Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Suppression of Insulin Secretion in the Treatment of Obesity: A Systematic Review and Meta-Analysis

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Objective: This proof-of-concept study aimed to evaluate the efficacy and safety of suppression of insulin secretion in the treatment of obesity.
Methods: A search of PubMed, Embase, and Cochrane databases was performed to identify randomized controlled trials (up to January 1, 2020) that used drugs that directly suppress insulin secretion (diazoxide or octreotide) in the treatment of obesity. The extracted data were analyzed using random-effects meta-analysis.
Results: A total of seven randomized controlled trials were included, with four using diazoxide and three using octreotide to suppress insulin secretion. Suppression of insulin secretion significantly reduced fasting insulin level (mean difference: –3.94 mIU/L; 95% CI: –7.40 to –0.47) but slightly increased fasting blood glucose level (mean difference: 0.48 mmol/L; 95% CI: 0.24 to 0.72). Following the suppression of insulin secretion, significant reductions in body weight (mean difference: –3.19 kg; 95% CI: –5.71 to –0.66), BMI (mean difference: –1.65 kg/m^2; 95% CI: –2.41 to –0.90), and fat mass (mean difference: –5.92 kg; 95% CI: –8.28 to –3.56) were observed compared with placebo in the pooled data. No significant difference in fat-free mass was observed (mean difference: 0.56 kg; 95% CI: –0.40 to 1.52).
Conclusions: Results suggest that suppression of insulin secretion may lead to reduced body weight and fat mass with slightly increased blood glucose in individuals with obesity.

Obesity (2020) **28**, 2098-2106.

Study Importance

What is already known?

- Hyperinsulinemia may play a causal role in the development of obesity.
- In obese rodent models, suppression of insulin secretion leads to reduced fat mass and improved glucose metabolism.
- In humans, clinical trials using drugs to suppress insulin secretion showed mixed results.

What does this study add?

- Our meta-analysis indicates that suppression of insulin secretion in patients with obesity leads to reduced body weight and fat mass and unchanged lean mass at the cost of slightly increased blood glucose.

How might these results change the direction of research or the focus of clinical practice?

- Our results support the concept that suppression of insulin secretion leads to reduced body weight and fat mass in people with obesity.
- Developing specific insulin suppression drugs with fewer side effects is encouraged in the future.

Introduction

The prevalence of obesity is increasing worldwide, causing a substantial health burden. Obesity is associated with a variety of diseases, including type 2 diabetes, cardiovascular diseases, and cancers. Individuals with obesity usually present with increased insulin secretion, or hyperinsulinemia, compared with lean individuals. The formation of hyperinsulinemia could be primary, as per the carbohydrate-insulin model (1), or secondary, because of hyperplasia and hypertrophy of pancreatic beta cells compensating for obesity-induced insulin resistance (2). On the contrary, chronic hyperinsulinemia may cause further insulin resistance by desensitizing insulin receptor signaling (3), increasing ectopic fat accumulation in muscle and liver (4), and increasing adipose tissue inflammation (5), thus forming

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 Received: 20 May 2020; **Accepted:** 23 June 2020; **Published online 5 November 2020. doi:10.1002/oby.22955**

a vicious cycle. A diet with low glycemic index (6) or low carbohydrate content (ketogenic diet) (7) in rodents is sufficient to lower insulin secretion with a concomitant reduction in fat accumulation. In addition, a 2012 study showed that high-fat diet–fed mice were prevented from gaining fat with reduced insulin gene dosage (8), suggesting a causal role of hyperinsulinemia in the development of obesity (9). These results indicate that suppression of insulin secretion may become a promising target in the treatment of obesity.

Currently, two types of drugs are used to suppress insulin secretion in the clinic: the ATP-sensitive potassium channel (K_{ATP} channel) opener diazoxide and the synthetic somatostatin analogue octreotide. Both drugs cause cell membrane hyperpolarization, leading to reduced action potential firing and reduced exocytosis in pancreatic beta cells, but through different intracellular mechanisms. Diazoxide opens K_{ATP} channels and promotes potassium efflux (10), whereas octreotide acts on somatostatin receptors (SSTRs) and leads to reduced cyclic AMP levels and Ca^{2+} influx (11). Because both K_{ATP} channels and SSTRs are highly expressed in human pancreatic beta cells, and the beta-cell mass expands in individuals with obesity, both drugs are able to suppress insulin secretion significantly in individuals with obesity.

Preclinical studies show significant insulin suppression and weight-lowering effects of both diazoxide and octreotide in obese animal models. Diazoxide reduced body weight in Zucker fatty rats (12-19), Otsuka Long–Evans Tokushima fatty rats (20,21), and diet-induced obese mice (22). Similarly, octreotide reduced body weight in high-fat–induced obese rats (23-26) and mice (27) in a short term of 8 to 10 days of treatment. Clinical trials using these two drugs in individuals with obesity were also conducted but showed mixed results (28-34). To clarify the effect of insulin secretion suppression in obesity, we conducted a meta-analysis of randomized controlled trials evaluating the efficacy and safety of insulin secretion suppression in patients with obesity.

Methods

Data sources

This meta-analysis was performed based on the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (35). Three databases, namely PubMed, Embase, and the Cochrane library, were scanned for randomized controlled trials without time and race restriction. PubMed was searched according to the following MeSH terms: "obesity," "randomized controlled trial," "diazoxide," or "octreotide."

