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The Effects of Semaglutide in Adults (18+) with Overweight or Obesity and Diabetes type 2. A Narrative Review

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ABSTRACT

Background and aim: Semaglutide (Ozempic) is one of the innovative medications relating to a family of GLP-1 receptor agonists which was produced by the pharmaceutical company Novo Nordisk to address a clinical need for the effective weight lowering treatment, particularly for the overweight and obese people with diagnosis of Diabetes type 2. Semaglutide was used as monotherapy or added as a supplemental treatment to a basal insulin or other oral anti-diabetic drugs. According to the results of several clinical trials, semaglutide showed an ability to provoke significant weight loss, improve glycemic control, cardiometabolic and cardiovascular parameters. However, despite undeniable benefits, treatment with semaglutide induced adverse effects, among which gastrointestinal disorders were the most frequently reported. The aim of this study is to investigate treatment effects, benefits and drawbacks of semaglutide in the overweight or obese adult (18+) patients with Diabetes type 2.

Methods: This study used a narrative synthesis of retrieved research data. The existing literature on the topic was searched through the PubMed, Clinicaltrials.gov and Google Scholar electronic databases: The search was limited to research studies conducted within 2016-2025 years, systematic reviews, clinical trials, randomized controlled trials, meta-analyses, editorials, published in English language, full-free text peer-reviewed articles. The following research finding were analyzed- efficacy parameters of semaglutide- glycaemic control (change in endogenous insulin secretion, C-peptide, change in the levels of HbA1c, fasting and postprandial plasma glucose, mean change in body weight, cardiometabolic parameters (total cholesterol, triglycerides, systolic and diastolic blood pressure, waist circumference); safety parameters – hypoglycaemia, gastrointestinal disorders (pancreatitis, nausea, diarrhoea, vomiting), malignant neoplasma.

Findings: The analysis of research findings on glycemic control, body weight, cardiometabolic parameters and adverse effects retrieved out of two reviews and six clinical trials demonstrated a high clinical effectiveness of both oral and subcutaneous semaglutide in reducing body weight, HbA1c levels, fasting plasma glucose levels. The effects of semaglutide are dosage-dependent, higher dosages of oral semaglutide were associated with a more pronounced effect. In addition to this, treatment with semaglutide resulted in an improvement in waist circumference, total cholesterol, triglycerides, systolic and diastolic blood pressure. Among adverse events, the most common side effects of semaglutide appeared to be nausea, diarrhoea and vomiting of mild severity and short-term duration, a few cases of pancreatitis and malignant neoplasms were identified; the rate for hypoglycemia was low. The frequency of these events was closely associated with higher dosages of semaglutide.

Conclusion: In conclusion, this narrative review revealed and confirmed that semaglutide significantly improves body weight, glycemic control and cardiometabolic parameters in overweight or obese adult (18+) patients with Diabetes type 2 in both oral and injectable formations. However, prescription of semaglutide must be arranged with cautions, excluding candidate with pre-existing gastrointestinal disorders like pancreatitis, cholelithiasis, gastritis and etc, family history of thyroid cancer, multiple endocrine neoplasia and other thyroid associated disorders. Generally, with compliance to above mentioned conditions, semaglutide can be used as an effective medication for monotherapy or a supplemental therapy in overweight or obese adult (18+) patients with Diabetes Type 2.

1. Introduction

The scientists today are still in search for the comprehensive and effective treatment of Diabetes type 2 because the number of people with diabetes is increasing worldwide with the highest proportion of patients diagnosed with Diabetes Type 2 (almost 90% of all cases of diabetes. According to the World Health Organization, the number of people with diabetes increased from 200 million in 1990 to 830 million in 2022. The World Health Organisation data on mortality showed that in 2021, the main cause of over 2 million deaths were diabetes and associated with diabetes renal and cardiovascular complications; around 11% of cardiovascular deaths were caused by high blood glucose[1]. According to the latest research, Diabetes Type 2 negatively impact neurocognitive functions of the brain, markedly accelerates brain aging and neurodegeneration involving atrophy of gray matter by 24% to 14% faster as compared to normal brain aging.[2]

Semaglutide is a novel drug approved for the treatment of obesity and Diabetes Type 2. It is a peptide relating to the incretin glucagon-like peptide (GLP)-1 receptor agonists family. Semaglutide mimics the effects of GLP-1 and induces higher insulin production, decreases blood glucose levels, slows gastric emptying, thus provoking weight loss. One of the advantages of semaglutide is that it can be used only once a week, in contrast to other GLP-1 receptor agonists like exenatide (twice daily) or lixinatide (once daily).[3] The most effective version of semaglutide – CagriSema represents the conjunction of carlinitide and semaglutide. Carlinitide is a newer amylin analogue which induces satiety through mechanisms such as delayed gastric emptying and actions on specific brain regions. CagriSema induces a significant weight loss and is the most effective medication among other GLP1-receptor agonists.[4,5]

Semaglutide was generated in 2012 and approved for the treatment of Diabetes Type 2 in the USA in 2017 and in Europe in 2019. [6]Initially, semaglutide was prescribed for patients with Diabetes type 2 with the main purpose of improving glycemic control and HbA1c levels. However, the observations showed that the GLP-1 agonist was highly effective in weight reduction and consequently semaglutide was included in the list of medication for the treatment of obesity among patients without Diabetes type 2. To 2022 year, the number of prescriptions substantially increased making semaglutide one of the most frequently prescribed drugs for the treatment of obesity and Diabetes type 2.[7,8]

The demand for the new type of treatment for patients with Diabetes type 2 occurred due to the insufficiency of the existing treatment options. [9] As most patients with Diabetes type 2 are usually overweight or obese and often use basal-bolus regimens with frequent injections, insulin therapy alone brings the unavoidable risk of weight gain associated with a risk of developing cardiovascular complications such as hypertension, hyperlipidaemia and congestive heart failure.[10] Despite its efficacy in glycemic control, insulin therapy has a well-researched and confirmed side-effect as a weight gain.[11]

