management of chronic obesity in patients with at least one weight-related comorbidity like type 2 diabetes, hypertension or CV diseases (57). Thus semaglutide has become the first weekly-once GLP-1 receptor agonist to be used for chronic weight management.

NON-ALCOHOLIC STEATOHEPATITIS (NASH)

Accumulation of excess fat in hepatocytes in absence or little consumption of alcohol is commonly known as non-alcoholic fatty liver disease (NAFLD), which may progress to liver cirrhosis or even to hepatocellular carcinoma. Based on pathological findings, it can be differentiated into two types- simple steatosis or non-alcoholic fatty liver (NAFL) with ballooned hepatocytes or non-alcoholic steatohepatitis (NASH) without ballooned hepatocytes (58, 59). Augmentation of *de novo* lipogenesis in hyperglycaemia provides a direct link between NAFLD and insulin resistance (60). Insulin resistance accompanied with obesity causes increased lipolysis to release free fatty acids from adipose tissue to the liver. Excess food intake causes increased free fatty acid (FFA) load to the liver which increase their oxidation and esterification to triglycerides (61). Impaired free fatty acid metabolism along with increased secretion of VLDL causes accumulation of triglycerides in the form of lipid drops inside hepatocytes, known as steatosis.

Disrupted insulin signalling, lipid peroxidation, activation of inflammatory pathways predisposes to liver injury and inflammation that leads to NAFLD or NASH (62). Various metabolic syndromes like diabetes, obesity, hypertension, atherosclerosis, and dyslipidaemia are commonly associated with NAFLD (63). Even, a direct link has been found to exist between type 2 diabetes and NAFLD (64). Unfortunately, no treatment approach apart from the diet and life style management has been approved till date for the management of NASH/NAFLD.

Although presence of GLP-1 receptor in hepatocytes is still controversial (65, 66), GLP-1 has shown indirect protective action on liver through the gut-pancreas-liver axis. It stimulates hepatic lipogenesis, glucose uptake, reduces hepatic gluconeogenesis and improves insulin resistance (4). GLP-1 receptor agonists have shown hepato-protection by improving hepatic mitochondrial function, insulin sensitivity and by inhibiting the stress response of injured endoplasmic reticulum. They also promotes autophagy to reduce accumulation of free fatty acids and reduces lipotoxicity (67, 68). Reports suggest that patients with NASH have impaired GLP-1 secretion (69); it strengthens the proposition of GLP-1 receptor agonists as a therapeutic option for management of NASH. Various GLP-1 receptor agonists like liraglutide, dulaglutide, semaglutide have shown to improve the pathogenesis of NASH (70). Tirzepatide, a dual agonist of GLP-1 and GIP has been found to improve various NASH-biomarkers in patients with type 2 diabetes (71). Semaglutide, apart from glycaemic control, has also been reported to decrease hepatic steatosis via stimulation of GLP-1 receptors and by reducing inflammation (65, 72, 73). Therefore, many trials have been investigating the effectiveness of semaglutide in the management of NASH/NAFLD (9).

Clinical Trials to Study the Efficacy of Semaglutide in Treatment of NASH

A phase-2 trial (NCT02970942) has been conducted on 320 patients with NASH and fibrosis to explore the efficacy and safety of daily-once s.c. semaglutide. The subjects were randomly assigned (3:3:3:1:1:1) to be given 0.1 mg (n = 80) or 0.2 mg (n = 78) or 0.4 mg (n = 82) semaglutide or daily-once s.c. placebo (n = 80) for 72 weeks. All the three doses (0.1, 02, 0.4 mg) of semaglutide improved NASH without worsening fibrosis in 40%, 36%, and 59% patients respectively as compared to 17% in placebo. However, no significant difference between various treatment groups was observed in improving fibrosis. Semaglutide was well tolerated in all the three doses but without any significant improvement in fibrosis (74).

A proof of concept, phase-2 trial (NCT03987074) explored the effectiveness of semaglutide, when taken alone or with firsocostat and cilofexor for treatment of NASH. This study involved 108 patients with NASH to take either weekly-once s.c. semaglutide (0.24 mg initial dose escalated to 2.4 mg), or semaglutide + daily-once oral 20 mg firsocostat, or semaglutide + daily-once oral 30 mg cilofexor, or semaglutide + daily-once oral 100 mg cilofexor, or semaglutide + daily-once oral 20 mg firsocostat + daily-once oral 30 mg cilofexor for 24 weeks. Significant improvement in NASH and fibrosis was observed with semaglutide monotherapy, but the combination regimen improved further reduction in hepatic steatosis. Semaglutide along with the combination regimen was well tolerated, but highest impact was observed in NAFLD activity score due to the combination regimen (75, 76).