Eligibility criteria and data extraction

Clinical trials were included if they satisfied the following criteria: 1) treatment duration for at least 8 weeks; 2) assessment of body weight, insulin levels, or indicators of glucose/lipid metabolism in individuals with obesity/overweight (BMI > 24 kg/m^2); 3) randomized controlled design. Studies were excluded under the following conditions: reviews and meta-analyses, case reports, intervention time less than 8 weeks, and trials with inadequate information.

The following data were extracted from every included trial by two independent researchers (WW and ZH): research characteristics (author, publication year, duration of treatment, sample size), baseline information of included individuals (i.e., age, sex, body weight, BMI), and baseline-subtracted change in clinical end points (body weight, BMI, fat mass, fasting glucose and insulin levels).

Assessment of bias

We assessed the level of bias within included articles using the Cochrane Collaboration tool. The following factors were assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other "miscellaneous" biases. Two independent investigators (WW and ZH) each evaluated the level of bias for these factors for all included articles.

Statistical analysis

Body weight, BMI, fat mass, and fat-free mass were evaluated to assess the efficacy of insulin suppression in the treatment of obesity, whereas fasting blood glucose and peak blood glucose during oral glucose tolerance tests were chosen to evaluate the safety of insulin suppression on glucose metabolism. Statistical analysis was performed by Review Manager software version 5.3 (Cochrane, London, UK). Odds ratios and 95% CI were selected to assess dichotomous outcomes. We also calculated the mean differences (MD) and 95% CI to assess continuous outcomes. A value of $P < 0.05$ was considered statistically significant. The random-effect model was selected to generate forest plots. The I^2 test was used to assess the levels of heterogeneity. Results were considered as having a high level of heterogeneity when $I^2 > 50\%$. Then sensitivity analysis investigated the source of heterogeneity.

Results

Selection process and characteristics of included trials

A total of 297 studies were identified by two independent investigators, consisting of 166 studies from Embase, 85 studies from Cochrane library, and 46 studies from PubMed. Of these articles, 18 were removed because of duplication, and 265 records—including 17 reviews and meta-analyses, 6 animal research, 35 nonrandomized controlled trials, and 207 unrelated research—were excluded by screening the abstracts. A full-text screen was further performed for those studies (a total of 14 articles) that were not excluded through abstract screening. Among the 14 articles, 7 fulfilled the inclusion criteria for meta-analysis. The selection process is shown in Figure 1. The baseline information was collected (Table 1), including study characteristics and patients' baseline information.

Efficacy of insulin secretion suppression

In order to evaluate the efficacy of insulin secretion suppression on obesity, we selected the parameters that could best reflect obesity phenotype: body weight, BMI, fat mass, and fat-free mass. We also selected fasting insulin levels to confirm the pharmaceutical property of the drugs on insulin suppression. The results showed a significant reduction in fasting insulin levels (MD = −3.94 mIU/L; 95% CI: −7.40 to −0.47; $I^2 = 37\%$; $P = 0.03$) (Figure 2A). This confirms the efficacy of the drug on the suppression of insulin secretion. In the context of obesity phenotype, we found a significant reduction of body

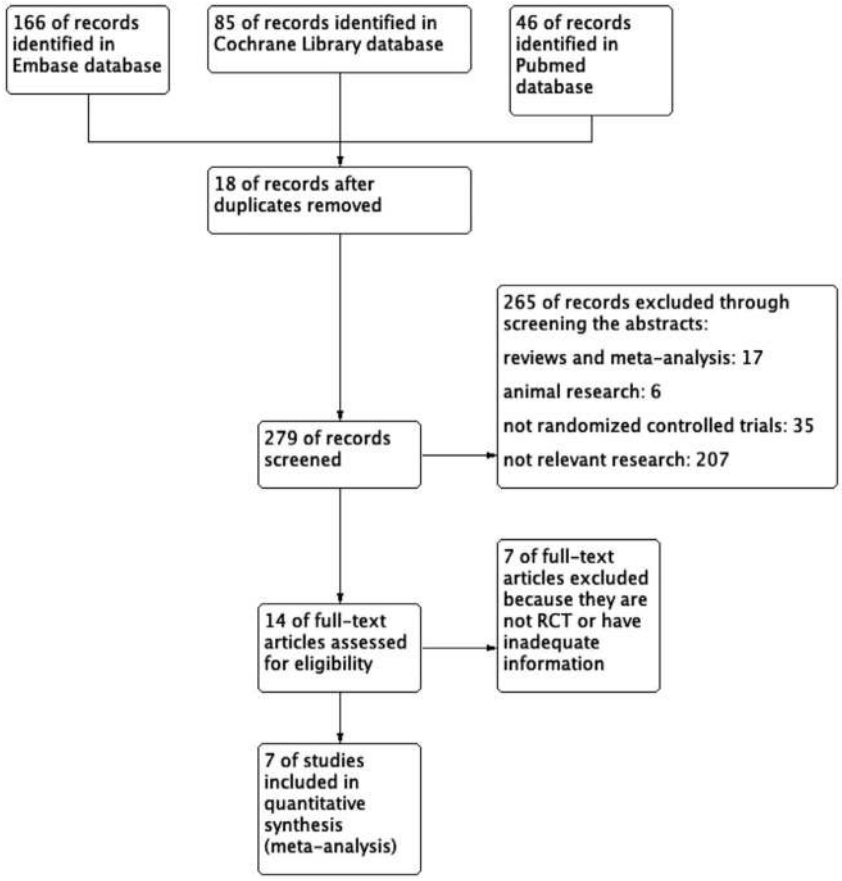

Figure 1 Review flow diagram. RCT, randomized controlled trial.

