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THE EFFECT OF ORLISTAT ADMINISTRATION IN HbA1c, WEIGHT LOSS AND FASTING BLOOD GLUCOSE (FBG) OF OBESITY OR OVERWEIGHT PATIENTS WITH TYPE 2 DIABETES MELLITUS: A META ANALYSIS

Chabib Fachry Albab[1], Almas Talida Habibah[2], Zaha El-Ma'i[3], Ardan Mulyarajasa Hanifullah[4], Azmil Permatasari[5]

Kedungadem Clinic Bojonegoro, Indonesia[1]
Ibnu Sina Hospital Bojonegoro, Indonesia[2]
Graha Medika Hospital Banyuwangi, Indonesia[3]
Dian Husada Hospital Mojokerto, Indonesia[4]
Dr. Soedomo General Hospital Trenggalek, Indonesia[5]
Email: fachryalbab55@gmail.com

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ABSTRACT

Orlistat has unique mechanism of action in the pharmacological agents for obesity management in patients with type 2 diabetes mellitus (T2DM). This meta-analysis was to consolidate the existing body of evidence regarding the effect of Orlistat administration on HbA1c levels, weight loss, and fasting blood glucose (FBG) levels in patients who are both obese or overweight and diagnosed with T2DM. The method used in this study was systematic review and meta-analysis which literature search was carried out using PubMed and Science Direct. A systematic review of published studies following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 was conducted. The protocol of this review was registered at PROSPERO. There were 9 selected randomized controlled trials with a total of 1935 patients were included. The analysis found there was significantly reduction in HbA1c (Mean differences [MD]: -0.67; 95% CI: -1.10 - -0.23; $p = 0.003$), weight loss (Mean differences [MD]: -2.85; 95% CI: -3.23 – -2.48; $p < 0.00001$), and fasting blood glucose (Mean differences [MD]: -1.23; 95% CI: -1.66 – -0.80; $p < 0.00001$). The conclusion obtained from the analysis that the effect of orlistat administration demonstrates significant reductions in HbA1c, body weight, and fasting blood glucose levels. It may have a benefical intervention for managing T2DM with obesity or overweight.

INTRODUCTION

The global burden of type 2 diabetes mellitus (T2DM) continues to rise, presenting a formidable challenge to public health systems worldwide (Khan et al, 2020). As a multifactorial and chronic metabolic disorder, T2DM is characterized by hyperglycemia resulting from insulin resistance and impaired insulin secretion (Goyal et al, 2023). One of the key drivers of this epidemic is the parallel surge in obesity rates, as obesity and T2DM are intricately intertwined (Ruze et al, 2023). The complex interplay between excess adiposity, insulin resistance, and T2DM underscores the urgent need for effective interventions aimed at managing both conditions.

Obesity is defined as an abnormal or excessive accumulation of body fat, not only serves as a precursor to T2DM but also exacerbates its clinical course (Lim dan Boster, 2023). The profound impact of obesity on T2DM lies in its contribution to insulin resistance and the increased production of proinflammatory adipokines and cytokines, which collectively promote the pathophysiological cascade of T2DM (Ruze et al, 2023). Therefore, the management of obesity in individuals with T2DM becomes an essential component of their care, with the potential to alleviate disease burden and enhance overall well-being.

Among the pharmacological agents explored for obesity management in patients with T2DM, Orlistat has garnered attention due to its unique mechanism of action (Mancini et al, 2008). Orlistat acts as a gastrointestinal lipase inhibitor, reducing the absorption of dietary fats and promoting weight loss (Bansal dan Khailili, 2022). While its efficacy in weight management is well-established, the impact of Orlistat on glycemic control, as reflected by changes in glycated hemoglobin (HbA1c) levels and fasting blood glucose (FBG) concentrations, remains a subject of ongoing investigation.

