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Efficacy of Glucagon-like Peptide-1 Receptor Agonists in Overweight/Obese and/or T2DM Adolescents: A Meta-analysis Based on Randomized Controlled Trials

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What is already known on this topic?

In adolescents, previous meta-analyses of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with type 2 diabetes mellitus (T2DM) and obesity have demonstrated that GLP-1RAs were beneficial for glycemic control and weight loss. However, only nine randomized controlled trials were included. Meanwhile, limited sample size prevented further subgroup analyses.

What this study adds?

This study expanded the sample size included. Meanwhile, our study confirms that GLP-1RAs reduced glycosylated hemoglobin A1c, fasting plasma glucose, and weight loss in overweight/obese and/or T2DM adolescents. The GLP-1RAs have a no significant effect on lower blood sugar in adolescents with simple obesity. Based on subgroup analysis, liraglutide was more effective than exenatide in terms of glucose reduction. Nevertheless, in terms of weight control, exenatide was more effective than liraglutide.

Abstract

Objective: The aim of this meta-analysis was to investigate the effect of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on blood glucose and weight in adolescents with overweight/obesity and/or type 2 diabetes mellitus (T2DM) aged < 18 years.

Methods: PubMed, Embase, Web of Science, and Cochrane Library were searched for all randomized controlled trials (RCTs) up to August 2023 comparing GLP-1RAs with placebo in overweight/obese and/or T2DM adolescents and extracted relevant data for meta-analysis.

Results: Fourteen RCTs were included in the meta-analysis with a total of 1,262 participants. Results revealed that the GLP-1RAs group had a more significant reduction in glycosylated hemoglobin A1c (HbA1c; risk difference (RD) = -0.34%, $p < 0.001$) than the control group. However, there was no difference in fasting plasma glucose [fasting plasma glucose (FPG); RD = -2.07 mg/dL, $p = 0.065$] between the two groups. Nonetheless, the experimental group that received exenatide showed no significant reduction in HbA1c ($p = 0.253$) and FPG ($p = 0.611$) between the two groups. The GLP-1RAs group had a more significant decline in body weight (RD = -4.28 kg, $p = 0.002$) and body mass index (BMI) (RD = -1.63 kg/m^2, $p = 0.002$) compared to the control group. The experimental group was given liraglutide (RD = -2.31 kg, $p = 0.038$) or exenatide (RD = -2.70 kg, $p < 0.001$). Compared to the control group, the experimental group had a more significant drop in body weight than the control group. However, for the experimental group that received liraglutide, the BMI had a no significant reduction between the two groups (RD = -0.81 kg/m^2, $p = 0.260$). For the experimental group using exenatide, BMI declined more significantly in the intervention group than in the control group (RD = -1.14 kg/m^2, $p < 0.001$).

Conclusion: This study showed that GLP-1RAs reduced HbA1c, FPG, and weight loss in overweight/obese and/or T2DM adolescents. Liraglutide was better than exenatide in terms of glucose reduction. Nevertheless, in terms of weight control, exenatide was more effective than liraglutide.

Keywords: Glucagon-like peptide-1 receptor agonists, overweight, obesity, type 2 diabetes, HbA1c, weight loss, FPG

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Introduction

Obesity is a global public health problem. More than two billion people worldwide suffer from obesity, and the number continues to increase (1). The global obese adolescent population was estimated to exceed 100 million (2). Adolescent obesity tends to persist and become adult obesity, which has been related to many chronic diseases, including type 2 diabetes mellitus (T2DM), cardiovascular disease, and cancer (3). Unfortunately, most treatments for childhood obesity are based only on prevention and lifestyle interventions. Until 2020, the European Medicines Agency (EMA) had not approved any pharmacological treatments for treating obesity in pediatric patients. In January 2021, the EMA authorized the use of a glucagon-like peptide (GLP)-1 analog, liraglutide, for treating adolescent (12-17 years) obesity (4). Morbidly obese adolescents could consider bariatric surgery, but both surgical complications and safety limited the promotion of surgery in adolescents (5).

The prevalence of T2DM was low in adolescents, but as rates of obesity have increased, T2DM has become increasingly prevalent in adolescents (2). T2DM in adolescence is manifested as severe progressive DM with frequent complications, such as diabetic retinopathy, cardiovascular disease, and nephropathy (6,7). Common clinical drugs used to treat T2DM include metformin, insulin and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. Although insulin is used to treat diabetes, insulin resistance is often present in obese adolescents and thus its efficacy is limited (8).

Liraglutide is a GLP-1 receptor agonist (GLP-1RAs) recently approved for T2DM treatment in adolescents aged ten years and older (9). GLP-1RAs stimulate postprandial insulin secretion, reduced glucagon secretion, delayed gastric emptying, and reduced appetite, thereby improving blood glucose control (10). In adolescents, previous meta-analyses of GLP-1RAs in patients with T2DM and obesity have demonstrated that GLP-1RAs were beneficial for glycemic control and weight loss (11,12). However, only nine randomized controlled trials (RCTs) were included because of the limited number of RCTs. Therefore, conducting further subgroup analyses to explore the effect of therapeutic regimen, treatment duration, and subject participants on the efficacy of GLP-1RAs was unfeasible. Recently, as more and pertinent RCTs have been reported, an update of the earlier meta-analysis is possible. The aim of the present meta-analysis was to investigate the effectiveness of GLP-1RAs in managing overweight/obese and/or T2DM in adolescents under 18, along with exploring the factors influencing efficacy.