Moreover, a considerable amount of diagnosed overweight diabetic patients with type 2 has already had cardiometabolic comorbidities and weight gain, in this situation, could worsen the course of existing disease.[12] The supplemental drug having a potential of decreasing this risk is highly recommendable and beneficial for this patient group. The attempts to generate the effective GLP-agonists started much earlier than the invention of semaglutide, but the main issue at that time was a short half-life of generated GLP-1 agonist in plasma and low affinity to GLP-1 receptors. When these barriers were overcome the newly designed semaglutide was presented and successfully tested on large groups of trial participants.[7] The addition of semaglutide to the insulin therapy not only improved glycemic control parameters such as the level of HbA1c and fasting plasma glucose, but also resulted in a significant weight loss.[9]

Semaglutide is produced in injectable and oral formulations. The dose for Diabetes type 2 is 1.0

mg while the dose for weight management is 2.4 mg which is injected subcutaneously once a week. The oral version is usually prescribed in a dose from 7 to 14 mg daily.[7, 8]

With regards to the existing literature and completed research studies and investigations, semaglutide showed the ability to significantly decrease HbA1c levels by 1,55% at a dosage of 1.0 mg and induce cardiovascular improvements in patients with Diabetes type 2.[13,14]

The results of PIONEER 1 trial conducted in 93 countries showed a significant decrease in weight loss and improvements in glycemic control in insufficiently controlled patients with Diabetes type 2 using diet and exercise.[15] According to the data of the PIONEER 6 and SUSTAIN 6 clinical trials along with other GLP-1 receptor agonists, semaglutide positively impacts adverse cardiovascular outcomes, particularly ischemic events and related mortality in patients with Diabetes type 2.[16] The results of the FLOW trial confirmed beneficial cardiovascular effects of semaglutide expressed in a reduced number of deaths and cardiovascular events among a high-risk population with Diabetes Type 2.[17] This efficacy parameter plays an important role in the treatment and management of this patient group because Diabetes type 2 increases the risk of developing and deteriorating of existing cardiovascular diseases, provokes myocardial infarction and stroke. [12] The main reason of cardiovascular complications in patients with insufficiently managed Diabetes type 2 is a persisting hyperglycemia, insulin resistance and excess fatty acids which increase oxidative stress and advanced glycation end-products, disrupt protein kinase C signaling that altogether result in vascular inflammation, vasoconstriction, thrombosis and atherogenesis.[18]

In addition to these improvements, according to Wilding et al, (2021) semaglutide demonstrated the reduction of 15% of baseline weight in obese adults at 68 weeks.[19] In terms of weight lowering effect produced by semaglutide, according to the results of SUSTAIN 8 trial, semaglutide reduced fat mass, lean mass and visceral fat mass after 52-week treatment in overweight and obese patients with Diabetes type 2. As visceral and intra-abdominal obesity is closely associated with insulin resistance and an increased risk for cardiovascular disease, semaglutide appeared to have a potential to effectively address these issues.[20]

Concerning the adverse effects of semaglutide, the most commonly reported side effects of treatment related to gastrointestinal disorders such as nausea, vomiting and diarrhea.[5] Based on animal studies a serious side-effect was also observed– medullary thyroid carcinoma.[21]

The main purpose of this study is to investigate safety and efficacy parameters of Semaglutide, the benefits and side effects of treatment with Semaglutide among adult (18+) patients with overweight or obesity and Diabetes type 2.

2. Methodology

RESEARCH QUESTION

What are the effects of the treatment with semaglutide in adults (18+) with overweight or obesity and Diabetes type 2?

STUDY DESIGN

The study design is arranged as a narrative review. Search strategy.

The existing literature on the topic was searched using the following electronic databases: PubMed and Google Scholar, in order to identify research studies conducted within 2016-2025 time period.

The following search terms with Boolean operators were used: PubMed: "semaglutide" OR "ozempic" AND "diabetes type 2" - 72 articles, Google Scholar: advanced search (filter "in the title of the article") - keywords: "semaglutide", "diabetes type 2" "obesity", type of the article – "any type" - 67 articles identified, Clinicaltrials.gov: "diabetes mellitus", "semaglutide","Ozempic" - 49 relevant trials were discovered.

The literature search was limited to reviews, systematic reviews, clinical trials, randomized controlled trials, meta-analyses, editorials, excluding preprints with the publication date not older than 2016 year, published on English language, full-free text peer-reviewed articles, studies including samples with both males and females, aged 19 years +. After the critical appraisal of the studies, six randomized controlled trials and two reviews were selected for the review. 178 studies were excluded due to the duplications or irrelevance to the research topic.

DATA EXTRACTION

Data extraction includes data on the following basic efficacy and safety parameters of semaglutide such as:

1) Efficacy parameters: change in body weight, cardiometabolic improvements (changes from baseline in waist circumference, systolic blood pressure, diastolic blood pressure (mmHg), total cholesterol, triglycerides), glycaemic control (change in endogenous insulin secretion, C-peptide, change the levels of HbA1c, change in fasting and postprandial plasma glucose levels from baseline).

2) Safety parameters: gastrointestinal disorders (nausea, diarrhea, vomiting, pancreatitis), hypoglycemia, malignant neoplasms.

DATA ANALYSIS

The research findings on predetermined efficacy and safety parameters of semaglutide, retrieved from electronic databases, will be analyzed through a narrative synthesis.

DESCRIPTION OF STUDIES INCLUDED IN THE ANALYSIS.