Another placebo-controlled, phase-2 trial (NCT03987451) is underway investigating the effectiveness of weekly-once s.c. semaglutide in NAFLD and cirrhosis patients. This study involves 65 subjects, who received semaglutide (0.25 mg escalated to 2.4 mg) or weekly-once s.c. placebo for 48 weeks. Magnetic resonance imaging (MRI) scans of liver would measure improvement in liver cirrhosis, fibrosis, changes in liver stiffness, liver fat content, NAFLD activity score (77).

A phase-3 trial (NCT04822181) is underway which aims to study the effect of weekly-once s.c. semaglutide monotherapy in NASH patients with no cirrhosis. Progression in cirrhosis, resolution of steatohepatitis, inflammation, histology of ballooned hepatocytes are some of the important end points which would be assessed during this 5 year long study (78).

As there is no clinically approved treatment available, except for dietary management along with exercise; semaglutide monotherapy or in a combination regimen is a ray of hope for successful treatment of NASH. Successful phase-2 trial results encouraged researchers for further clinical evaluation of semaglutide to develop it into a first drug candidate against NAFLD/NASH.

NEURODEGENERATIVE DISEASES

Neurodegenerative diseases like Parkinson's and Alzheimer's diseases are the common form of progressive neurodegeneration which mentally incapacitates a person. Recently, the role of insulin resistance in brain has been deciphered which elucidates a direct link with the pathology of Alzheimer's and Parkinson's disease (79, 80). GLP-1 plays important role in augmenting insulin signalling inside the brain. GLP-1 receptors, present inside the brain, are also involved in cognition, synaptic transmission in hippocampal neurons, and cell apoptosis. Overexpression of this receptor is responsible for cognition enhancement and neuroprotection, while deficiency increases the chances of seizure and neurodegeneration

(81, 82). Therefore, GLP-1 receptors are considered as validated target for exploring candidates with better neuroprotection and cognition enhancing abilities (83). After discovering neuroprotective effects of exenatide, gradually other GLP-1 receptor agonists got the attention for a possible new therapeutic application in the arena of neurodegenerative disorders. Based on drug repurposing strategy, researchers focused on FDA approved GLP-1 receptor agonists with known safety profiles for further exploring their neuroprotective efficacy (84). GLP-1 receptor agonists have been reported to regulate dopamine levels in Parkinson's disease and also aggregation of amyloid β peptides in Alzheimer's disease (7).

Although GLP-1 receptors are expressed in discrete regions of brain like- hypothalamus, brain stem, septal nucleus, and many other neurons (9), till date no data confirms permeation of semaglutide across the Blood Brain Barrier (BBB) in humans. However, certain report suggests that the non-protien form of semaglutide may get access to the GLP-1 receptors in brain through leaks in BBB to carry out it's centrally mediated action (35). Another possibility is that the acylated form of liraglutide and semalgutide helps it in facilitating their entry into some additional regions of the brain (85). Gabery *et al*. have reported that semaglutide doesn't interact with endothelial cells of BBB (86). Salameh *et al*. have also reported that semaglutide do not cross BBB while studying pharmacokinetics of ^{125}I-labeled exendin-4, liraglutide, lixisenatide, semaglutide in adult mice (82).

Alzheimer's Disease (AD)

AD is characterized by impaired memory and cognition affecting speech, behaviour, visuo-spatial orientation and motor system. AD, the most common reason of dementia, is caused by progressive neurodegeneration, often associated with cerebrovascular lesions in brain. The pathogenesis includes cortical atrophy, enlarged frontal and temporal horns in the lateral ventricles of brain, and decreased brain weight. However, presence of extracellular amyloid plaques, intracellular neurofibrillary tangles, cerebral amyloid angiopathy, Hirano bodies, tau-positive neurophil threads, activated microglia and reactive astrocytes are commonly found in AD (87).

Clinical Trials for Alzheimer's Disease

Animal Studies

Zhang *et al*. have demonstrated that daily-once semaglutide (25 nmol/kg) improved the motor impairment, reduced the oxidative injury, inflammation and apoptosis in methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mice model (88). A similar study carried out by the same research group has shown that semaglutide protects dopaminergic neurons from injury by reducing the aggregation of α-synuclein and by enhanced expression of "glial cell line-derived neurotrophic factor" (GDNP), a growth factor. It also augmented the dopamine levels by supplementing tyrosine hydroxylase levels in brain (89). Yang *et al*. have demonstrated the neuroprotective efficacy of semaglutide in the rat model of stroke through decreased inflammation, apoptosis and stabilizing the neurogenesis process (90).