Methods

Search Strategy

This meta-analysis design and reporting followed the PRISMA 2020 updated guidelines (13) and was registered in PROSPERO 2023 (CRD42023467678). The aim of the present study was to investigate the effects of GLP-1RAs on blood glucose and weight in adolescents with overweight/obese and/or T2DM.

Two researchers independently searched four databases up to August 2023, including PubMed, Web of Science, Embase, and Cochrane Library. The search terms were: glucagon-like peptide-1 receptor agonist OR exenatide OR liraglutide OR dulaglutide OR lixisenatide OR semaglutide OR albiglutide OR taspoglutide OR loxenatide) AND (Children OR Adolescents OR Teens OR Teenagers OR Youths OR Adolescents, Female OR Adolescents, male. Moreover, reference lists in all retrieved articles were searched. The primary outcomes of the included articles involved glycosylated hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and body weight. Articles were filtered according to PICOS principles including when no consensus could be reached, a third person would be recruited for their opinion.

Inclusion and Exclusion Criteria

The included studies were based on the following PICOS principles: 1) overweight/obese and/or T2DM in adolescents aged < 18 years; 2) the intervention group received GLP-1RAs; 3) the control group received placebo; 4) the primary outcomes were HbA1c, FPG, and body weight; and 5) included studies were RCTs.

The exclusion criteria were: 1) full text not available; 2) participants included adults; 3) non-English articles; 4) unextracted data; and 5) updated RCTs. When updating published articles for the same study cohort, the most recent or largest population studies were selected.

Data Extraction and Quality Assessment

Two researchers extracted the data separately using pre-designed forms. Extracted data included: 1) the authors, publication year, country, and registration number of the study; 2) subject participants details, such as comorbidity, mean body mass index (BMI), age; 3) recruitment time, therapeutic regimen, treatment duration, sample sizes for experimental and control groups; 4) outcomes, including HbA1c, FPG, and body weight.

Following Cochrane guidelines, RCTs were assessed by two review authors. The labels "high risk," "low risk," and "unclear risk" were used to describe several bias types, including

random serial generation, allocation concealment, blinding of participants and staff, blinding of outcome assessment, insufficient outcome data, and selective reporting, among others. In the case of a disagreement, the two researchers solved the problem through discussion. When necessary, a third person was enlisted.

Statistical Analysis

This meta-analysis was explored using Stata Software 12.0 (Stata Corporation, College Station, TX, United States) and Review Manager 5.3 (RevMan version 5.3; Oxford, UK). The definition of risk difference (RD) is actually the mean difference. RD and 95% confidence intervals were used to assess the association of GLP-1RAs with HbA1c, FPG, and body weight. Heterogeneity between studies was assessed by the chi-square test with an inconsistency index (I^2): I^2 < 25% indicated low heterogeneity; I^2 = 25-50% indicated moderate heterogeneity; I^2 > 50% indicated significant heterogeneity (14). Due to potential heterogeneity in the participant population and experimental design, this study was analyzed using a unified random-effects model to increase our result credibility. All tests were two-sided and $p < 0.05$ was considered significant (15).

Results

Description of the Studies

In accordance with the search criteria, 3,120 records from four databases were thoroughly examined, and no more studies could be located in other sources. After duplicate articles were removed, 2,235 articles remained, while a further 2,111 irrelevant articles were removed by investigating article titles and abstracts. Through reading the full published texts, 110 more studies were eliminated, of which 45 were not RCTs, 42 included adults, 10 had no reported outcomes of interest, 5 were not in English, 5 were updated articles, and 3 had inaccessible data. Eventually, fourteen RCTs were included in the meta-analysis (Figure 1) (16-29).

The 14 RCTs were selected to research GLP-1RAs in adolescents who were overweight/obese and/or had T2DM. In these studies, most participants were aged 12-18 years, with an average BMI greater than 30 kg/m^2. All studies were in Western countries or predominantly Western multicenter studies with a treatment duration of 5-68 weeks. Six studies used liraglutide, five used exenatide, two used semaglutide, and one used dulaglutide. All participants included obesity, T2DM, and overweight combined with T2DM. In total, 754 adolescents were allocated to GLP-1RAs therapy, and 508 were treated with the placebo. Patients with T2DM had previously received metformin, insulin, or exercise therapy. Most trials combined lifestyle, diet, and exercise interventions. Table 1 and Supplementary Table 1 contain a list of the characteristics of the analyzed studies in this meta-analysis.

Quality Evaluation

Figures S1 and S2 depict the included studies assessments. We used the Cochrane Collaboration method to assess each RCTs quality. All included studies were assessed as low risk regarding random sequence generation and allocation concealment. Most studies were rated as low risk in blinding of participants and personnel and selective reporting, whereas a small number were rated as unclear. Most studies were classified as low risk, while only a small number were evaluated as high risk, and a few were at unknown risk concerning blinding of outcome assessment and incomplete outcome data. For other biases, the included studies were assessed as being of unclear risk.