weight (MD = −3.19 kg; 95% CI: −5.71 to −0.66; $I^2 = 73\%$; $P = 0.02$) (Figure 2B), BMI (MD = −1.65 kg/m^2; 95% CI: −2.41 to −0.90; $I^2 = 40\%$; $P < 0.0001$) (Figure 2C), and fat mass (MD = −5.92 kg; 95% CI: −8.28 to −3.56) (Figure 2D) in the intervention group compared with the placebo group. There were no significant differences in fat-free mass (MD = 0.56 kg; 95% CI: −0.40 to 1.52]; $I^2 = 0$; $P = 0.26$) (Figure 2E) between the two groups. Please note that the greater fat mass loss than body weight loss was not relevant to increased fat-free mass. Rather, it is due to the difference in the studies included for body weight and fat mass analysis (all seven articles had body weight data but only three of them had fat mass data). The outcomes of the meta-analyses are summarized in Table 2.

Safety of insulin secretion suppression

We selected fasting blood glucose and peak blood glucose during oral glucose tolerance tests to determine the impact of insulin suppression on glucose metabolism. There was a slight but significant increase in fasting blood glucose (MD = 0.48 mmol/L; 95% CI: 0.24-0.72; $I^2 = 27\%$; $P < 0.0001$) (Figure 2F) and peak glucose (MD = 1.88 mmol/L; 95% CI: 0.97-2.78; $I^2 = 0\%$; $P < 0.0001$) (Figure 2G) in the intervention group compared with the placebo group. Neither fasting nor peak blood glucose levels reached the diagnostic criteria for diabetes in the intervention group.

Sensitivity analysis

When including all studies for the analysis of body weight, BMI, and fat mass, the heterogeneity was 69%, 80%, and 91%, respectively. Therefore, sensitivity analysis was performed. The heterogeneity of the body weight decreased from 69% to 13% (Table 3) with the exclusion of data from Due et al. (36) and Lustig et al. (29). However, the estimated mean change did not largely alter with (−2.92 kg; 95% CI: −4.45 to −1.38; $P = 0.0002$) or without (−3.05 kg; 95% CI: −5.52 to −0.57; $P = 0.02$) the exclusion. Therefore, although the inclusion of Due et al. (36) and Lustig et al. (29) led to high heterogeneity, it did not alter the estimates.

For the estimated mean change of BMI, the heterogeneity decreased from 80% to 40% after the exclusion of data from Due et al. (36) and Brauner et al. (32). The heterogeneity of the mean change of fat mass also decreased from 91% to 0% after the exclusion of data from Due et al. (36). The possible source of heterogeneity comes from the subjects in these two studies. In the study by Due et al. (36), the baseline fasting insulin was significantly different between the treatment and placebo groups (Table 1). This may cause bias when studying the drug, which directly targeted insulin secretion. The patients in the Brauner et al. study (32) were children with hypothalamic-pituitary lesions, in which diazoxide failed to reduce insulin levels (32). Because the hypothalamus plays a crucial role in the regulation of

TABLE 1 Baseline characteristics of included articles

	Author/year	Study design	Age (y)	Number of subjects	Intervention	Co-intervention	Duration of therapy	Mean weight (kg)	Mean BMI	Mean fasting glucose (mmol/L)	Mean fasting insulin (mIU/L)
Diazoxide	Alemzadeh et al., 1998 (28)	RCT	31.0 (4.2) vs. 28.0 (3.8) (Pl)	12 vs. 12 (Pl)	2 mg/kg/d	Low-calorie diet (1,260 kcal/d for females and 1,570 kcal/d for males)	2 months	111.8 (23.9) vs. 120.3 (21.8) (Pl)	40.4 (8.0) vs. 42.9 (4.8) (Pl)	5.2 (0.45) vs. 5.4 (0.4) (Pl)	23.4 (6.9) vs. 28.4 (10.0) (Pl)
	Due et al., 2007 (36)	RCT	33.5 (28.4) vs. 37.6 (31.8) (Pl)	17 vs. 18 (Pl)	2 mg/kg/d	Energy-deficit diet, 600 kcal/d	2 months	118.4 (22.3) vs. 125.4 (28.4) (Pl)	39.6 (6.6) vs. 43.3 (8.5) (Pl)	6.0 (0.9) vs. 5.95 (0.6) (Pl)	21.9 (6.2) vs. 16.6 (4.7) (Pl)*
	Brauner et al., 2016 (32)	RCT	14 [12-17] vs. 14 [10-15] (Pl)	13 vs. 17 (Pl)	4 mg/kg/d	Low-calorie diet (mean 1,400 kcal/d)	6 months	74 [68-82] vs. 84 [49-108] (Pl)	NA	4.5 [4.2- 4.7] vs. 4.3 [4-4.5] (Pl)	15 [11-17] vs. 15 [10 -23] (Pl)
	Loves et al., 2018 (33)	RCT	41.9 (9.3) vs. 46.6 (6.0) (Pl)	9 vs. 12 (Pl)	200-800 mg/d	Low-calorie diet (75% of daily recommendation); walk for 30 minutes after lunch and dinner	6 months	124.5 (14.7) vs. 118.5 (7.6) (Pl)	34.9 (2.4) vs. 34.8 (2.2) (Pl)	5.6 (0.3) vs. 5.6 (0.6) (Pl)	15.5 (7.8) vs. 13.1 (5.4) (Pl)
Octreotide	Lustig et al., 2003 (29)	RCT	13.8 (3.8) vs. 14.2 (2.8) (Pl)	10 vs. 10 (Pl)	5-15 ug/kg/d	None	6 months	95.4 (27.8) vs. 98.1 (24.3) (Pl)	36.4 (7.6) vs. 36.2 (4.1) (Pl)	4.0 (1.5) vs. 3.0 (1.4) (Pl)	29.2 (15.6) vs. 36.9 (21.4) (Pl)
	Gambineri et al., 2005 (30)	RCT	23.2 (5.6) vs. 24.7 (6.2) (Pl)	10 vs. 10 (Pl)	Octreotide-LAR (10 mg, q28d)	Energy-deficit diet, 500 kcal/d	6 months	97.3 (18.0) vs. 94.1 (25.0) (Pl)	35.8 (7.0) vs. 35.7 (7.5) (Pl)	NA	NA
	Lustig et al., 2006 (31)	RCT	39.6 (11.3) vs. 38.7 (11.8) (Pl)	44 vs. 44 (Pl)	Octreotide-LAR (60 mg, q28d)	None	6 months	107.3 (18.9) vs. 107.2 (24.0) (Pl)	39.5 (6.02) vs. 38.6 (5.6) (Pl)	NA	NA

