Glycaemic Control, Obesity Management, and Cardiovascular Outcomes of Semaglutide for Type 2 Diabetes Mellitus Patients: An Umbrella Review and Meta-meta-analysis

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OBJECTIVE

To evaluate glycaemic control, obesity management, and cardiovascular outcomes associated with semaglutide in patients with type 2 diabetes mellitus (T2DM)

INTRODUCTION

- As of 2024, an estimated 540 million adults (aged between 20-79 years) are living with diabetes, with 90% diagnosed with T2DM. This is projected to increase to 643 million by 2030 and 783 million by 2045[1]
- Diabetes led to approximately 966 billion USD in global health expenditure, a 316% rise over the past 15 years[1]
- Semaglutide, developed to treat T2DM and obesity, is the only GLP-1 receptor agonist currently available as both peroral (PO) and subcutaneous (SC) formulations

METHODS

- A comprehensive literature search was conducted using multiple databases from inception till June 2024.
- Studies were screened at two levels (title-abstract and full-text) based on pre-specified inclusion and exclusion criteria to identify meta-analyses of randomized controlled trials (RCTs) comparing semaglutide with placebo or other anti-diabetic drugs (OADs)
- Meta-meta-analyses were conducted to combine the meta-analysis results from reviews with comparable outcome using the 'meta' package in R software

Databases

PubMed®, Europe PMC, Epistemonikos, Google Scholar

Include

- Meta-analyses of RCTs comparing Semaglutide (oral or subcutaneous) with placebo or OADs in T2DM patients.
- Outcomes: change in HbA1c %, body weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP)

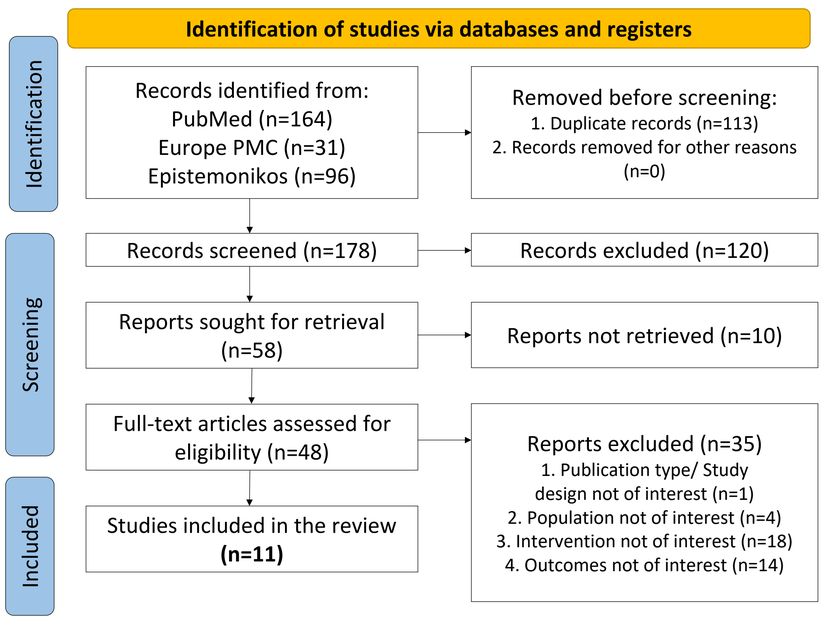
Exclude

- Mixed or paediatric populations, and studies assessing single trials for semaglutide

RESULTS

- Eleven studies were included in this review (**Figure 1**)[2-12]
- The characteristics of the meta-analyses included in the review are presented in **Table 1**
- All the studies reported data on glycaemic control, ten reported obesity, and six reported cardiovascular outcomes. Risk of bias assessment of the included studies using AMSTAR 2.0 checklist was conducted