Result Analysis

Figure 2 summarizes the effects of GLP-1RAs on HbA1c and FPG in the whole population. Nine studies reported HbA1c results, revealing that participants in the GLP-1RAs group had a more significant reduction in HbA1c compared to the control group [RD = -0.34%, $p < 0.001$, 95% confidence interval (CI) = -0.51, -0.18; Figure 2a]. However, the heterogeneity was 91.2%. Ten studies reported FPG findings, indicating that FPG had a greater decrease in the

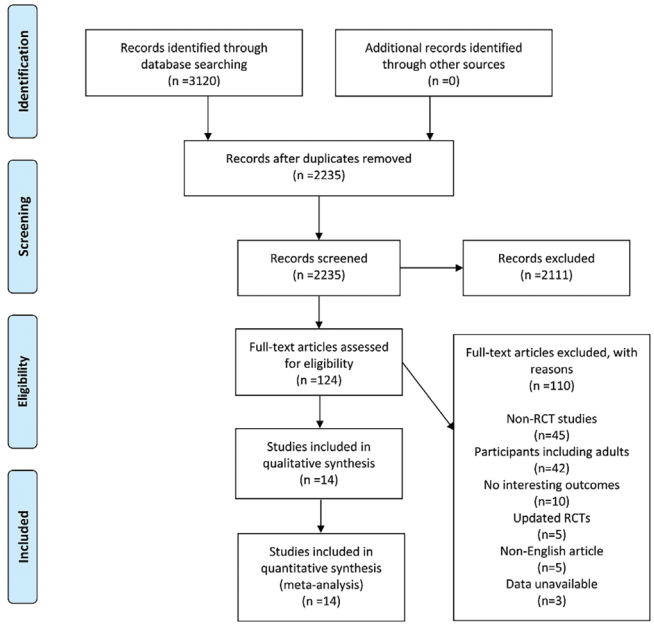

Figure 1. Flow diagram of selection

RCTs: randomized controlled trials

Table 1. Characteristics of all the studies included in the meta-analysis

Author	Year	Participants	Mean age (years)	Experimental group (number)	Control group (number)	Intervention	Target dose	Treatment duration (weeks)
Weghuber et al. (17)	2022	Obesity	15.4	134	67	Semaglutide	2.4 mg weekly	68
Arslanian et al. (29)	2022	Overweight, T2DM	14.5	103	51	Dulaglutide	0.75 mg weekly, 1.50 mg weekly	26
Tamborlane et al. (18)	2022	T2DM	15	58	24	Exenatide	2.00 mg weekly	24
Diene et al. (27)	2022	Obesity	14.3	19	12	Liraglutide	3.00 mg daily	16, 52
Fox et al. (22)	2022	Obesity	16	33	33	Exenatide	2.00 mg weekly	52
Kelly et al. (25)	2023	Obesity	15.4	133	67	Semaglutide	2.40 mg weekly	75
Mastrandrea et al. (20)	2019	Obesity	9.9	16	8	Liraglutide	3.00 mg weekly	8
Kelly et al. (23)	2012	Obesity	12.7	5	6	Exenatide	0.02 mg daily	13
Klein et al. (21)	2014	Overweight, T2DM	14.8	14	7	Liraglutide	1.80 mg daily	5
Tamborlane et al. (19)	2019	Overweight, T2DM	14.6	66	68	Liraglutide	1.80 mg daily	26, 52
Danne et al. (28)	2017	Obesity	14.9	14	7	Liraglutide	3.00 mg daily	5
Kelly et al. (24)	2020	Obesity	14.5	125	126	Liraglutide	3.00 mg daily	56
Weghuber et al. (16)	2020	Obesity	14	22	22	Exenatide	2.00 mg weekly	24
Kelly et al. (22)	2013	Obesity	15.2	12	10	Exenatide	0.02 mg daily	13

T2DM: type 2 diabetes mellitus

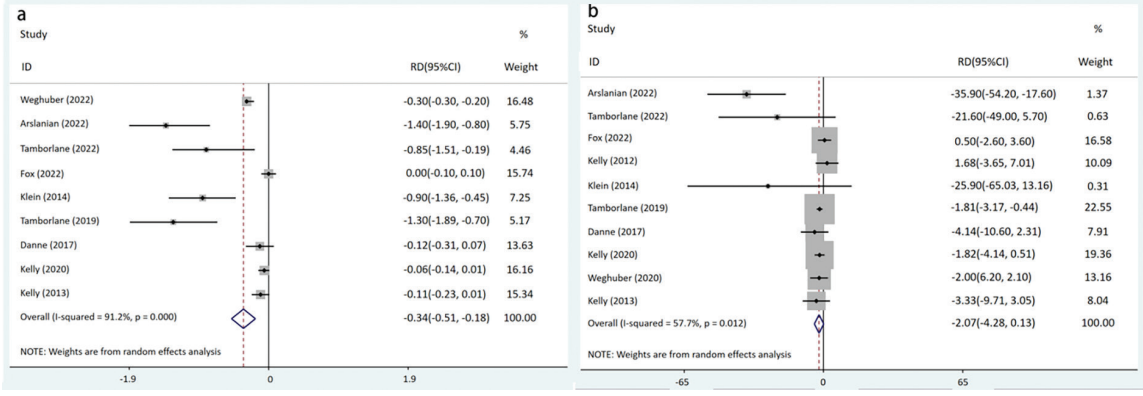

Figure 2. Forest plot of meta-analysis of the effect of GLP-1RAs on HbA1c and FPG in all participants. a) HbA1c, $p < 0.001$; b) FPG, $p = 0.065$