1. Novo Nordisk, (2024)	The study with a randomized pragmatic study design. Study participants were randomized into two groups, where the first group received injectable semaglutide subcutaneously once weekly in addition to oral antidiabetic drugs (OAD) for 2 years. The other commercially available OADs, excluding semaglutide, were prescribed to the second group. The study sample included 1278 multi-ethnic participants, 644 (48.1% female, 51,9% male) in the semaglutide group and 634 (43.5% female, 56.5% male) in the other OAD group; completed the study 463 in the first group and 447 in the second one.[22]
2.Pantalone K M, (2024)	The study was designed as a randomized controlled trial, open-label design. The study participants (Black, American Indian, Asian and White races) were randomly allocated to the group which will be transitioned from their existing regimen to the rapid-acting insulin aspart and their basal insulin switched to once-daily insulin degludec combined with once weekly semaglutide (Ozempic). The second group used insulin degludec once a day as a long-acting medication and Novolog as a rapid acting insulin and was allowed to continue correction rapid-acting insulin, in addition to their prandial doses of rapid-acting insulin, during the study duration. Semaglutide using sample consisted of 40 participants (female -42.5%, male-57.5%) and only insulins using sample included 20 participants (female 40,0%, male 60,0%). Inclusion criteria was limited to those patients having HbA1c less than 7.5 %, with no family or personal history of medullary thyroid carcinoma, Multiple Endocrine Neoplasia syndrome type 2, acute or chronic pancreatitis, severe liver disease or LFT's > 2.5X ULN, or severe disease of digestive tract.[9]
3. Davies et al, (2017)	The trial was designed as a randomized, parallel-group, dosage-finding trial with 5 dosages of oral semaglutide groups, one subcutaneous semaglutide and placebo

	groups. The duration of the trial – 26 weeks with 5-week follow-up at 100 sites including research centers, hospitals and general practices in 14 countries. 632 participants with type 2 diabetes and inadequate glycaemic control using diet and exercise alone or a stable dose of metformin were randomized and prescribed a trial medication. Randomization was stratified by metformin use. Placebo and oral semaglutide doses were blinded from both the investigator and the patient. Baseline characteristics were similar in all randomized groups (mean age- 57.1 years; male- 62.7%, female- 38,3%); mean HbA_{1c} level, 7.9% (SD, 0.7%); diabetes duration, 6.3 years (SD, 5.2); body weight, 92.3 kg (SD, 16.8); BMI, 31.7 (SD, 4.3).[23]
4. Yao et al, (2024).	This systematic review and meta-analysis contain an extensive research data on effects of 15 different GLP1- receptor agonists (GLP1-RA) including two medications with pure semaglutide and semaglutide combined with cagrilintide (CagriSema), a dual amylin and calcitonin receptor agonist, compared with placebo. 76 randomized controlled trials with a total number of 39246 adult participants were included in this meta-analysis. Most trial contain multi-national samples with the trial duration from 12 weeks to 78 weeks. Baseline characteristics include mean age- 56,79 years(SD 9.59), mean proportion of male -54,06%, mean duration of diabetes – 8,47 years, mean BMI – 31,73 (SD 6,55), mean HbA1c- 8,13%(SD 0,93).[5]
5. Wang et al, (2025).	The 26-week trial followed a randomized controlled study design with double-blinding of investigators and participants. A total of 521 participants were randomized to three interventional treatment groups receiving monotherapy of oral semaglutide (3 mg,7 mg, 14 mg, and one placebo control group. Mean proportion of male participants was 63,7%, mean age – 52 years. Mean HbA1c at baseline – 8,0% and body weight - 79.6 kg.[24]
6. Thethi et al, (2020).	This research study represents a review of 10 PIONEER trials. The PIONEER program was designed to test oral semaglutide among different Diabetes Type 2 patient groups. Oral semaglutide in doses ranging from 3 to 14 mg was tested across groups managed by diet and exercise and those using daily insulin injections, patients with comorbidities like cardiovascular diseases (CVD) and chronic kidney disease (CKD), with duration of diabetes from 3,5 to 15 years. Semaglutide was tested against placebo or active comparators (liraglutide, sitagliptin, empagliflozin) in a randomized controlled trial format. Baseline characteristics of the participants- age > 18 years, with the diagnosis of Diabetes Type 2 at least 3 months before screening, baseline HbA1c within the range of 7,0% to 9,5%. Mean age ranged from >50 to >70. Participants with comorbidities was older than 60 and have a longer mean duration of Diabetes type 2 - 14 years. Trials duration ranged from 26 to 52 weeks.[25]
7. Dahl et al, (2021).	The study was designed as randomized, placebo-controlled, double-blind, crossover trial conducted at a single site in the UK (Covance Clinical Research Unit Ltd, Leeds, UK). Two treatment periods of 12-week duration, with the last 4 days of in-house meal test period. Treatment with semaglutide was separated by 5–9 weeks of wash-out period. 15 subjects were enrolled for the trial. Baseline characteristics included mean age 58,2 years, HbA1c 6.9%, body weight 93.9

	kg, diabetes duration 3.1 years, 86,7% males. The following endpoints were assessed – glucose, insulin and C-peptide (fasting) and over the 5 h postmeal (postprandial). The primary point was the area under the concentration–time curve (AUC) from 0 to 5 h after the start of the meal (AUC_{0-5h}).[26]
8. Kapitza, (2017).	The 12-week trial with 5-week follow up was conducted at the Profil Institut für Stoffwechselforschung, Germany and designed as a single-centre, randomised, double-blind, placebo-controlled trial with 75 participants having diagnosis of Diabetes type 2 and a healthy comparator group (n= 12). Healthy participants were included with the intention to evaluate beta cell responsiveness to graded glucose infusion. Participants with Diabetes type 2 were randomised to once-weekly subcutaneous semaglutide 1.0 mg (n=37) with a fixed-dose escalation regimen or placebo (n= 38). Participants followed a fixed-dose escalation regimen (0,25, 0,5, 1 mg). Healthy comparator group did not receive any treatment. Baseline characteristics of participants: mean age – 55,9 years, mean HbA1c – 7,3%, mean body weight- 91,6 kg, BMI- 29,6, diabetes duration -8,5 years, male -27%, male- 68,1%. The primary endpoints included the change from baseline to the end of treatment in fasting and postprandial glucose levels, C-peptide- the indicator of endogenous insulin production, first and second -phase insulin secretion rate and glucagon; change in body weight was a secondary endpoint.[27]