Values in Brauner et al. (32) are presented as median [interquartile range]. All other values are presented as mean (SD).
LAR, long-acting release; NA, not available; Pl, placebo; RCT, randomized controlled trial.
*$P < 0.001$.

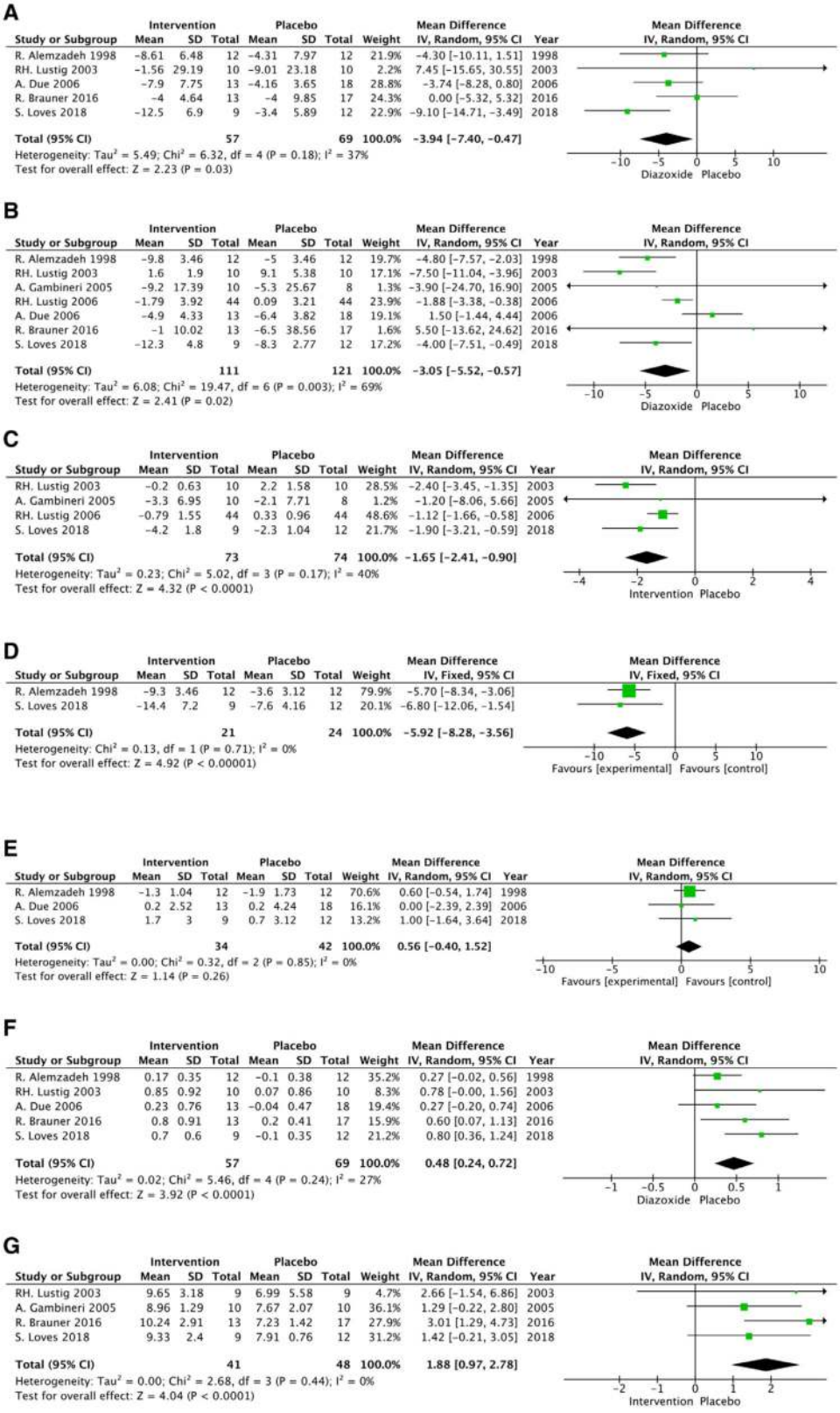

Figure 2 Forest plots for meta-analysis comparing insulin secretion suppression group with the placebo group in (**A**) fasting insulin, (**B**) body weight, (**C**) BMI, (**D**) fat mass and (**E**) fat-free mass, (**F**) fasting blood glucose, and (**G**) peak blood glucose. df, degrees of freedom; IV, inverse variance. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Summary of outcomes in studies that suppress insulin secretion in individuals with obesity