GLP-1RAs: glucagon-like peptide-1 receptor agonists, HbA1c: glycosylated hemoglobin A1c, FPG: fasting plasma glucose

intervention group than in the control group (RD = -2.07 mg/dL, 95% CI = -4.28, 0.13), but the difference was not significant ($p = 0.065$; Figure 2b). The heterogeneity was 57.7%.

For HbA1c, subgroup analysis was performed by participant type, showing that HbA1c exhibited no significant reduction between the two groups for obese participants (non-T2DM) ($p = 0.087$; Figure 3a). Notably, for T2DM patients, HbA1c showed a more significant decrease in the intervention group than in the control group (RD = -1.10%, $p < 0.001$, 95% CI = -1.38, -0.83; Figure 3b). Further subgroup analysis was conducted in terms of HbA1c in the whole population (Table 2-1). For the study of the participant number in the

Table 2-1. Subgroup analysis of HbA1c and fasting plasma glucose

	No. of studies	RD	95% CI	p	Heterogeneity
					I^2
HbA1c (%)					
Experimental group (number) <50	4	-0.17	-0.35, 0.02	0.079	80.4%
Experimental group (number) ≥50	5	-0.55	-0.82, -0.29	<0.001	93.4%
Liraglutide	4	-0.47	-0.84, -0.11	0.011	89.5%
Exenatide	3	-0.11	-0.30, 0.08	0.253	73.5%
Treatment duration <52 weeks	6	-0.66	-1.03, -0.29	<0.001	88.0%
Treatment duration ≥52 weeks	4	-0.23	-0.44, -0.02	0.034	94.8%
Fasting plasma glucose (mg/dL)					
Experimental group (number) <50	6	-0.83	-2.86, 1.20	0.421	0.9%
Experimental group (number) ≥50	4	-4.29	-8.93, 0.35	0.070	80.3%
Liraglutide	4	-1.91	-3.07, -0.75	0.001	0.0%
Exenatide	5	-0.62	-3.00, 1.76	0.611	12.8%
Treatment duration <52 weeks	8	-3.51	-7.10, 0.09	0.056	63.2%
Treatment duration ≥52 weeks	3	-1.52	-2.62, -0.42	0.007	0.0%

HbA1c: glycosylated hemoglobin A1c, RD: risk difference, CI: confidence interval

experimental group <50, HbA1c revealed a no significant decrease between the two groups (p = 0.079). For the study of the participant number in the experimental group ≥50, the GLP-1RAs group had a more significant reduction than the control group (RD = -0.55%, p < 0.001). For the experimental group that used liraglutide, HbA1c underwent a more significant decline in the intervention group than the control group (RD = -0.47%, p = 0.011). However, for the experimental group that used exenatide, HbA1c showed a no significant reduction between the two groups (p = 0.253). For treatment duration, both <52 (RD = -0.66%, p < 0.001) and ≥52 weeks (RD = -0.23%, p = 0.034), the experimental group had a more significant decrease in HbA1c than the control group.

The FPG was analyzed in subgroups, indicating that for adolescents with obesity, no significant differences were found in FPG reduction between the two groups (p = 0.119) (Figure 4a). For T2DM adolescents, FPG level exhibited a greater decrease in the intervention group than in the control group (RD = -19.48 mg/dL, 95% CI = -41.20, 2.24), but the difference did not reach statistical significance (p = 0.079; Figure 4b). Further subgroup analysis was performed in terms of FPG in the whole population (Table 2-1). For the study of participant number in the experimental group, both <50 (p = 0.421) and ≥50 (p = 0.070), FPG levels had a no significant reduction between the two groups. For the experimental group that used liraglutide, FPG exhibited a more significant decline in the intervention group than the control group (RD = -1.91 mg/dL, p = 0.001). For the experimental group that used exenatide, there was no statistically significant reduction in FPG between the two