3. Results

The results for glycemic control parameters comprised measurements of HbA1c, fasting and postprandial glucose levels. HbA1c parameter was examined in six studies. The results showed a similar statistically significant, dose-dependent reduction from baseline to the end of trial across all studies: Novo Nordisk AS, (2024)- changes in the level of HbA1c (unit of measure: percentage-point of HbA1c), from baseline to year 1 - by 1,46 in the semaglutide group and 1,14 in the other OAD group; from baseline to year 2- by 1,45) in the semaglutide group and 0,98 in the other OAD group. Confidence interval (CI) for both [1,03 to 1,79]; p -value -0,033. HbA1c less than 7.0 % (53 mmol/mol) at year 2 - 206 in semaglutide group and 162 in the other OAD group; HbA1c less than 7.0% (53 mmol/mol) without experiencing hypoglycaemia at year 2 - semaglutide group- 108, other OAD group – 76.[22]

The study of Pantalone,(2024), Yao et al, (2024), Wang et al (2025), Davies et al,(2017) and Thethi et al, (2020) revealed a similar significant decrease in HbA1c concentrations: Pantalone,(2024) – the mean change in HbA1C ≤ 7.5% from baseline to 26 weeks (unit of measure: % glycated haemoglobin) - the semaglutide group -0,5 (0,7 to 0,3), the other OAD group- no change 0(-0,3 to 0,3) (p-0,009); Yao et al,(2024) - change in the mean HbA1c levels - semaglutide - MD -1,40 (CI -1,67 to -1,12) and CagriSema - MD -1,80 (CI -2,87 to -0,73) as compared to placebo; Wang et al,(2025)- the estimated treatment differences (ETDs) for oral semaglutide 3,7,14 mg versus placebo –11 (CI95%,–13 to –9) mmol/mol, –16 (CI95%, –18 to –13) mmol/mol and –17 (CI95%,–19 to –15) mmol/mol, respectively.[5,9,24]

A statistically and clinically significant reduction in oral semaglutide and standard and fast escalation groups were indicated by Davies et al, (2017) – mean HbA1c level reduced by 1,8% versus 0,3% for placebo group – (ETD, –1,5% [95% CI –1,7% to –1,2%]; p < 0,001. ETDs for dosage-dependent oral semaglutide versus placebo −0,4% (95% CI, –0,7% to –0,1%] for the 2.5-mg group; –0,9% [95% CI, –

1,2% to –0,6%] for the 5-mg group; –1,2% [95% CI, –1,5% to –0,9%] for the 10-mg group; –1,4% [95% CI, –1,7% to –1,1%] for the 20-mg group; and –1,6% [95% CI, –1,9% to –1,3%] for the 40-mg standard escalation group (p- 0,007 for the 2.5-mg group, <0,001 for other dosages); subcutaneous semaglutide - decrease by 1,9%.[23]

The study of Thethi et al, (2020) representing the data from PIONEER trials, revealed a similar decrease in HbA1c among patients with moderate renal impairment, long-standing diabetes and those at high cardiovascular risk- PIONEER 1: oral semaglutide versus placebo [ETD 0 –0.6% [3 mg] to −1.1% [14 mg], p < 0,001; PIONEER 8: ETD −0.5% [3 mg] to −1.2% [14 mg]; P < 0,0001); PIONEER 5: oral semaglutide 14 mg against placebo [ETD –0.8%; p < 0,0001]; PIONEER 5: oral semaglutide −1,0% versus −0,3% placebo; PIONEER 9 and 10: similar findings were observed with oral semaglutide 14 mg compared with placebo.[25]

Regarding the change in fasting plasma glucose parameter, the results also favored all interventional semaglutide receiving groups versus placebo, showing a significant decrease at the end of trial. The results were consistent across all six studies: Davies et al, (2017) - MD - 1,1(–9,6 to –7,5), oral semaglutide 2,5 mg group - MD -17,3(–9,6 to –7,5), oral semaglutide 10 mg group - MD -42,1(–50,4 to –33,9), oral semaglutide 40 mg group - MD -51,2 (–60,0 to –42,4); subcutaneous semaglutide 1 mg group - MD –56,3 (–65,3 to –47,4).[23]

The study of Yao et al,(2024) reported- oral semaglutide - MD -1,99 (CI -2,41 to -1,58) , CagriSema - MD -2,79 (CI- 4,30 to -1,28); Wang et al,(2025)- ETD CI95% oral semaglutide 3 mg (–1,30(CI-1,68 to -0.91)), oral semaglutide 7 mg – (-2,05 (CI-2,44 to -1,67)) oral semaglutide 14 mg (-2,20 (CI -2,58 to -1,81).[5,24]

For Thethi et al,(2020) - the results reached statistical significance and ranged from -0,9 to 2,6 across trials; Dahl et al(2021)- blood glucose level before the standard breakfast: oral semaglutide versus placebo- ETR, 0,78 (CI95%, 0,70 to 0,87), after the fat-rich breakfast (postprandial): oral semaglutide - glucose AUC0–8h- (ETR, 0.77; 95% CI, 0.68 to 0.87; p = 0,0007), p = 0,000; Kapitza,(2017)- semaglutide was superior to placebo in the reduction of fasting blood glucose - ETR 0,78 (CI95% 0,74 to 0,83).[25,26,27]

Concerning the effect of semaglutide on beta-cell sensitivity, the results of two studies showed that semaglutide was effective in increasing C-peptide and insulin levels. The results for glucose graded infusion tests also benefit semaglutide: Dahl et al, (2021) - fasting insulin: oral semaglutide versus placebo (ETR, 1,47; 95% CI, 1,11 to 1,96; p = 0,0132); fasting C-peptide: oral semaglutide group versus placebo (ETR, 1,25; 95% CI, 1,05 to 1,48; p = 0,0191); glucose AUC0–5h [ETD], −1.25 mmol/L; 95% CI, −2.04 to −0.45; p = 0,0053).[26]