This meta-analysis seeks to consolidate the existing body of evidence regarding the effect of Orlistat administration on HbA1c levels, weight loss, and FBG levels in patients who are both obese or overweight and diagnosed with T2DM. By systematically reviewing and quantitatively synthesizing data from relevant studies, we aim to provide a comprehensive evaluation of the potential therapeutic benefits and clinical significance of Orlistat in this context. Furthermore, we intend to explore potential sources of heterogeneity across studies, offering insights into patient subgroups that may derive greater benefit from Orlistat therapy

METHOD

The present review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 (page et al, 2020). No ethical approval was required as no patients directly participated in this study and all the used data have already been published. The protocol of this review is in the registration process at PROSPERO (CRD42023465763).

Eligibility

We performed a systematic search on randomized control trial of the effect of orlistat administration in HbA1c, weight loss, and fasting blood glucose of obesity or overweight patients with type 2 diabetes mellitus. Studies reporting patient without type 2 diabetes mellitus are excluded. The publication year has no limitation. Any studies written in languages other than English, those with no available full text and with nonhuman subjects were excluded. Duplicate articles were resolved before the title and abstract screening.

Search Strategy and Selection of Studies

We conducted a comprehensive systematic database search on August 20, 2023. in PubMed and ScienceDirect by two authors working independently. The keywords that will be used are derived from "orlistat" AND "obesity" AND "overweight" AND "diabetes" AND "HbA1c" AND "Weight" AND "Fasting Blood Glucose", along with their related MeSH terms, synonyms, and elaboration. Review articles will be excluded but their references will be screened for potentially missed relevant studies. Titles and abstracts of the articles to identify potentially eligible studies were independently screened for full-text review.
Inclusion criteria (the guidelines to select the eligible studies which could be included in the process of the analysis) and exclusion criteria were chosen as follows.

Inclusion Criteria

The inclusion criteria in this study were: (1) Age > 18 years; (2) Obesity (BMI > 25 kg/m^2) (3) Diagnosed with type 2 diabetes mellitus who was currently on diabetes treatment or who had just been given diabetes treatment at the start of the study; (3) The study design was a randomized controlled trial; (4) Investigation of the effect of orlistat administration in HbA1c, weight loss, and fasting blood glucose of obesity or overweight patients with type 2 diabetes mellitus ; (5) Providing sufficient information on the effect of orlistat administration in HbA1c, weight loss, and fasting blood glucose of obesity or overweight patients with type 2 diabetes mellitus.

Exclusion Criteria

The exclusion criteria in this study were: (1) experimental studies and uncontrolled studies; (2) T2DM treatment discontinued when the study was started; (3) Lack of sufficient information on baseline and change of HbA1c, weight loss, and fasting blood glucose; (4) Review articles, reviews, case reports, letters to editors, and abstracts of scientific meetings in languages other than English.

Article Extraction

We independently extracted relevant articles from the included studies using a structured and standardized form. The following information was extracted: author/year of publication, country, study design, sample size, male, age, BMI, duration of follow up, study groups (orlistat and control), HbA1c (baseline-change), weight (baseline-change), and fasting blood glucose (baseline-change). Any discrepancy will be resolved by consensus between all authors involved in the data extraction process.

Quality Assessment

The tool used for assessment will be Cochrane's tool for Risk of bias assessment-2 (RoB-2) for randomized clinical trials. Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) will be used to assess quality of evidence.

Quantitative Data Synthesis

Review Manager 5.4.1 software was used in this meta-analysis. We analyze three main outcomes, consisting of HbA1c, weight loss, and fasting blood glucose. Net changes in measurements (change scores) were calculated as follows: measure at the end of follow up – measure at baseline. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5.

Publication Bias

Visual inspection of asymmetry in the Begg`s funnel plots as well as Egger`s weighted regression and "fail safe N" test was used to explore the presence of potential publication bias in the analysis.

RESULT AND DISCUSSION

Search Results and Study Characteristics

A comprehensive electronic database search provided 206 studies for review, and manual search identified no additional studies. After review, 9 RCTs the effect of orlistat administration in HbA1c, weight loss, and fasting blood glucose of obesity or overweight patients with type 2 diabetes mellitus remained and were included in analysis (Figure 1).

A total of 1935 patients were included in our final analysis, with maximum age 75 years. There were 3 studies in the Americas, 4 studies in Europe, and 2 studies in Asia. There were 962 patients in the orlistat group and 973 patients in control group. A summary of demographic characteristic of the included patients is detailed in table 1.