	No. of studies (active vs. placebo sample size)	Weighted placebo-subtracted mean difference (95% CI)	*P* value
Fasting insulin (mIU/L)	5 (57 vs. 69)	−3.94 (−7.40 to −0.47)	<0.05
Body weight (kg)	7 (111 vs. 121)	−3.05 (−5.52 to −0.57)	<0.05
BMI (kg/m^2)	4 (73 vs. 74)	−1.65 (−2.41 to 0.90)	<0.0001
Fat mass (kg)	2 (21 vs. 24)	−5.92 (−8.28 to −3.56)	<0.0001
Fat-free mass (kg)	3 (34 vs. 42)	0.56 (−0.40 to 1.52)	0.26
Fasting blood glucose (mmol/L)	5 (57 vs. 69)	0.48 (0.24 to 0.72)	<0.0001
Peak blood glucose (mmol/L)	4 (41 vs. 48)	1.88 (0.97 to 2.78)	<0.0001

TABLE 3 Sensitivity analysis of primary outcomes

	Original model			Exclusion of Due et al. (36) (body weight, BMI, fat mass), Lustig et al. (29) (body weight), and Brauner et al. (32) (BMI)		
	Sample size (active vs. placebo)	Mean difference (95% CI)	I^2	Sample size (active vs. placebo)	Mean difference (95% CI)	I^2
Weight (kg)	111 vs. 121	−3.05 (−5.52 to −0.57)	69%	88 vs. 93	−2.92 (−4.45 to −1.38)	13%
BMI (kg/m^2)	99 vs. 109	−0.93 (−1.88 to 0.02)	80%	73 vs. 74	−1.65 (−2.41 to −0.90)	40%
Fat mass (kg)	34 vs. 42	−3.54 (−8.70 to 1.61)	91%	21 vs. 24	−5.92 (−8.28 to −3.56)	0%

glucose metabolism, including control of insulin secretion via the autonomic nervous system (37), children with hypothalamic-pituitary lesions may have a different reaction to diazoxide compared with individuals with intact hypothalamic neuronal circuits, which is likely to be the possible source of heterogeneity. Therefore, we excluded the Due et al. (36) and Brauner et al. (32) studies from the meta-analysis of BMI and fat mass (Table 3).

Assessment of bias

Risk of bias of included articles was assessed by Review Manager (Figure 3). Gambineri's study (30) had high performance and detection bias because of a single-blind intervention. However, no other significant bias was observed.

Discussion

We performed a meta-analysis of randomized controlled trials evaluating the efficacy and safety of insulin secretion suppression in people with obesity. We pooled the data from clinical trials using the drugs diazoxide and octreotide. Both drugs significantly suppressed fasting insulin secretion in individuals with obesity. Suppression of insulin secretion coincided with reduced body weight and BMI. Moreover, the overall body composition appeared to improve, with reduced fat mass and unchanged fat-free mass (Table 2). However, it is unknown whether the beneficial effects of insulin suppression in terms of reduced body weight and improved body composition in obesity may be further extended to the prevention of any obesity-related complications, such as type 2 diabetes, cardiovascular diseases, and cancers.

The efficacy of weight loss due to insulin secretion suppression was similar to other antiobesity drugs. A meta-analysis showed that currently approved antiobesity medications lead to 3 to 5 kg of placebo-subtracted weight loss (2.87 kg for orlistat, 4.16 kg for sibutramine, and 4.67 kg for rimonabant) in 1-year trials (38), which represents an intervention time window with the most significant change (39). The suppression of insulin secretion resulted in a 3.05-kg placebo-subtracted weight loss in only 2- to 6-month trials. More weight loss may be expected to occur if the treatment was prolonged to 1 year or more, as indicated in the study by Loves et al. (33).

Overall, the beneficial effects of insulin suppression seen in human obesity, including body weight loss and fat mass reduction, are consistent with most of the findings in animal studies. Although direct mechanistic studies in humans attempting to unveil the cause-effect of these drugs in obesity remain limited, the mechanisms discovered in animal studies may be applied to human studies to some extent. For example, the effect of insulin secretion suppression was studied by a delicate experiment that used gene modification to reduce the dosage of the insulin gene in mice (8). In this study, mice with reduced insulin gene expression were protected from diet-induced obesity, with a concurrent increase in white adipose tissue browning and increase in energy expenditure (8). Using streptozotocin to reduce beta-cell mass and hyperinsulinemia in obese animals showed similar results, including reduced ectopic lipid accumulation and reduced adipose tissue inflammation (5,40). These led to reduced fat mass and improved insulin sensitivity following the reduction of insulin secretion. Therefore, reduction of insulin secretion may serve as a major mechanism in reducing fat accumulation in human obesity.