According to Kapitza,(2017) - insulin (1,30 [CI95%, 1,11 to 1.53]) and C-peptide (1,23 [1,14 to 1,32]) were higher with semaglutide. Similarly, ISR AUC 5–12mmol, pmol/kg, Slope ISR versus glucose, pmol × l/(min mmol−1 kg−1) were significantly higher in the semaglutide group as compared to the placebo group (ETR) [95% CI] 2,45 [2,16 to 2,77] and 2,78 [2,44 to 3,16], respectively; p < 0,0001.[27]

The body weight parameter was examined in seven studies where semaglutide showed a significant reduction of body weight across all studies from baseline to the end of trial. The following results were reported in the study of Novo Nordisk, (2024)- percentage change in body weight from baseline to year 2 in the semaglutide group: MD -4,47 (12,204) and -2,68 (7,988) in the other OAD group; Pantalone, (2024) - a considerable reduction in body weight with semaglutide: MD -8,6 (CI95%, -9,6 to -7,6) as compared to the other OAD group 1,4 (0 to 2,8). In contrast to semaglutide group, weight gain was detected in the second group. The results showed a high statistical significance – p-value < 0,001.[22,9]

For Davies et al, (2017)- the results showed a significant difference between placebo and

semaglutide groups with the highest reduction in groups using semaglutide with a dosage higher or equal to 10 mg : the placebo group MD–1,4 [–2,5 to –0,2], oral semaglutide 10 mg MD –5.2 [–6,4 to –4,1], oral semaglutide 20 mg MD –6.6 [–7,9 to –5,4] , oral semaglutide 40 mg MD –7,6 [–8,7 to –6,4] and subcutaneous semaglutide 1 mg MD –7,3 [–8,5 to –6,1].[23]

The study of Wang et al, (2025) demonstrated similar findings - a statistically significant reduction in BMI (kg/m2) from baseline was detected in oral semaglutide 7 mg (–0,8) and oral semaglutide 14 mg (–1,1) groups. The result for 3 mg group did not reach statistical significance. The dosage of 14 mg led to the highest decrease in BMI. A significant decrease in body weight was observed in both oral semaglutide 7 mg and 14 mg groups, except oral semaglutide 3mg; estimated treatment difference with a placebo group, oral semaglutide 7 mg: (CI95% –1,2 kg [–2.0 kg to –0,4 kg; p<0,01], oral semaglutide 14 mg: (–2,0 kg [–2.8 kg to–1,2 kg; p<0,001].[24]

The findings of Yao et al, (2024) and Kapitza,(2017) confirmed the efficacy of semaglutide in body weight reduction: a significant decrease in body weight was induced by CagriSema - MD −14.03 kg (CI95% −17,05 to −11,00). Semaglutide showed a moderate reduction in body weight -3,13(CI95% -3,95 to -2,31). 5 The study of Kapitza,(2017) revealed that body weight decreased by 4,2 kg in the semaglutide group, compared with 0,1 kg for placebo (ETD [95% CI] −4,1 [−5,1 to −3,1]) over 12 weeks.[27]

The results of PIONEER trials presented in the study of Thethi et al, (2020) showed similar reductions in body weight gain in different patient groups, including those with comorbidities: PIONEER 1- in patients with early diabetes type 2, managed with diet or exercise oral semaglutide in all 3,7,14 doses demonstrated a significant reduction in body weight at week 26 [ETD −0.1 kg [3 mg] to −2.3 kg [14 mg]; p < 0,001] versus placebo; similar results were observed in PIONEER 7 trial- ETD −1.9 kg; p < 0,0001 at week 52.

For PIONEER 8,5,6 trials: in patients with advanced diabetes type 2 receiving insulin, oral semaglutide 3, 7 and 14 mg were superior to placebo in reducing body weight at week 26 [ETD −0,9 kg [3 mg] to −3,3 kg [14 mg]; p ≤ 0,04] and week 52 [ETD −1,3 kg to −4,3 kg; p ≤ 0,0101]; in patients with moderate renal impairment, oral semaglutide 14 mg induced a significant weight reduction at week 26 [ETD −2, 5 kg; p < 0,0001] versus placebo; in patients with CVD, CKD and cardiovascular risks the mean weight loss was -4,2 kg with oral semaglutide and -0,8 with placebo.[25]

The research findings on cardiometabolic parameters were presented in six studies and generally favours semaglutide treatment groups. The lower levels of blood lipids, cholesterol, systolic and diastolic pressure were detected with semaglutide.

The results for waist circumference presented in studies of Davies et al,(2017), Thethi et al,(2020), Yao et al,(2024) and Wang et al,(2025) showed a statistically significant decrease in groups receiving both oral and subcutaneous semaglutide: Davies et al,(2017) - placebo group MD –1.7 [–2.9 to –0.4], oral semaglutide 40 mg MD –5.8 [–7.0 to –4.5], subcutaneous semaglutide 1 mg –6.2 [–7.4 to –5.0]; Thethi et al,(2020) - the reduction was higher with oral semaglutide versus placebo and other active comparators; Yao et al,(2024) - the reduction was significantly higher with semaglutide vs placebo – (SUCRA) surface under the ranking curve -97.6. Higher surface under the curve reflects higher probability of association with waist circumference; Wang et al, (2025)- higher reduction in oral semaglutide 14 mg group (-2,8) versus placebo control one (-1,3).[5,23,24,25]

The results for systolic and diastolic blood pressure were examined in the studies of Novo Nordisk, (2024) and Davies et al, (2017). Both studies confirmed superiority of semaglutide versus placebo in reducing systolic and diastolic blood pressure: Novo Nordisk, (2024) - change in systolic blood pressure (SBP)

from baseline to year 2 in the first group reduced by – 3,0 (17,03), in the second group by -2.8(16,91) mmHg. Change in DBP from baseline to year 2 in the semaglutide group -1,9 (10,58), the second group -1,4 (9,92) mmHg.[22]

For Davies et al,(2017)- SBP- significant decrease in all dosage groups: oral semaglutide 10 mg group MD –7,8 [–10,9 to –4,6]; oral semaglutide 2,5 mg –5,4 [–8,5 to –2,3] – oral semaglutide 5 mg -6,6 [–9,8 to –3,5] ; oral semaglutide 20 mg –6,2 [–9,6 to –2,7]; oral semaglutide 40 mg –6.1 [–9,5 to –2,6]; subcutaneous semaglutide 1 mg –5,7 [–9,2 to –2,2]; the placebo group –2.7 [–5,7 to 0,4]; DBP - oral semaglutide 10 mg group - MD –3.1 [–5.1 to –1.2], the placebo group - MD –2.4 [–4.3 to –0.5].[23]

In terms of cardiometabolic parameters like blood lipids and cholesterol, these data were investigated in three studies, with similar findings- treatment with semaglutide was associated with lower levels of cholesterol, low-density lipoproteins (LDL) and triglycerides.