Human Studies

Chang *et al*. have demonstrated the neuroprotective property of semaglutide in human neuroblastoma (SH-SY5Y) cell line against amyloid-β plaques (hallmark of Alzheimer's disease), possibly mediated by enhanced autophagy and inhibition of apoptosis (91). Various pre-clinical and phase-2 study results supported 14 mg oral semaglutide to proceed for phase-3 clinical trials on Alzheimer's patients (92).

Two placebo-controlled phase-3 trials (EVOKE NCT04777396 and EVOKE Plus NCT04777409) have been initiated to study the efficacy of oral semaglutide (14 mg) in patients with early Alzheimer's disease. Change in clinical dementia rating, time taken to reach dementia, change in the Alzheimer's Disease Composite Score are some of the important outcomes that would be assessed from these trials (93, 94).

Parkinson's Disease (PD)

PD is caused by degradation of dopaminergic neurons in substantia nigra followed by loss of axons of these neurons projecting towards nigrostriatal pathway. It is characterized by various motor and non-motor symptoms which includes bradykinesia, tremors, rigidity, ataxia, shuffling gait, and sleep disorder, psychosis. Accumulation of α -synuclein protein in the form of Lewy bodies and activation of microglia, astrocytes are some of the important pathological features in PD. Mutations in several genes like PARK7, PINK1, SNCA, and LRRK2 are responsible for development of various familial and idiopathic forms of PD (95).

Clinical Trials for Parkinson's Disease

A phase-2 clinical study for exploring the effectiveness of semaglutide in Parkinson's disease has been designed and registered by the Oslo University hospital since 2018, but it has not yet started (NCT03659682) (96). This placebo-controlled trial aims to study the neuroprotective and anti-inflammatory effect of semaglutide on both motor and non-motor symptoms, nigrostriatal degeneration, cognitive function, and on quality of life. In addition, this study will confirm the penetration of semaglutide into BBB.

Safety & Tolerability

Adverse Effects

Semaglutide shows mild to moderate gastrointestinal side effects like nausea, vomiting, diarrhoea which is generally dose-dependent and subsides within 2 weeks (97). A few other adverse events like headache, nasopharyngitis, urinary tract and upper respiratory tract infections, increased level of pancreatic enzymes, increased heart and pulse rate, cholecystitis, cholelithiasis have also been reported but were infrequent and not of much concern (31, 39, 98–101). Semaglutide needs dose reduction when it is co-administered with insulin analogues or other hypoglycaemic drugs. SUSTAIN-6 trial has reported 76% higher risk of retinopathy related complications in semaglutide treatment population (102).

Precautions

Semaglutide can't be used in children, adolescents and for treatment of type 1 diabetes and ketoacidosis (103, 104). Although no evidence of pancreatitis has been found with semaglutide treatment (105), still it is advised to discontinue semaglutide in patients with acute pancreatitis. It should be avoided in patients with medullary thyroid carcinoma and MEN 2 (multiple endocrine neoplasia syndrome type 2) (103, 104). European Medicines Agency advises to avoid semaglutide in patients with congestive heart failure (106, 107).

Cardiovascular Safety

Both SUSTAIN-6 and PIONEER-6 study have reported that semaglutide therapy is associated with 24% reduction in various cardiovascular adverse effects (108).

Patient Adherence

Semaglutide can be safely used without any dose reduction in adults, geriatric patients, or in those suffering from renal and hepatic impairment. Semaglutide has not been found to interfere with the bioavailability of digoxin, metformin, lisinopril, oral contraceptives, warfarin, furosemide, atorvastatin, rosuvastatin, and omeprazole (109–113). Therefore, semaglutide is considered as well tolerated among the patients.