Figure 1. PRISMA flow diagram depicting study selection process

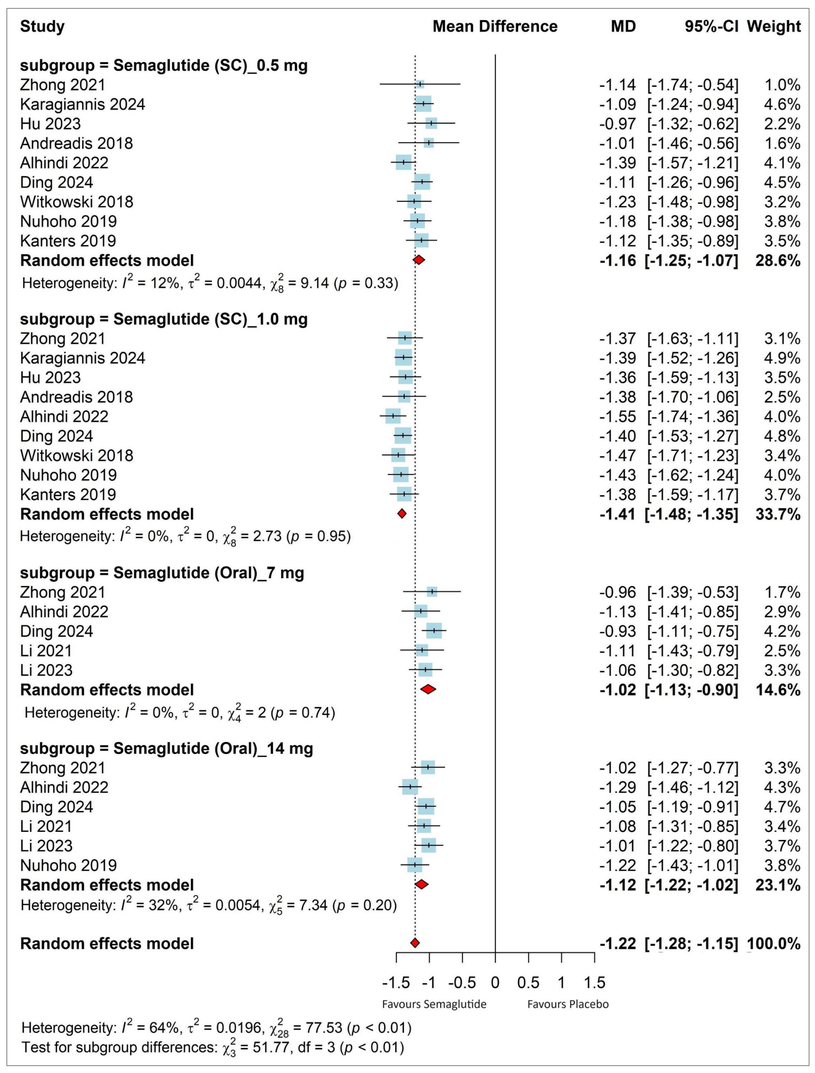


Abbreviations: PRISMA, preferred reporting items for systematic reviews and meta-analyses

1. Glycaemic control

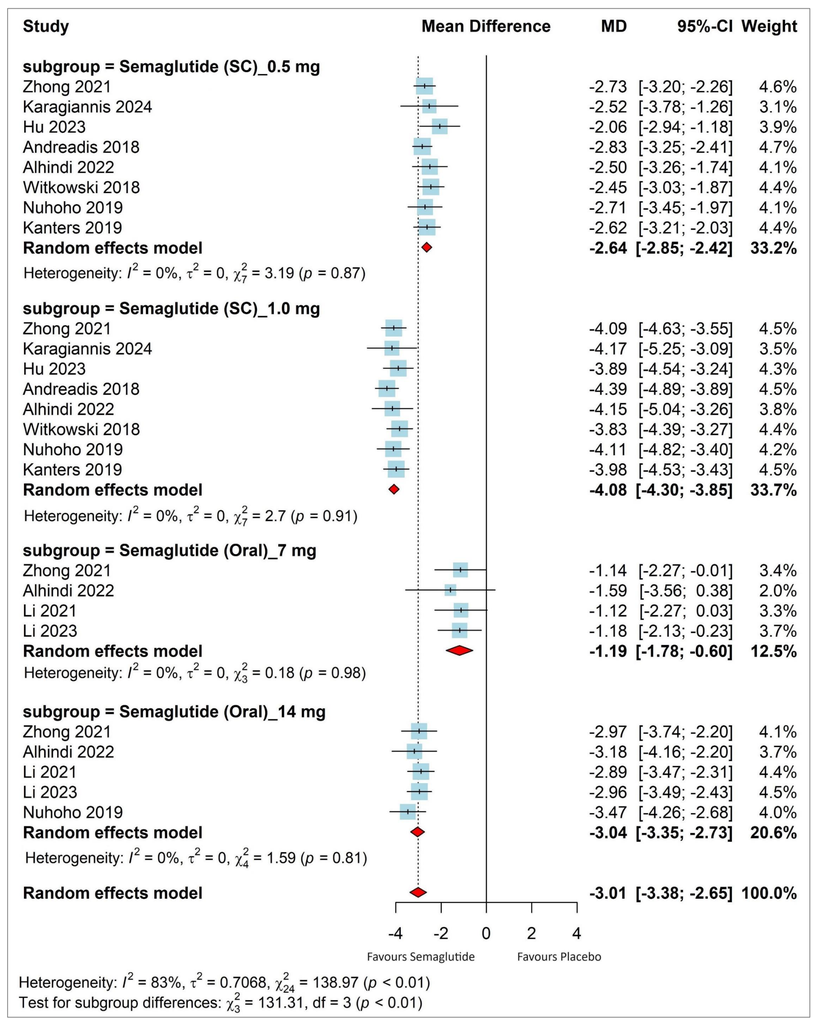
- The findings demonstrate that semaglutide is more effective than placebo in reducing HbA1c levels across various dosages and administration routes (mean difference [MD]: -1.22; 95% CI: -1.28, -1.15) (**Figure 2a**)