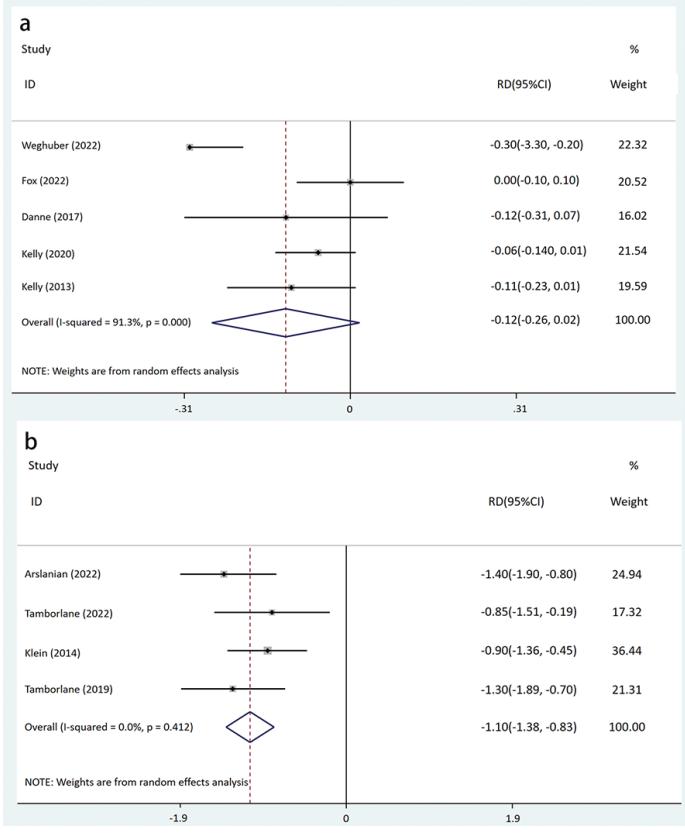

Figure 3. Forest plot of meta-analysis of the effect of GLP-1RAs on HbA1c. a) obesity, p = 0.087; b) T2DM, p < 0.001

GLP-1RAs: glucagon-like peptide-1 receptor agonists, HbA1c: glycosylated hemoglobin A1c, T2DM: type 2 diabetes mellitus

groups (p = 0.611). For treatment duration, both < 52 (RD = 3.51 mg/dL, p = 0.056) and ≥52 weeks (RD = -1.52 mg/dL, p = 0.007), FPG had a significantly greater decrease in the intervention group than in the control group, but the former difference was not statistically significant.

Figure 5 summarizes the effects of GLP-1RAs on body weight and BMI in the whole population. Nine studies reported results for body weight. Participants in the GLP-1RAs group had a more significant decline in body weight compared to the control group (RD = -4.28 kg, p = 0.002, 95% CI = -6.95, -1.60; Figure 5a). Eight studies reported BMI, and BMI decreased significantly more in the intervention group treated with GLP-1RAs compared with controls (RD = -1.63 kg/m^2, p = 0.002, 95% CI = -2.68, -0.57; Figure 5b).

Table 2-2 lists further subgroup analyses of body weight and BMI. For the study of the participant number in the experimental group < 50 (RD = -2.64 kg, p < 0.001) and ≥50 (RD = -7.64 kg, p = 0.070), body weight decreased more in the intervention group than in the control group, but the latter difference was not significant. The experimental group that used liraglutide had a mean weight reduction of -2.31kg (p = 0.038) while the exenatide group exhibited

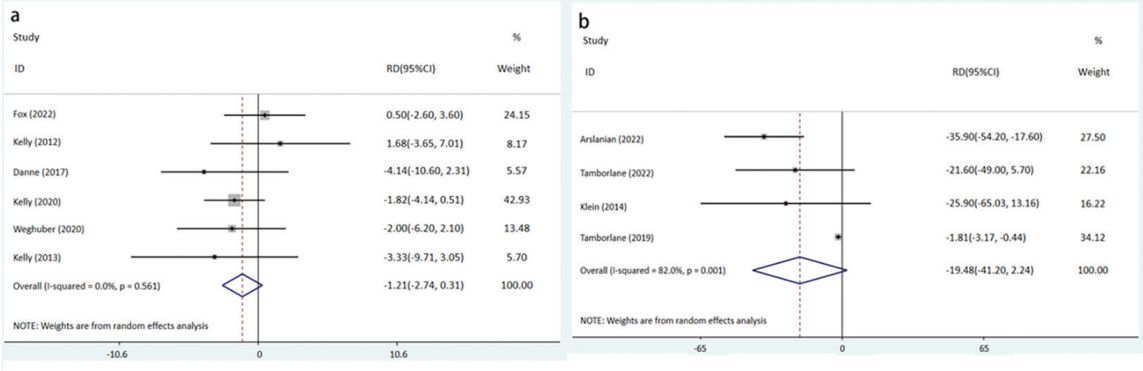

Figure 4. Forest plot of meta-analysis of the effect of GLP-1RAs on FPG. a) obesity, p = 0.119; b) T2DM, p = 0.079

GLP-1RAs: glucagon-like peptide-1 receptor agonists, FPG: fasting plasma glucose, T2DM: type 2 diabetes mellitus