DISCUSSION

Drug repurposing strategy is an effective approach for searching different therapeutic opportunities of already established drug molecules. It helps in reducing the cost as well as time needed for successfully launching a drug with known safety and pharmacokinetics profile into the market. GLP-1 receptor agonists improve insulin resistance in liver as well as brain, regulate energy intake in obesity, provide hepato-protective and neuro-protective effect. Reports suggest that various metabolic disorders, NASH are linked to carbohydrate and fat metabolism, insulin resistance, obesity and CV factors. Even neurodegeneration and its progress are linked with insulin resistance and defective insulin signalling in brain. As semaglutide is a clinically approved drug for treatment of type 2 diabetes, obesity and has been proved to reduce CV risk factors, scientists took keen interest in repurposing it for therapeutic use in patients with NASH and neurodegenerative disorders. Semaglutide can be truly considered as a quintessential of GLP-1 receptor agonist which has the potential to act as a drug with versatile therapeutic utilities.

During phase-3 SUSTAIN trials s.c. semaglutide was found to decrease the body weight by reducing energy and calorie intake. The clinical efficacy of semaglutide in obese individuals without type 2 diabetes was studied in STEP-1, STEP-3, STEP-4, STEP-5, and STEP-8 trials; whereas those with type 2 diabetes or with HbA1c greater than 6.5% were included in the STEP-2, STEP-6, STEP-7 and STEP-TEENS. In addition, two of the STEP trials have included individuals from a specific geographical region such as East Asian in STEP-6 and Chinese subjects in STEP-7 trials. STEP-TEENS restricted the study to obese adolescent participants with or without type 2 diabetes. Most of the STEP trials were carried out for a duration of 68 weeks, whereas STEP-5 trial was conducted for 108 weeks investigating the long-term efficacy of semaglutide. Although many of these trials were conducted on obese participants with or without type 2 diabetes, none of them included obese patients with renal impairment or diabetic retinopathy. The primary outcome of all the STEP trials is to determine the mean % reduction in body weight. In addition, various secondary outcomes like change in waist circumference, body mass index, HbA1c, Blood pressure, cholesterol, lipids, triglycerides, free fatty acids, pulse rate, amylase and lipase levels are also studied in these trials. Semaglutide (s.c.) has shown greater efficacy in reducing body weight as compared to placebo and liraglutide in STEP trials. The CV risk attenuating ability and anti-obesity efficacy of semaglutide is being studied in SELECT and STEP-TEENS trial respectively. Encouraging results obtained from the phase-3 STEP trials established the use of weekly-once 2.4 mg semaglutide (s.c.) for management of chronic obesity, as approved by USFDA as well as EMA. Oral semaglutide have also shown weight reducing property in PIONEER trials, although the efficacy was not superior to that of the placebo, still it is expected that very soon trials would be

started regarding anti-obesity effect of oral semaglutide to increase the patient convenience and adherence. Hence, semaglutide can provide dual benefit to patients with type 2 diabetes and obesity (diabesity).

Semaglutide has also shown hepato-protective property and is currently being accessed in phase-3 trial for exploring it's efficacy both in mono- as well as in combination therapy with other drugs in management and prevention of NASH. GLP-1 receptors have been expressed in various regions of the brain and has been linked with brain insulin sensitivity, neuroprotection and cognition abilities. After the neuroprotective effects of exenatide was discovered, gradually other GLP-1 receptor agonists got the attention for a possible new therapeutic application in the arena of neurodegenerative disorders. Based on Drug repurposing strategy, researchers focused on FDA approved GLP-1 receptor agonists with known safety profiles for further exploring their neuroprotective efficacy (73).

An ongoing phase-2 SEMPATICO trial will further explore the efficacy of semaglutide in alleviating myocardial injury in COVID-19 patients with diabetes, obesity, hypertension and CV diseases. This study will also reveal the ability of semaglutide to reduce morbidity in COVID-19 patients (114).

CONCLUSION

Semaglutide is a clinically approved drug for type 2 diabetes, obesity, and a clinical trial candidate for management of NASH, Parkinson's and Alzheimer's disease. Semaglutide is well tolerated and can be safely used in patients with renal, hepatic and CV diseases. Hepatoprotective and neuroprotective role of semaglutide in abating NASH and neurodegenerative diseases respectively has been proved in phase-2 trials and still under study. It improves insulin resistance in periphery as well as in brain, reduce body weight, reduce fat content in liver by acting as agonist on GLP-1 receptor. The efficacy of semaglutide in alleviating cardiac injury in COVID-19 patients with diabetes, obesity, hypertension and CV diseases is being studied. Based on drug repurposing strategy, researchers are trying their best to explore various therapeutic potential of semaglutide. Clinical efficacy in different therapeutic fields proved semaglutide to be an indispensable treatment option for better management of "diabesity" and an emerging cynosure for management of NASH and neurodegenerative diseases.

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Conflicts of Interest The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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