Table 1. Characteristics of Included Studies

Authors / Year of Publication	Country	Population (n)		Age	BMI (kg/m^2)	Follow-up
		Orlistat	Placebo			
Hollander / 1998	United States	162	159	> 18	28 – 40	52 weeks
Miles / 2002	United States, Canada	249	254	40 – 65	28 – 43	52 weeks
Berne / 2005	Sweden	111	109	30 – 75	28 – 40	52 weeks
Lindgarde / 2000	Germany	68	60	18 – 75	28 – 38	48 weeks
Halpern / 2003	Brazil, Argentina, Colombia, Costa Rica, Mexico	139	141	18 – 70	≥ 27	24 weeks
Guy-Grand / 2004	France	97	96	18 – 65	≥ 28	24 weeks
Shi / 2005	China	117	119	18 – 65	25 – 40	24 weeks
Kuo / 2006	China	30	30	≥ 18	≥ 24	12 weeks
Derosa / 2011	Italy	113	121	≥ 18	≥ 30	12 weeks

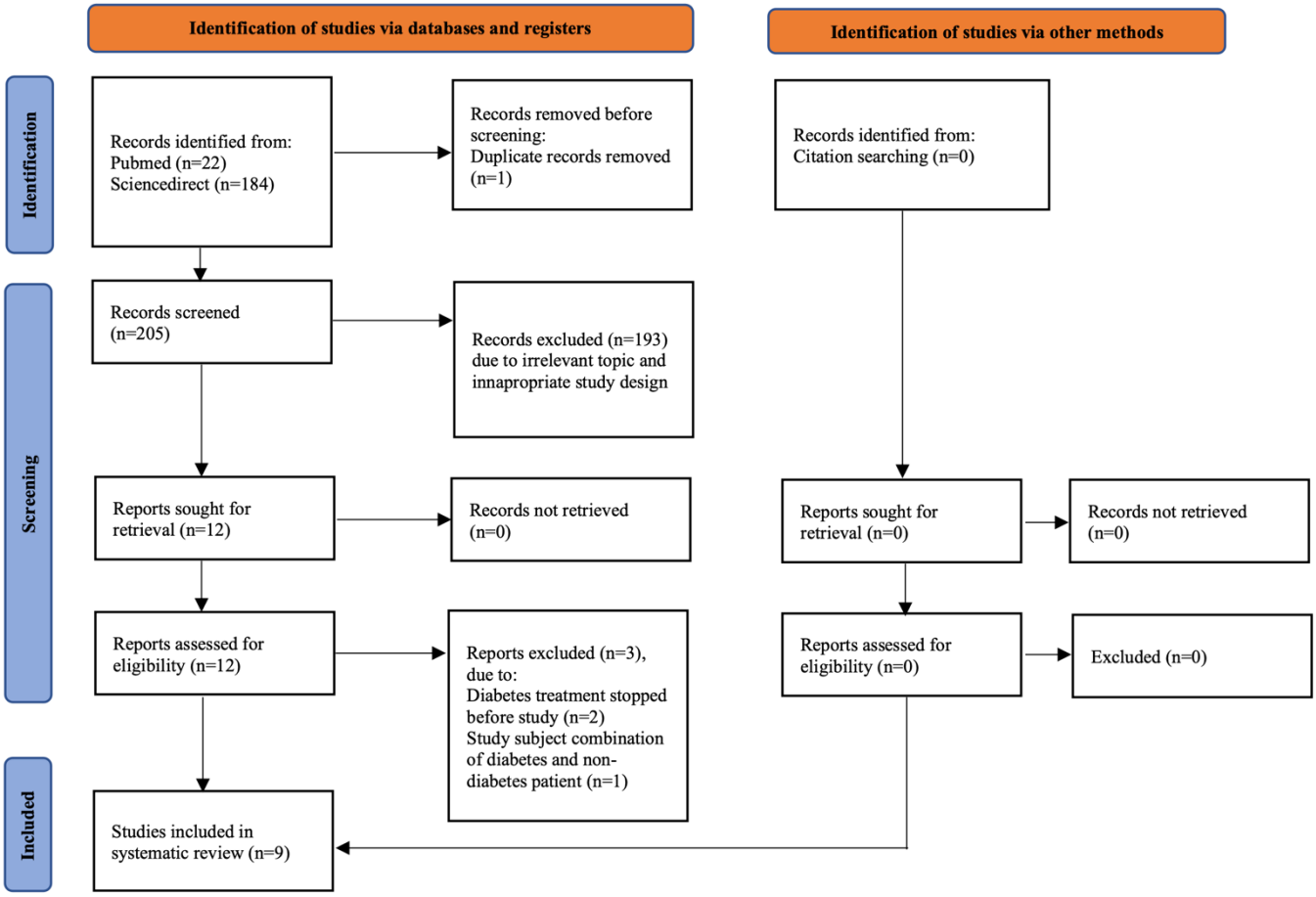

Figure 1. PRISMA flowchart of the literature selection

Risk of Bias Among Included Studies

Assessment of the study quality was carried out using the criteria of Risk of bias assessment-2 (RoB-2) for randomized clinical trials. In the selection aspect, all included studies reported a good selection process, as the included populations were fairly representative of the effect of orlistat administration in HbA1c, weight loss, and fasting blood glucose of obesity or overweight patients with type 2 diabetes mellitus (Figure 5).