Apart from the reduction of hyperinsulinemia, diazoxide and octreotide exert their beneficial effects in obese animals through other

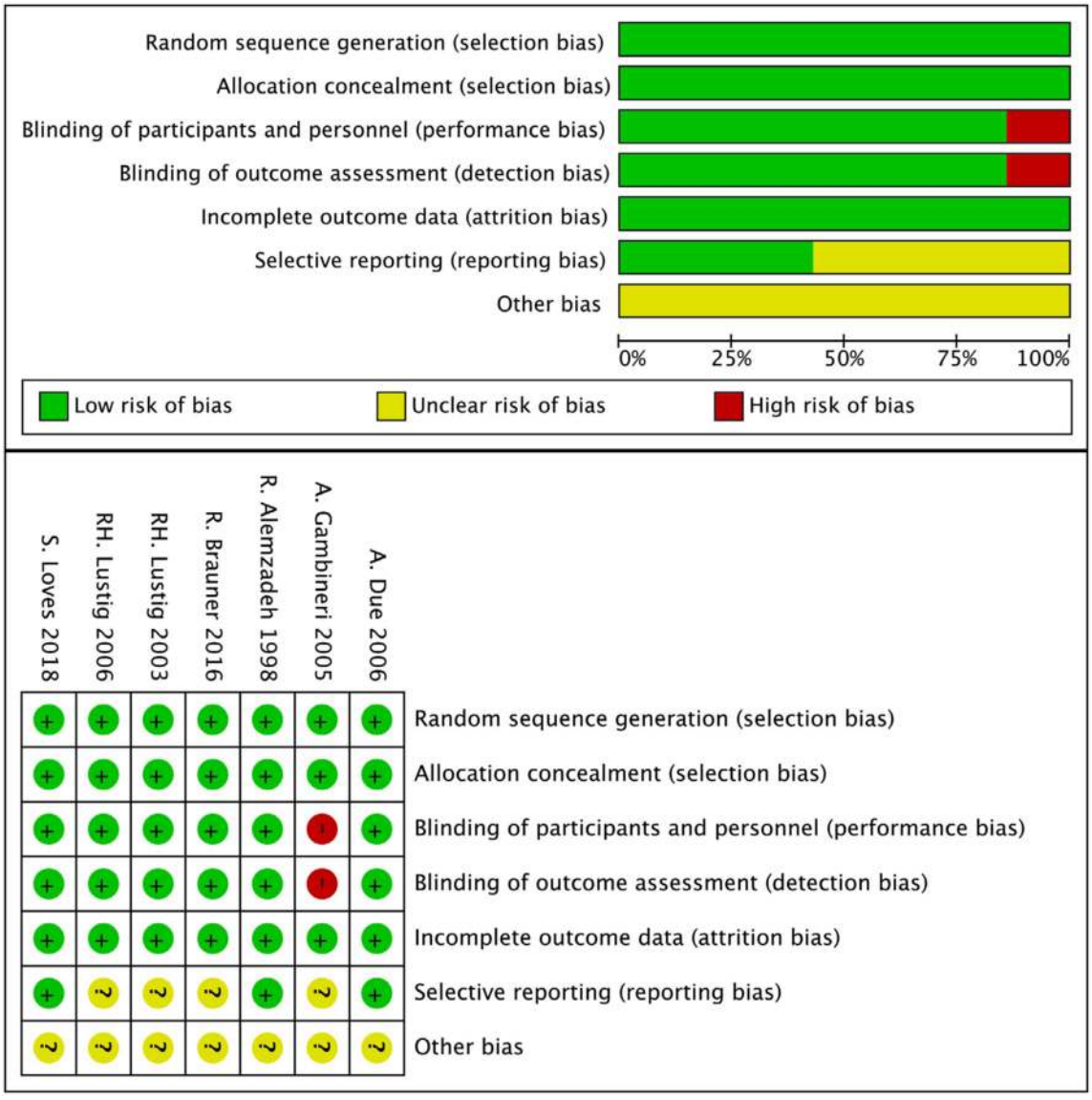

Figure 3 Bias assessment of included articles. Red color: high risk of bias; yellow color: unclear risk of bias; green color: low risk of bias. [Color figure can be viewed at wileyonlinelibrary.com]

mechanisms. Diazoxide reduces food intake in most of the animal studies (14,17-21). One animal study suggested that the reduction of food intake was through suppression of insulin secretion and restoration of the impaired insulin uptake into the brain (14). Similar food intake reduction effects occurred in two clinical studies with octreotide, whereas the recalled calorie intake in patients with obesity was decreased during the octreotide treatment period (41,42). The effect of both drugs on food intake in individuals with obesity requires further investigation. In addition, a 2011 study suggested that diazoxide acutely inhibited gluconeogenesis in the liver in both humans and rats (43).

However, in clinical trials, suppression of insulin secretion led to a slight but significant increase in fasting blood glucose (Table 2). This indicates a slight impairment of glucose metabolism following insulin suppression treatment in the setting of obesity. This side effect contradicts the glucose metabolism results in most animal studies, in which glucose metabolism was improved by either diazoxide (14,17,19,21,22) or octreotide (24,27). The glucose metabolism following long-term insulin suppression is mainly dependent on two factors: the insufficient insulin secretion, which increases glucose levels, and the improved insulin sensitivity, which reduces glucose levels. It is likely that, because of the difference in species, the former factor dominates in clinical trials, whereas the latter dominates in animal studies. However, limited data on insulin sensitivity are available from the clinical trials with inconsistent results. Loves et al. (34) showed a significant reduction of homeostatic model assessment of insulin resistance in the diazoxide group, whereas Brauner et al. (32) showed no significant difference between diazoxide and placebo groups. Whether prolonged insulin secretion suppression leads

to better insulin sensitivity with improved glucose metabolism needs further investigation. Although with increased blood glucose levels, only three teenaged patients with hypothalamic-pituitary lesions during childhood developed diabetes following drug treatment in one study (32) among all seven studies selected (less than 3%). This indicates that insulin suppression by diazoxide or octreotide is not likely to cause diabetes in individuals with obesity.