Table 2-2. Subgroup analyses of body weight and BMI

	No. of studies	RD	95% CI	p	Heterogeneity
					I^2
Body weight (kg)					
Experimental group (number) < 50	6	-2.44	-3.64, -1.24	< 0.001	0.0%
Experimental group (number) ≥50	3	-7.64	-15.90, 0.61	0.070	95.8%
Liraglutide	3	-2.31	-4.50, -0.13	0.038	49.9%
Exenatide	5	-2.70	-4.05, -1.36	< 0.001	0.0%
Treatment duration < 52 weeks	6	-2.09	-3.18, -0.99	< 0.001	0.0%
Treatment duration ≥52weeks	3	-8.86	-17.52, -0.20	0.045	93.5%
BMI (kg/m^2)					
Experimental group (number) < 50	5	-0.88	-1.59, -0.17	0.015	60.0%
Experimental group (number) ≥50	3	-2.50	-5.38, 0.38	0.089	96.9%
Liraglutide	2	-0.81	-2.22, 0.60	0.260	87.2%
Exenatide	4	-1.14	-1.69, -0.59	< 0.001	0.0%
Treatment duration < 52 weeks	5	-0.56	-1.08, -0.04	0.034	70.7%
Treatment duration ≥52 weeks	4	-2.79	-5.44, -0.14	0.039	95.6%
BMI (%)					
Experimental group (number) < 50	4	-2.47	-4.96, 0.01	0.051	77.6%
Experimental group (number) ≥50	3	-13.24	-22.62, -3.87	0.006	96.2%
Exenatide	4	-2.47	-4.96, 0.01	0.051	77.6%
Treatment duration < 52 weeks	3	-2.15	-4.85, 0.55	0.119	81.2%
Treatment duration ≥52 weeks	4	-11.02	-18.71, -3.34	0.005	95.0%

RD: risk difference, BMI: body mass index, CI: confidence interval

a -2.70 kg weight reduction ($p < 0.001$). The experimental group had a more significant drop in body weight than the control group. For treatment duration < 52 (RD = -2.09 kg, $p < 0.001$) and ≥52 weeks (RD = -8.86 kg, $p = 0.045$), the experimental group had a more significant decrease in body weight than the control group.

For the analysis of the participant number in the experimental group < 50, the BMI decline in the experimental group was more significant than in the control group (RD = -0.88 kg/m^2, $p = 0.015$). When the participant number in the experimental group ≥50, there was no significant reduction in BMI between the two groups ($p = 0.089$). For the experimental group that used liraglutide, BMI showed a no significant reduction between the two groups ($p = 0.260$). However, for the experimental group that used exenatide, BMI showed a significant decline in the intervention group than in the control group (RD = -1.14 kg/m^2, $p < 0.001$). For treatment durations, both < 52 (RD = -0.56 kg/m^2, $p = 0.034$) and ≥52 weeks (RD = -2.79 kg/m^2, $p = 0.039$), BMI fell significantly in the intervention group compared to the control group. Furthermore, this study was further analyzed from a BMI perspective (%) (Table 2-2).

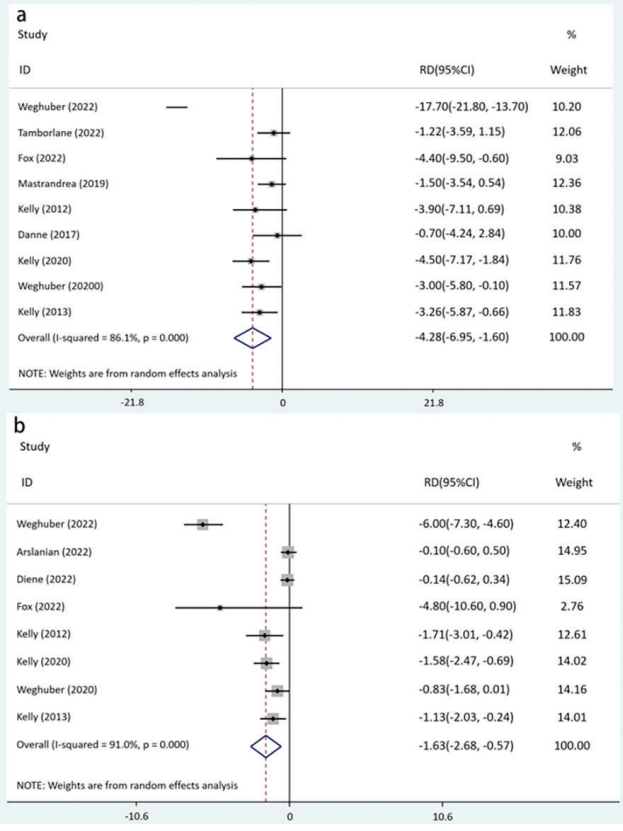

Figure 5. Forest plot of meta-analysis of the effect of GLP-1RAs on body weight and BMI in all participants. a) body weight, $p = 0.002$; b) BMI, $p = 0.002$

GLP-1RAs: glucagon-like peptide-1 receptor agonists, BMI: body mass index

Subgroup analysis was performed for participants with obesity regarding body weight (kg) and BMI (kg/m^2 and %). Body weight showed a more significant decrease in the intervention group than in the control group (RD = -4.72 kg, $p = 0.002$; Figure 6a). Furthermore, BMI also showed a significant drop in magnitude in the experimental group than in the control group (RD = -1.93 kg/m^2, $p = 0.003$; RD = -7.31 %, $p = 0.004$; Figures 6b, 6c).