HbA1c Reduction

Study analysis on HbA1c reduction of obesity or overweight patients with type 2 diabetes mellitus was performed in nine included studies, comprising 1935 patients. There was significantly reduction in HbA1c of obesity or overweight patients with type 2 diabetes mellitus who where administrated orlistat (Mean Difference [MD]: -0.67; 95% CI: -1.10 - -0.23; $p = 0.003$) as depicted in Figure 2. A random effect model was used for this outcome, as as the heterogeneity between studies was found to be high ($p < 0.00001$).

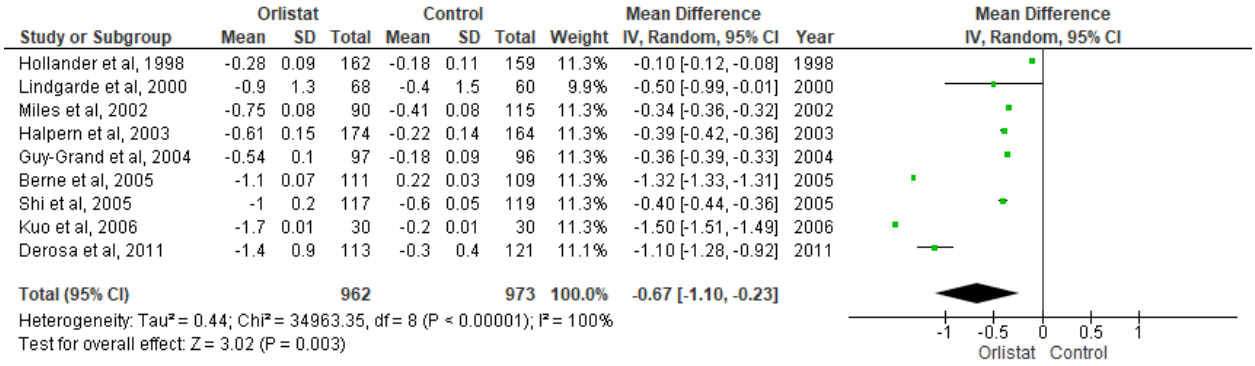

Figure 2. Forest Plot for HbA1c Reduction

Weight Loss

Meta analysis on weight loss of obesity or overweight patients with type 2 diabetes mellitus was performed in nine included studies. The pooled analysis found that the weight loss was significant (Mean differences [MD]: -2.85; 95% CI: -3.23 – -2.48; $p < 0.00001$) as depicted in Figure 3. A random-effect model was used for this outcome, as the heterogeneity between studies was found to be high ($p < 0.00001$).