Other side effects are not common among all the clinical trials using diazoxide and octreotide. Edema is one of the side effects in diazoxide treatment (28,33,36) and it can be resolved after 2 weeks of therapy (28). Hirsutism develops in some females with obesity following diazoxide treatment (32). Diarrhea and cholelithiasis occur in some patients treated with octreotide (31). These adverse effects are likely drug-specific rather than because of suppression of insulin secretion.

This study has a few limitations. First, the relatively short duration of the drug intervention in all included studies (8-24 weeks) and the inability to collect other metabolic parameters—such as homeostatic model assessment of insulin resistance, plasma triglyceride, free fatty acid, and cholesterols—may constrain the long-term vision on obesity-related complications, such as the development of diabetes. Second, the sample size of this meta-analysis was relatively small. This may cause bias as well as the inability to perform age-based subgroup analysis for the two studies in teenagers (29,32). Third, the effect of insulin secretion suppression on the treatment of obesity may be driven by some effects other than suppression of insulin secretion following diazoxide or octreotide treatment (e.g., octreotide may inhibit gut and pancreatic endocrine and exocrine secretion, thus causing malabsorption, which may contribute to weight loss (44)). Therefore, more detailed emerging clinical studies are needed to address these limitations.

In conclusion, the present meta-analysis suggests that suppression of insulin secretion in the short term in patients with obesity is likely to contribute to an improved phenotype (e.g., reduced body weight and fat mass). Although glucose metabolism may be slightly impaired, the suppression of insulin secretion is not likely to induce diabetes. Given that previous findings support a causal role of hyperinsulinemia in the development of obesity (9), it is reasonable to speculate that the suppression of insulin secretion is an emerging target in the treatment of obesity. Development of specific insulin secretion suppression drugs with fewer side effects is encouraged in the future. Also, longer clinical trials are encouraged so as to thoroughly evaluate the efficacy and risk of insulin secretion suppression in the treatment of obesity.O

Acknowledgments

We thank Professor Ken Ho for his suggestions for the manuscript. Zhengxiang Huang is a recipient of a China Scholarship Council PhD scholarship and The University of Queensland International PhD scholarship.

Funding agencies: This work was supported by a National Health and Medical Research Council grant, Australia (NHMRC Project grant) and National Natural Science Foundation of China (grants 81670763 and 81471050).

Disclosure: The authors declared no conflict of interest.