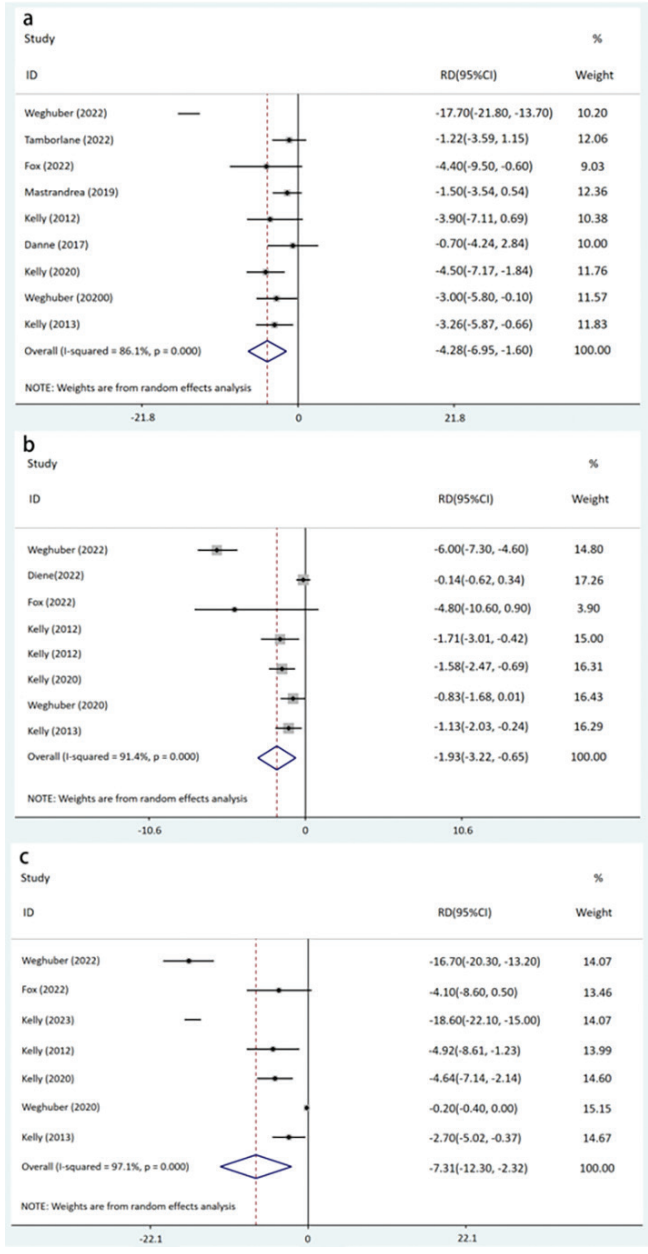

Figure 6. Forest plot of meta-analysis of the effect of GLP-1RAs on weight control in obesity. a) body weight, $p = 0.002$; b) BMI (kg/m2), $p = 0.003$; c) BMI (%), $p = 0.004$

GLP-1RAs: glucagon-like peptide-1 receptor agonists, BMI: body mass index

Discussion

This study indicated that GLP-1RAs, compared to placebo, decrease HbA1c, FPG, and body weight in adolescents with overweight/obesity and/or T2DM. Remarkably, GLP-1RAs had no significant effect on HbA1c and FPG in adolescents with non-T2DM obesity. In T2DM, liraglutide was more effective in adolescents than exenatide in lowering HbA1c and FPG. In contrast, exenatide was more effective than liraglutide for weight control. With the treatment prolongation, the efficacy of GLP-1RAs on glucose control decreased, but weight control was more effective. Moreover, Weghuber et al. (17) demonstrated that in obese adolescents, semaglutide plus lifestyle intervention treatment resulted in a more significant reduction in BMI than lifestyle intervention alone. Tamborlane et al. (19) showed that liraglutide effectively improved blood sugar in T2DM adolescents.

The GLP-1RAs mainly reduce glucose through the following mechanisms. GLP-1RAs can stimulate insulin secretion to lower blood sugar (30). GLP-1RAs also increase intracellular Ca^{2+} concentration through ligand-gated calcium channels or voltage-dependent Ca^{2+} channels on the endoplasmic reticulum, enhancing insulin secretion (31,32). Notably, GLP-1RAs only increase insulin release in cases of hyperglycemia and so are not associated with hypoglycemia (33), which is confirmed again in the present study. In obesity (non-T2DM), GLP-1RAs did not significantly decrease blood glucose. Studies have suggested that GLP-1RAs induce an increase in β-cell mass through enhanced cellular regeneration and apoptosis inhibition (34,35).

GLP-1RAs can inhibit glucagon secretion in a glucose concentration-dependent manner, lowering blood sugar. Some studies have reported the possibility that GLP-1R directly mediates α-cell inhibition to suppress glucagon secretion (36). The GLP-1R can also indirectly inhibit glucagon by directly stimulating increased somatostatin secretion (37,38).