The results are following: Yao et al,(2024)- a moderate effectiveness in lowering the levels of low-density lipoprotein (MD−0,16 mmol/L (95% CI−0,30 to −0,02 and total cholesterol (−0,48 mmol/l (−0.84 to −0,11) in semaglutide treatment groups; Wang et al, (2025)- oral semaglutide 14mg was associated with a clinically and statistically significant reduction in total cholesterol treatment ratio (95% CI) 0,93 (0,89 to 0,96) p< 0,001, LDL cholesterol 0,93 (0.87 to 0,99) p< 0,05 and triglycerides: 0,90 (0,80 to 1.00) p< 0,05.[5,24]

For Dahl et al, (2021)- fasting LDL: ETR 0,88 (CI95%, 0,84 to 0,94; p = 0.0005), total cholesterol: ETR, 0,88; (0,84 to 0.91; p < 0,0001), triglycerides: ETR 0,81; (0,72 to 0,92; p = 0,0036). The postprandial data demonstrated similar reductions: ETD, −0,36 mmol/L; (CI 95%, −0,68 to −0,04; p = 0,0317) for triglycerides, very low-density lipoprotein: ETR 0,79; (0,68 to 0,93; p = 0.0102).[26]

With regards to safety of semaglutide, generally, the adverse events were higher with semaglutide as compared to placebo. Mostly, these events related to gastrointestinal disorders. The most frequently reported adverse events related to gastrointestinal disorders like nausea, vomiting, diarrhoea, constipation, dyspepsia, pancreatitis and abdominal pain of mild and moderate severity.

The following results were presented in eight studies: Davies et al, (2017)- nausea and vomiting were higher with oral semaglutide (31%-77%; 255 of 490 patients) and subcutaneous semaglutide (54%; 37 of 69 patients) as compared to placebo group (28%; 20 of 71 patients). Fewer nausea events were reported in the lower dosage groups (2.5 mg and 5 mg). Three cases of pancreatitis were also reported in semaglutide groups with dosage 20 and 40 mg, and subcutaneous semaglutide group; a considerable increase of amylase and lipase was revealed in the study of Thethi et al,(2020), however, no cases of acute pancreatitis were observed.[23,25]

The study of Pantalone, (2024) reported pain, vomiting and colitis in the groups receiving oral semaglutide; similar observations were made by Wang et al, (2025) - nausea, vomiting and diarrhoea of short duration and mild severity were higher with oral semaglutide 3 mg: 16.2%, 7 mg: 32.3% and 14 mg: 31.8%) than with placebo (9.2%).[9,23,24]

The similar results were revealed in studies of Dahl et al,(2021): 51 events of gastrointestinal disorders were reported in oral semaglutide receiving groups against and 13 events in placebo groups; the study of Kapitza,(2017) has similar revelations- higher percent of gastrointestinal disorders was reported in the semaglutide treatment group- 51.4% participants (nausea -18,9%, vomiting -16,2%, diarrhoea- 10,8%), as compared to 15.8% participants in the placebo group.[26,27]

The study of Yao et al,(2024) showed that CagriSema and semaglutide were positively associated with nausea, vomiting and diarrhoea compared with placebo: odds ratios for semaglutide: nausea OR 3,86 (ci 95% 2,76 to 5,40), vomiting OR 4,25 (ci 95% 2,69 to 6,74), diarrhoea or 2,37 (ci 95% 1,84

to 3,06); odds ratios for CagriSema: nausea or 8,21 (ci 95% 1,95 to 34,61), vomiting or 4,25 (ci 95% 13,67 to 163,98); diarrhoea or 6.60 (ci95% 1.16 to 37.76).[5]

The rates for hypoglycemia were low across all eight studies. 2 episodes of hypoglycemia was reported in the study of Novo Nordisk, (2024); 2 episodes in subcutaneous semaglutide group and oral semaglutide 40-mg group in the study of Davies et al,(2017); 3 hypoglycemic events were detected in the study of Wang et al,(2025); in PIONEER trials, about 8% of participants receiving oral semaglutide experienced mild hypoglycemic episodes, with most cases in insulin requiring patient groups.[22,23,24,25]

Concerning cardiological adverse events- the study of Novo Nordisk,(2024) reports fewer cases of acute myocardial infarction and coronary artery disease in semaglutide receiving group; a similar cardioprotective effect was observed in the PIONEER 6 trial: a lower incidence of CV-related death (HR = 0,49 [95%CI, 0,27 to 0,92]) and all-cause death (1,4% vs 2,8%; HR = 0,51 [0,31 to 0,84]) was observed in semaglutide treatment groups as compared to placebo.[22,25]

Regarding malignant neoplasms, a few cases were identified in the study of Thethi et al,(2020).[25]

4. Discussion

This review comprehensively evaluated the efficacy and safety of treatment with the innovative GLP-1RA semaglutide in adults having excess body weight and Diabetes type 2.

The effectiveness of glycaemic control, impact on cardiometabolic and body weight parameters, frequency and severity of adverse events were assessed through six randomized controlled trials involving 2213 participants and two reviews including pooled analysis of 76 studies and review of the PIONEER program data, investigating effect of semaglutide along with other GLP1- RA.