References

1. Ludwig DS, Ebbeling CB. The carbohydrate-insulin model of obesity: beyond "calories in, calories out". *JAMA Intern Med* 2018;178:1098-1103.
2. Cerf ME. Beta cell dysfunction and insulin resistance. *Front Endocrinol (Lausanne)* 2013;4:37. doi:10.3389/fendo.2013.00037
3. Shanik MH, Xu Y, Skrha J, Dankner R, Zick Y, Roth J. Insulin resistance and hyperinsulinemia: is hyperinsulinemia the cart or the horse? *Diabetes Care* 2008;31(suppl 2):S262-S268.
4. Morita I, Tanimoto K, Akiyama N, et al. Chronic hyperinsulinemia contributes to insulin resistance under dietary restriction in association with altered lipid metabolism in Zucker diabetic fatty rats. *Am J Physiol Endocrinol Metab* 2017;312:E264-E272.
5. Pedersen DJ, Guilherme A, Danai LV, et al. A major role of insulin in promoting obesity-associated adipose tissue inflammation. *Mol Metab* 2015;4:507-518.
6. Pawlak DB, Kushner JA, Ludwig DS. Effects of dietary glycaemic index on adiposity, glucose homoeostasis, and plasma lipids in animals. *Lancet* 2004;364:778-785.
7. Kennedy AR, Pissios P, Otu H, et al. A high-fat, ketogenic diet induces a unique metabolic state in mice. *Am J Physiol Endocrinol Metab* 2007;292:E1724-E1739.
8. Mehran AE, Templeman NM, Brigidi GS, et al. Hyperinsulinemia drives diet-induced obesity independently of brain insulin production. *Cell Metab* 2012;16:723-737.
9. Templeman NM, Skovso S, Page MM, Lim GE, Johnson JD. A causal role for hyperinsulinemia in obesity. *J Endocrinol* 2017;232:R173-R183.
10. Ashcroft FM, Gribble FM. ATP-sensitive K+ channels and insulin secretion: their role in health and disease. *Diabetologia* 1999;42:903-919.
11. Braun M. The somatostatin receptor in human pancreatic β-cells. *Vitam Horm* 2014;95:165-193.
12. Alemzadeh R, Slonim AE, Zdanowicz MM, Maturo J. Modification of insulin resistance by diazoxide in obese Zucker rats. *Endocrinology* 1993;133:705-712.
13. Alemzadeh R, Jacobs W, Pitukcheewanont P. Antiobesity effect of diazoxide in obese Zucker rats. *Metabolism* 1996;45:334-341.
14. Alemzadeh R, Holshouser S. Effect of diazoxide on brain capillary insulin receptor binding and food intake in hyperphagic obese Zucker rats. *Endocrinology* 1999;140:3197-3202.
15. Standridge M, Alemzadeh R, Zemel M, Koontz J, Moustaid-Moussa N. Diazoxide down-regulates leptin and lipid metabolizing enzymes in adipose tissue of Zucker rats. *FASEB J* 2000;14:455-460.
16. Hensley IE, Lawler JE, Alemzadeh R, Holshouser SJ. Diazoxide effects on hypothalamic and extra-hypothalamic NPY content in Zucker rats. *Peptides* 2001;22:899-908.
17. Alemzadeh R, Holshouser S, Massey P, Koontz J. Chronic suppression of insulin by diazoxide alters the activities of key enzymes regulating hepatic gluconeogenesis in Zucker rats. *Eur J Endocrinol* 2002;146:871-879.
18. Alemzadeh R, Tushaus KM. Modulation of adipoinsular axis in prediabetic Zucker diabetic fatty rats by diazoxide. *Endocrinology* 2004;145:5476-5484.
19. Alemzadeh R, Karlstad MD, Tushaus K, Buchholz M. Diazoxide enhances basal metabolic rate and fat oxidation in obese Zucker rats. *Metabolism* 2008;57:1597-1607.
20. Aizawa T, Taguchi N, Sato Y, et al. Prophylaxis of genetically determined diabetes by diazoxide: a study in a rat model of naturally occurring obese diabetes. *J Pharmacol Exp Ther* 1995;275:194-199.
21. Guo Z, Bu S, Yu Y, et al. Diazoxide prevents abdominal adiposity and fatty liver in obese OLETF rats at prediabetic stage. *J Diabetes Complications* 2008;22:46-55.
22. Surwit RS, Dixon TM, Petro AE, Daniel KW, Collins S. Diazoxide Restores β3-adrenergic receptor function in diet-induced obesity and diabetes. *Endocrinology* 2000;141:3630-3637.
23. Liu R, Wei N, Guo W, et al. Octreotide alleviates obesity by reducing intestinal glucose absorption and inhibiting low-grade inflammation. *Eur J Nutr* 2013;52:1067-1075.
24. Huang W, Liu R, Ou Y, et al. Octreotide promotes weight loss via suppression of intestinal MTP and apoB48 expression in diet-induced obesity rats. *Nutrition* 2013;29:1259-1265.
25. Li M, Ye T, Wang XX, et al. Effect of octreotide on hepatic steatosis in diet-induced obesity in rats. *PLoS One* 2016;11:e0152085. doi:10.1371/journal.pone.0152085
26. Wang XX, Ye T, Li M, et al. Effects of octreotide on hepatic glycogenesis in rats with high fat diet-induced obesity. *Mol Med Rep* 2017;16:109-118.
27. Li W, Shi YH, Yang RL, et al. Effect of somatostatin analog on high-fat diet-induced metabolic syndrome: involvement of reactive oxygen species. *Peptides* 2010;31:625-629.
28. Alemzadeh R, Langley G, Upchurch L, Smith P, Slonim AE. Beneficial effect of diazoxide in obese hyperinsulinemic adults. *J Clin Endocrinol Metab* 1998;83:1911-1915.
29. Lustig RH, Hinds PS, Ringwald-Smith K, et al. Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2003;88:2586-2592.
30. Gambineri A, Patton L, De Iasio R, et al. Efficacy of octreotide-LAR in dieting women with abdominal obesity and polycystic ovary syndrome. *J Clin Endocrinol Metab* 2005;90:3854-3862.
31. Lustig RH, Greenway F, Velasquez-Mieyer P, et al. A multicenter, randomized, double-blind, placebo-controlled, dose-finding trial of a long-acting formulation of octreotide in promoting weight loss in obese adults with insulin hypersecretion. *Int J Obes (Lond)* 2006;30:331-341.
32. Brauner R, Serreau R, Souberbielle JC, et al. Diazoxide in children with obesity after hypothalamic-pituitary lesions: a randomized, placebo-controlled trial. *J Clin Endocrinol Metab* 2016;101:4825-4833.
33. Loves S, van Groningen L, Filius M, et al. High-dose, diazoxide-mediated insulin suppression boosts weight loss induced by lifestyle intervention. *J Clin Endocrinol Metab* 2018;103:4014-4022.
34. Loves S, van Groningen L, Filius M, et al. Effects of diazoxide-mediated insulin suppression on glucose and lipid metabolism in nondiabetic obese men. *J Clin Endocrinol Metab* 2018;103:2346-2353.
35. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097. doi:10.1371/journal.pmed.1000097
36. Due A, Flint A, Eriksen G, et al. No effect of inhibition of insulin secretion by diazoxide on weight loss in hyperinsulinaemic obese subjects during an 8-week weight-loss diet. *Diabetes Obes Metab* 2007;9:566-574.

37. Roh E, Song DK, Kim MS. Emerging role of the brain in the homeostatic regulation of energy and glucose metabolism. *Exp Mol Med* 2016;48:e216. doi:10.1038/emm.2016.4
38. Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. *BMJ* 2007;335:1194-1199.
39. Franz MJ, VanWormer JJ, Crain AL, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *J Am Diet Assoc* 2007;107:1755-1767.
40. Ning J, Hong T, Yang X, et al. Insulin and insulin signaling play a critical role in fat induction of insulin resistance in mouse. *Am J Physiol Endocrinol Metab* 2011;301:E391-E401.
41. Velasquez-Mieyer PA, Umpierrez GE, Lustig RH, et al. Race affects insulin and GLP-1 secretion and response to a long-acting somatostatin analogue in obese adults. *Int J Obes* Relat Metab Disord 2004;28:330-333.
42. Lustig RH, Rose SR, Burghen GA, et al. Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. *J Pediatr* 1999;135(2 Pt 1):162-168.
43. Kishore P, Boucai L, Zhang K, et al. Activation of K(ATP) channels suppresses glucose production in humans. *J Clin Invest* 2011;121:4916-4920.
44. Harris AG. Somatostatin and somatostatin analogues: pharmacokinetics and pharmacodynamic effects. *Gut* 1994;35(3 suppl):S1-S4.