Figure 2a. Change in HbA1c (%) from baseline



Abbreviations: CI, confidence interval; df, degree of freedom; HbA1c, glycated haemoglobin; MD, mean differences; mg, milligram; SC, subcutaneous

Figure 2b. Change in body weight from baseline



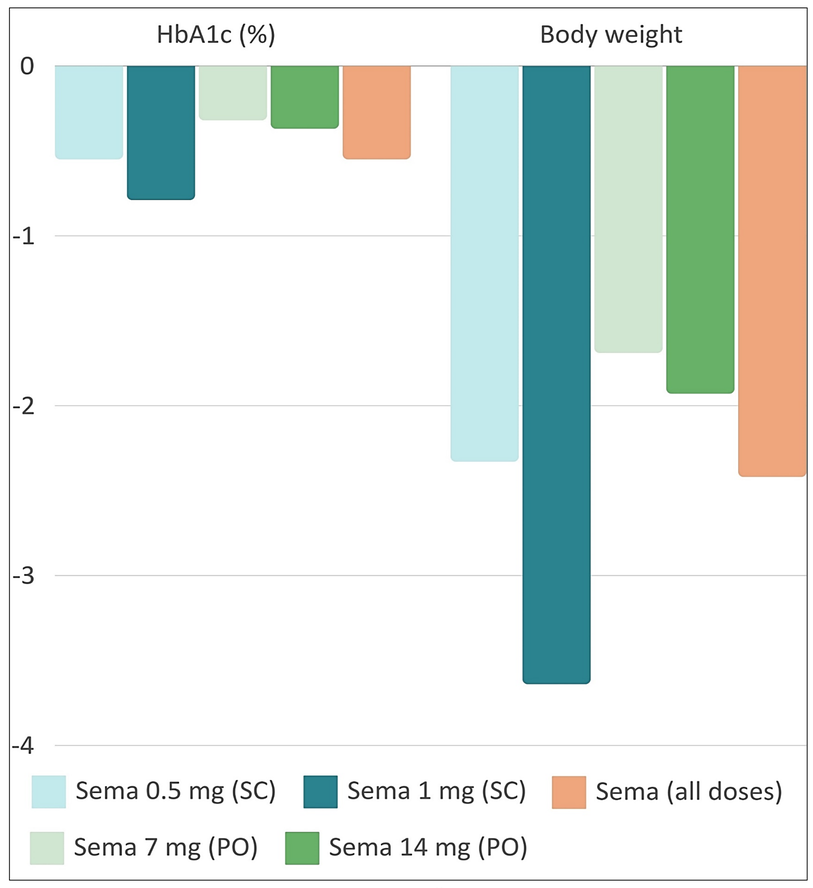
Abbreviations: CI, confidence interval; df, degree of freedom; MD, mean differences; mg, milligram; SC, subcutaneous

- The most substantial reduction was observed at the 1.0 mg SC dose (MD: -1.41; 95% CI: -1.48, -1.36)
- When compared with other anti-diabetic drugs (OADs), semaglutide shows a consistent HbA1c reduction across all subgroups (MD: -0.55; 95% CI: -0.69, -0.42), with the largest reduction evident at the 1.0 mg SC dose (MD: -0.79; 95% CI: -1.00, -0.59) (**Figure 3**)