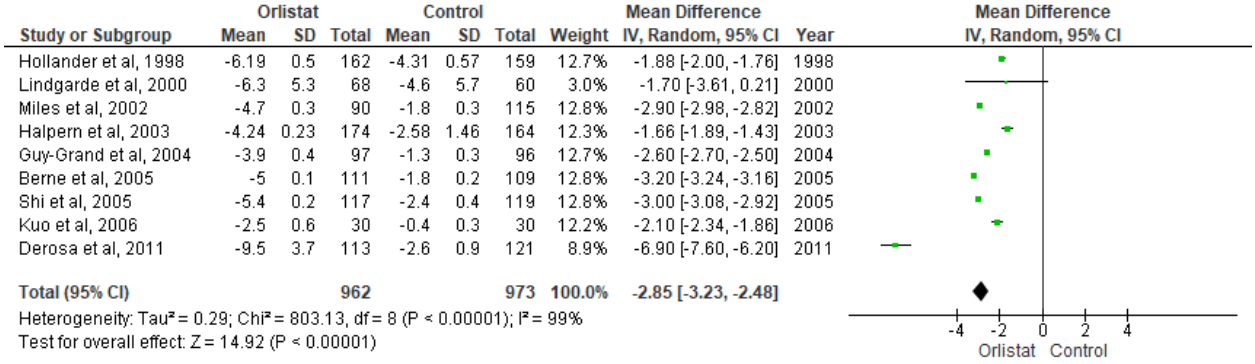

Figure 3. Forest Plot for Weight Loss

Fasting Blood Glucose Reduction

Meta analysis on fasting blood glucose reduction of obesity or overweight patients with type 2 diabetes mellitus was performed in nine included studies. The pooled analysis found that the fasting blood glucose reduction was significant (Mean differences [MD]: -1.23; 95% CI: -1.66 – -0.80; $p < 0.00001$) as depicted in Figure 4. A random-effect model was used for this outcome, as the heterogeneity between studies was found to be high ($p < 0.00001$).

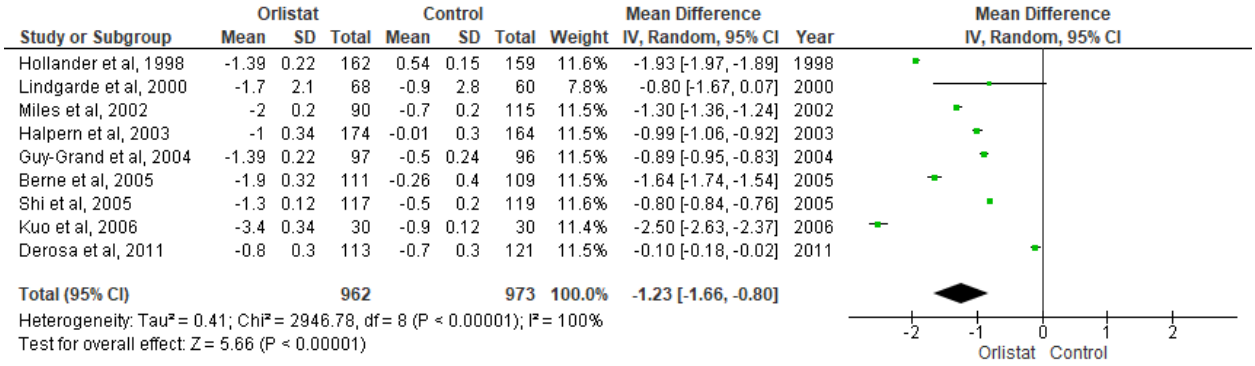

Figure 4. Forest Plot for Fasting Blood Glucose Reduction

Discussion

This meta-analysis investigated the effect of orlistat administration on HbA1c, weight loss, and fasting blood glucose (FBG) in overweight or obese patients with type 2 diabetes mellitus (T2DM). Our findings revealed that orlistat administration significantly reduced HbA1c, body weight, and FBG compared to controls. These results support the potential of orlistat as an adjunctive therapy for improving glycemic control in patients with T2DM alongside lifestyle modifications.