For glycaemic control, semaglutide showed a significant reduction in both fasting and postprandial glucose levels, HbA1c concentrations compared with placebo across all the reviewed studies. The parameter of glycated haemoglobin was examined in six studies. The reduction of HbA1c levels ranging from 0,5 to 1,9% and associated with semaglutide was observed across all studies, including samples with patients having cardiovascular or renal comorbidities. The reductions increased with the escalation of the dose, in a dose -dependent manner. For the subcutaneous semaglutide groups, the decrease in mean HbA1c levels was similar to the results for 20mg and 40 mg oral semaglutide groups.[22,23] In addition to this, the number of participants who achieved HbA1c less than 7.0% without experiencing hypoglycaemia was higher in semaglutide receiving groups versus placebo.[22]

Concerning the change in fasting plasma glucose parameter, which was considered in six studies, a considerable dosage-dependent decrease was observed in subcutaneous and oral semaglutide groups with the highest decrease observed in semaglutide subcutaneous 1 mg groups.[24,25] The other measurement of glucose involved before and after meal analyses, considered in two trials. According to the study of Dahl, (2021), fasting glucose before the standard breakfast was 22% lower with oral semaglutide. The similar reductions were observed in after the fat-rich breakfast (postprandial) results.[26]

Another benefit of semaglutide is a positive impact on ß-cell sensitivity. Two studies identified that semaglutide increased a C-peptide level, insulin secretion- both fasting and after meal, however, partly these effects might be the result of body weight loss induced by semaglutide.[26,27] Concerning the markers of beta cell responsiveness, glucose graded infusion tests demonstrated that beta cell responsiveness improved after the treatment with semaglutide and resembled that of healthy participant- glucose AUC0–5h was 29% lower in semaglutide receiving group.[26] Reductions in glucose levels with semaglutide were identified in both fasting and postprandial states. The increase in the indicators of insulin secretion from baseline to end of treatment were significantly higher in the semaglutide groups as

compared to the placebo groups. The results for fasting insulin and fasting C-peptide, in the group treated with oral semaglutide, were greater than in placebo group by 47% and 25%, respectively.[26]

In general, the analysis of effects observed in oral semaglutide treatment groups showed an increase in ß-cell sensitivity as compared to placebo groups. The same beneficial effect was identified with body weight parameter, examined in seven studies. Semaglutide demonstrated a consistent and stable decrease in body weight in all patient groups with different diabetes duration, age, with and without comorbidities like cardiovascular or renal complications of diabetes. These effects showed dose-dependency with the strongest effect observed in dosages 14mg and higher. Drawing on the summary results for body weight reduction in the PIONEER program, oral semaglutide was effective in reducing body weight across all PIONEER trials. The weight lowering effect was higher in 7 and 14mg doses reflecting dose-dependent efficacy.[25]

With regards to the meta-analysis of Yao et al, (2024), a pooled analysis of 53 trials demonstrated an extreme effectiveness of treatment with GagriSema leading to a significant decrease in body weight. CagriSema in this category was identified as a most effective medication. Semaglutide showed a moderate reduction in body weight but also proved its weight lowering effect.[5]

Drawing on the results of this review, semaglutide possesses an ability to improve cardiometabolic parameters lowering lipid levels (low density lipoprotein, cholesterol, triglycerides), waist circumference, systolic and diastolic blood pressure. These parameters were examined in six studies, with the most comprehensive data extracted from the PIONEER program.

In the PIONEER 6 trial, with participants facing a high cardiovascular (CV) events risk, oral semaglutide was associated with a lower incidence of CV-related death in comparison with placebo. In other PIONEER trials, the incidence of cardiovasclular events remained low across all groups (placebo, oral semaglutide and other glucose-lowering drugs).[25] Regarding lipid levels examined in three studies, treatment with oral semaglutide resulted in a stable and clinically significant reduction of low-density lipoprotein, cholesterol and triglycerides which was maintained over time. The reduction in systolic and diastolic blood pressure was similar or slightly higher in comparison with other GLP1-RA used as active comparators.[5,24,25]

The parameters like systolic and diastolic blood pressure were examined in two studies, and the results demonstrated clinically significant decrease in all dosage groups with the highest numbers in oral semaglutide 10 mg group.[5,24,25,22] For this cardiometabolic parameter, oral semaglutide in dosage > or = 5mg appeared to be more effective in the reduction of blood pressure. Changes in diastolic blood pressure showed less variety and were generally lower than those for systolic blood pressure – the highest decrease was in oral semaglutide 10 mg.

The results for waist circumference parameter presented in four studies, reflected a statistically significant decrease and were generally higher in semaglutide receiving groups, peaking at dosage 40 mg for oral semaglutide and subcutaneous semaglutide 1 mg.[5,25,23]. According to Thethi et al, (2021), waist circumference was also reduced with oral semaglutide more effectively than with placebo or other comparators. The reduction was dosage dependent.[25]

In general, drawing on the results of PIONEER trials, it can be concluded that semaglutide is effective not only among patients without comorbidities, but also in those having renal impairment and cardiovascular diseases. Regarding weight loss, semaglutide proved to be more effective medication than other OADs and placebo in patients with different stages of obesity and Diabetes type 2, especially in conjunction with carlinitide.

Concerning safety of semaglutide considered in all research studies, the reports of malignant thyroid

neoplasms raised a concern. Even though only one study reported this adverse event in a few participants, close attention to this fact is still required.[25] The incidence of hypoglycaemia was generally low across all studies. Among other adverse events transient gastrointestinal disorders were the most frequently observed, including diarrhoea, nausea and vomiting of mild and moderate severity. These three side-effects of treatment with semaglutide were reported in all the reviewed studies. Few cases of pancreatitis were also observed.[5,25]

Generally, adverse events in semaglutide treatment groups were higher as compared to placebo groups. These data coincide with the data obtained from the FAERS database and social media reviews. From 2018 to 2023 years, 76.83% of adverse events reports were submitted by health professionals and by 22.24% by consumers. The analysis revealed that 30.19% of total adverse events in oral semaglutide and 27.76% in subcutaneous semaglutide constitute gastrointestinal disorders. Although the source of data can be biased, in general, the FAERS database is professional and comprehensive.[8] A similar observations were made in the study of Smith and Van Raalte (2021), reporting a wide range of gastrointestinal disorders such as nausea, vomiting, diarrhoea, constipation, colitis and pancreatitis among patients receiving semaglutide.[28]