2. Obesity management

- Semaglutide shows greater reduction in body weight compared to placebo across all dosages and administration routes (MD: -3.01; 95% CI: -3.38, -2.65) (**Figure 2b**); largest reduction observed at the 1.0 mg SC dose (MD: -4.08; 95% CI: -4.30, -3.85)
- When compared with OADs, semaglutide reduces body weight across all subgroups (MD: -2.42; 95% CI: -2.84, -2.00), with the 1.0 mg SC dose showing the most substantial reduction (MD: -3.64; 95% CI: -3.99, -3.30) (**Figure 3**)

Figure 3. Change from baseline in HbA1c (%) and body weight between semaglutide and other anti-diabetic drugs (OADs)



Abbreviations: HbA1c, glycated haemoglobin; mg, milligram; PO, peroral; SC, subcutaneous; Sema, semaglutide

3. Cardiovascular outcomes

Systolic blood pressure (SBP)

- Semaglutide showed reduction in SBP compared to placebo across all subgroups (MD: -3.55; 95% CI: -4.40, -2.69). Semaglutide SC 1.0 mg showed largest reduction (MD: -4.42; 95% CI: -5.63, -3.21)
- Compared to OADs, semaglutide consistently lowered SBP across all subgroups (MD: -1.80; 95% CI: -2.64, -0.96)

Diastolic blood pressure (DBP)

- Compared to placebo, semaglutide showed a slight reduction in DBP (MD: -0.03; 95% CI: -0.06, -0.00)
- Only two studies compared changes in DBP between semaglutide SC (doses of 0.5 mg and 1.0 mg) and OADs (MD: -0.42; 95% CI: -0.74, -0.10), indicating a reduction in DBP

Table 1. Characteristics of the included meta-analyses

Studies	Trials included	Semaglutide	Comparators	Study type
Ding 2024[2]	38 trials (n = 34166)	PO: 7 mg and 14 mg, SC: 0.5 mg and 1 mg	Placebo, OADs	NMA (Bayesian)
Karagiannis 2024[3]	28 trials (n = 23622)	SC: 0.5 mg and 1 mg	Placebo, OADs	NMA (Frequentist)
Hu 2023[4]	17 trials (n = 14940)	SC: 0.5 mg and 1 mg	Placebo, OADs	MA
Li 2023[5]	11 trials (n = 9821)	PO: 7 mg and 14 mg	Placebo, OADs	MA
Alhindi 2022[6]	12 trials (n = 6840)	PO: 7 mg and 14 mg, SC: 0.5 mg and 1 mg	Placebo, OADs	NMA (Frequentist)
Li 2021[7]	10 trials (n = 8536)	PO: 7 mg and 14 mg	Placebo, OADs	MA
Zhong 2021[8]	24 trials (n = 22185)	PO: 7 mg and 14 mg, SC: 0.5 mg and 1 mg	Placebo, OADs	MA
Kanters 2019[9]	21 trials (n = NR)	SC: 0.5 mg and 1 mg	Placebo	NMA (Bayesian)
Nuhoho 2019[10]	27 trials (n = NR)	PO: 14 mg, SC: 0.5 mg and 1 mg	Placebo	NMA (Bayesian)
Andreadis 2018[11]	12 trials (n = NR)	SC: 0.5 mg and 1 mg	Placebo, OADs	MA
Witkowski 2018[12]	41 trials (n = NR)	SC: 0.5 mg and 1 mg	Placebo	NMA (Bayesian)

Abbreviations: MA, meta-analysis; NMA, network meta-analysis; NR, not reported; OADs, other anti-diabetic drugs; PO, peroral; SC, subcutaneous; T2DM, type 2 diabetes mellitus.
Note: All studies had T2DM as the patient population, except Kanters (2019), which focused on 'inadequately controlled T2DM' patients.

CONCLUSIONS

Semaglutide consistently demonstrates robust efficacy in reducing HbA1c level, body weight, DBP, and SBP across various doses and administration routes. Subgroup analysis reveals that the 1.0 mg SC dosage has the largest mean reduction when compared to oral forms. These findings are consistent with previous studies[8]

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