GLP-1RAs promote glycogen synthesis in liver cells, lowering blood glucose concentrations (39). GLP-1RAs balance food intake by activating multiple nuclei of the hindbrain and hypothalamus (periventricular nuclei, posterior brain area, and nucleus tractus solitarius). Moreover, GLP-1RAs activated brain regions of the mid-limbic system to inhibit reward behavior and palatability. The combined effect of GLP-1RAs on homeostasis and hedonic eating may contribute to their appetite suppression (40). Finally, GLP-1RAs could also delay gastric emptying and peristalsis of the gastrointestinal tract and reduce gastric acid secretion stimulated by pentapeptide gastrin (41).

Our study indicated that liraglutide was more effective in adolescents than exenatide regarding blood sugar control. In the LEAD-6 study, liraglutide lowered HbA1c more than exenatide (42). The probable cause was that exenatide has a short half-life and a higher plasma concentration within 4-8 hours after a single subcutaneous injection (43). However, approximately 99% of the liraglutide molecules are typically bound to plasma albumin, and the bound molecule has a half-life of 11-13 hours (41). Therefore, liraglutide concentration in plasma is more persistently high, and the hypoglycemic effect is better. Our research demonstrated that the degree of glucose reduction declined with prolonged treatment duration. The probable cause was that blood sugar does not drop continuously. Only in cases of hyperglycemia do GLP-1RAs raise insulin release to reduce blood sugar. When blood sugar drops to the normal range, the ability of GLP-1Ra to lower blood sugar only plays a role in maintaining blood sugar concentration (44).

Our research suggested that GLP-1RAs can lower weight in adolescents compared to a placebo. The weight loss mechanism is probably as follows. 1) As mentioned earlier, GLP-1RAs promote weight loss by reducing food intake and prolonging gastric emptying (40,41). 2) GLP-1RAs activate brown fat and increase rodent energy expenditure independently of locomotor activity through sympathetic nervous system (SNS) pathways. 3) GLP-1RAs also reduce peripheral lipid storage in white adipocytes in mice by a mechanism that relies on SNS activation (45). 4) In mice and monkeys, GLP-1RAs target pathways that reduce body weight and improve many metabolic parameters by producing GLP-1 bispecific molecules (46). 5) Studies have demonstrated that obese teenagers can lose weight through these mechanisms, as well as increased fat and reduced carbohydrate oxidation (47). Our study indicated that exenatide was more effective than liraglutide for weight loss. One reason may be that exenatide and lowering glucose have been shown to improve lipid homeostasis, reduce body weight, improve insulin resistance, and reduce hepatic steatosis (48,49). Another factor may be that exenatide treats obesity by regulating *CTRP3* and *PPAR*-γ gene expression, which are related to lipogenesis (50). Nevertheless, the meta-analysis conducted by Ryan et al. (12) has indicated that no significant difference existed between the effectiveness of liraglutide or exenatide for adolescent weight loss. This may be due to their inclusion of a limited number of RCTs. Our research revealed that GLP-1RAs were more effective in reducing body weight with prolonged treatment. This may be because GLP-1 produces anorexic effects on the mediation of the brainstem and hypothalamic nucleus (43). The severity of anorexia increases with therapy duration, resulting in greater weight loss.

This meta-analysis is an updated study of published RCTs on the effectiveness of GLP-1RAs in treating overweight/obesity and/or T2DM in adolescents. Our study once again confirms the effectiveness of GLP agonists in lowering glucose and weight in adolescents. In addition, we explored the different effects of exenatide and liraglutide on hypoglycemic and weight reduction in adolescents. Additionally, we found that prolonged treatment may affect the efficacy for controlling glucose and weight.

Study Limitations

Our study also has some limitations. First, our study included multiple GLP-1RAs, but subgroup analyses of all drugs were impossible because of limited data. Second, a few subgroup analyses of the included studies affected credibility to some extent. Third, because there were some differences in the included studies, the heterogeneity of the final analysis was higher, which reduced credibility. Therefore, a random-effects model was used for analysis. Fourth, the included studies were all multicenter studies in Western countries; consequently, the results could not be directly generalized to other countries.

Conclusion

This study confirmed that GLP-1RAs reduced HbA1c, FPG, and weight loss in adolescents with overweight/obesity and/or T2DM. However, GLP-1RAs had no significant effect on blood glucose reduction in obese adolescents. For adolescents with T2DM, liraglutide was superior to exenatide in lowering glucose. However, when it comes to weight control, exenatide was more effective than liraglutide. When the duration of treatment is prolonged, the magnitude of the drop in blood glucose tends to stabilize while weight loss continues.

Ethics

Ethics Committee Approval and Informed Consent: Not applicable (this paper was provided based on research in global databases).

Authorship Contributions

Concept: Cong Zhou, Design: Min Dai, Zhiyi Xiang, Siyu Lu, Cong Zhou, Data Collection or Processing: Senjie Dai, Lihu Gu, Zhiyi Xiang, Anyi Xu, Analysis or Interpretation: Min Dai, Lihu Gu, Siyu Lu, Yang Yang, Cong Zhou, Literature Search: Min Dai, Senjie Dai, Lihu Gu, Zhiyi Xiang, Anyi Xu, Siyu Lu, Yang Yang, Writing: Min Dai, Senjie Dai, Cong Zhou.

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