Overall, drawing on the results of this review, the introduction of semaglutide in clinical practice can benefit patients having Diabetes type 2 with and without comorbidities. Treatment with semaglutide as an additional or monotherapy can be particularly beneficial for overweight and obese adult patients with Diabetes type 2 using insulin therapy. To be precise, the frequency of insulin injections will decrease which can be considered as an additional benefit due to the conveniency for patients, who struggle to adjust to the insulin regimens in a real-world setting.[9,22] Also, the reduced dose of insulin minimizes a risk of insulin-induced weight gain.[11]

Another benefit is that this may reduce the risk of local lipodystrophy. The additional benefit is that semaglutide promotes the secretion of endogenous insulin which can be suppressed by high doses of insulin.[9,22] The successful transition to once-weekly semagutide and once-daily basal insulin can be transformational for patients with Diabetes type 2 and tremendously impact their quality of life.

STRENGTHS

This review provides data on the most essential efficacy and safety parameters of semaglutide. Regarding validity of the reviewed studies, out of six randomized controlled trials, only two followed an open-label design, the remaining studies include double-blinding of both patients and investigators. Masking is essential to avoid the risk of observer/participant bias and therefore these results possess high internal validity.[29] Most trials included in the reviews of Thethi et al, (2020) and Yao et al, (2024) included large, multi-ethnic and multi-national samples, participants either using diet and exercise or glucose lowering medications like metformin, other OADs and insulin therapy. Recruitment was performed in general practices, medical institutions, hospitals according to eligibility criteria. Samples with insulin requiring patients with Diabetes type 2 and those with comorbidities were also presented.[5,25] This diversity increases reliability and generalizability of results.[30]

The one study followed a pragmatic design, which also increases generalizability and provides evidence for adoption of a new intervention into the real-world clinical practice.[31] All studies included in this review used quantitative research methods and were performed with high methodological rigor. Despite many cases of gastrointestinal adverse events, the rate of discontinuations and withdrawals from a trial remained low.

The meta-analysis of Yao et al, (2024) provides an extensive data retrieved out of 76 studies making this study the most comprehensive existing research on the topic with high quality of evidence.[5,32] As all of the included studies followed a randomized controlled trial design, the research findings possess a high internal validity especially in experimental interventions.[29,33]

In general, the studies included in the review possess high methodological quality, the study duration ranged from 12 to 52 weeks with follow-ups, a wash-out periods from 5-9 weeks were organized in studies with crossover designs to minimize a risk of a carryover effect.[34] All the included studies are ethically sound, with written informed consent provided from all participants.

LIMITATIONS

This review has several limitations. Firstly, the meta-analysis of Yao et al, (2024) included trials with varied population characteristics, follow-up durations and different measurements of blood samples like HbA1c level measured in percentage-point and mmol/mol and fasting blood glucose in mg/DL and mmol/l. Although the results across studies remained consistent, it may lead to imprecise effect estimates.[5] Secondly, blood glucose levels and body weight might be influenced by the different diet and exercise over which trial participants had a little control. Thirdly, some trials did not present properly information about the randomisation, allocation concealment and blinding for investigators.[5]

Two studies included in this review had a short duration of the trial, long-term data would provide more precise information about efficacy and safety parameters of semaglutide. Also, the results for insulin secretion and C-peptide were obtained from two trials with short-duration and low number of participants, which may affect the precision of the results.[26,27] The low number of participants may lead to a random error , wide confidence intervals and low precision of the results.[35]

In addition to this, almost all trials had a design of a randomized controlled trial which has a limitation like low external validity. The results may differ in a real-world settings with a more diverse population characteristics and lack of supervision; the applicability of these results to wider population groups may raise a concern.[29,36]

Another limitation is that patients with retinopathy and other vision impairment diseases associated with Diabetes type 2 were excluded from the trials; the same exclusions were made for those with severe obesity, the mean BMI ranged from 25,1 to 30.[24] Concerning the mean age of the trials' participants, the largest proportion constitute patients aged > 65 years; the older category was underrepresented. Also, male participants prevailed, and female patients were underrepresented.

Finally, although most of the included studies stuck to a rigorous methodology and protocols, some trials had a potential risk of bias, such as open label design and pharmaceutical industry funding.[5,22,29]

5. Conclusion

In conclusion, the thorough analysis of six randomized controlled trials and two reviews showed that semaglutide in both oral and subcutaneous formations produces following effects in the treatment of overweight or obese adults (18+) with Diabetes Type 2: semaglutide is efficacious in reducing the level of HbA1c, fasting and postprandial blood glucose levels in monotherapy and as an additional supplement to other OADs and insulin.

Therefore, semaglutide has a potential to improve overall glycemic control in patients with Diabetes type 2. Additionally, semaglutide demonstrated a high efficacy in reducing body weight and improving cardiovascular outcomes expressed in a clinically significant decrease of cardiovascular events among semaglutide treated groups. Also, semaglutide possesses the ability to enhance cardiometabolic parameters like blood lipids, waist circumference, systolic and diastolic blood pressure across all patient groups. However, despite numerous benefits of semaglutide, the frequent reports of gastrointestinal disorders must be taken into consideration. The medication can be prescribed with precautions, and a scrupulous analysis of pre-existing gastrointestinal diseases should not be overlooked.

Overall, drawing on the above mentioned facts, semaglutide may be used in clinical practice with precautions and exclusion of patients who have family history of thyroid cancer, or pre-existing

thyroid associated and gastrointestinal disorders. A regular screening is also required. With regards to further research, the inclusion of patients with severe obesity and those having higher baseline HbA1c levels is justified to explore its potential in patients who are inadequately controlled. Also, markers of beta cell responsiveness like C-peptide, glucose graded tests and insulin secretion should be analysed through trials with a larger number of participants and longer duration.

Conflict of Interest:

None

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None

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