In this study, there was significantly reduction in HbA1c of obesity or overweight patients with type 2 diabetes mellitus who where administrated orlistat (Mean Difference [MD]: -0.67; 95% CI: -1.10 - -0.23; p = 0.003). This is in accordance with research by Jacob et al in 2010 which stated that orlistat 120 mg appears to improve glycaemic control more than would be predicted by weight loss alone in overweight or obese patients with type 2 diabetes (Jacob et al, 2010). Orlistat exerts its effect on HbA1c reduction in type 2 diabetes mellitus through a multifaceted mechanism. Primarily, it acts as a lipase inhibitor within the gastrointestinal tract. Lipases, both gastric and pancreatic in origin, are responsible for hydrolyzing dietary triglycerides into absorbable free fatty acids and monoglycerides. By inhibiting these enzymes, orlistat prevents a portion of the ingested fat from undergoing digestion and subsequent absorption (Bansal and Khalili, 2022). This unabsorbed fat is then eliminated in feces. This reduction in fat absorption can lead to weight loss, which is a well-established contributor to improved glycemic control in type 2 diabetes. Weight loss enhances insulin sensitivity at the cellular level, allowing for more efficient blood sugar uptake (Schenk et al, 2009). Beyond its weight-loss effects, orlistat may also directly influence glycemic control through alterations in gut hormone profiles. Studies suggest that orlistat might increase the secretion of glucagon-like peptide-1 (GLP-1), a gut hormone known to stimulate insulin secretion and suppress glucagon release (Damci et al, 2004). Additionally, orlistat might decrease the release of gut hormones that oppose insulin action, such as gastric inhibitory polypeptide (GIP). This hormonal modulation can further contribute to improved blood sugar control (Enc et al, 2009). Furthermore, orlistat might directly impact glucagon secretion. Glucagon, a pancreatic hormone, raises blood sugar levels by stimulating hepatic glucose production. Orlistat has been shown to decrease glucagon release, offering another potential avenue for HbA1c reduction (Ellrichmann et al, 2008).

This study also found that administration of orlistat was able to reduce body weight significantly in overweight or obese patients with type 2 diabetes mellitus (Mean differences [MD]: -2.85; 95% CI: -3.23 – -2.48; p < 0.00001). Jain et al in 2011 also supported these results. In his research it was found that compared to placebo, orlistat caused significant reduction (P<0.05) in

weight (4.65 kg vs 2.5 kg; orlistat vs placebo, respectively), BMI (1.91 kg/m2 vs 0.64 kg/m2) and waist circumference (4.84 cm vs 2 cm), cholesterol (10.68 mg vs 6.18 mg) and LDL level (5.87 mg vs 2.33 mg) (Jain et al, 2011). Orlistat exerts its effect by inhibiting lipases, enzymes responsible for breaking down dietary fats (triglycerides) into smaller, absorbable components like free fatty acids and monoglycerides. Orlistat acts within the lumen of the stomach and small intestine by forming a bond with lipases, rendering them inactive. Consequently, triglycerides remain largely undigested. Since these unhydrolyzed fats cannot be absorbed by the intestinal wall, they are ultimately eliminated through feces. This reduction in fat absorption translates to a decrease in overall calorie intake, promoting weight loss (Bansal and Khalili, 2022) (Heck et al, 2000).

The pooled analysis found that the fasting blood glucose reduction was significant (Mean differences [MD]: -1.23; 95% CI: -1.66 – -0.80; $p < 0.00001$). Beyond its established role in weight management, orlistat's potential to improve fasting blood sugar extends through several mechanisms. By inhibiting fat digestion, orlistat may lead to lower overall dietary fat absorption (Guerciolini, 1997). This, combined with a slower and less complete breakdown of carbohydrates, could result in a more gradual rise in blood sugar. Additionally, orlistat might improve insulin sensitivity, allowing cells to utilize glucose more effectively, and potentially reduce circulating free fatty acids that can impair insulin action (Kujawska-Łuczak et al, 2017). Furthermore, orlistat's possible contribution to decreased visceral fat and stimulation of GLP-1 secretion could further enhance glycemic control (Damci et al, 2004).

This study has several limitations. The meta-analysis results may not be generalizable to all populations with overweight/obesity and type 2 diabetes mellitus. Factors like ethnicity, dietary habits, and baseline medication use could influence the effectiveness of orlistat. While the meta-analysis examines HbA1c and FBG, it might not explore the broader impact of orlistat on other aspects of diabetes management or long-term complications

CONCLUSION

In conclusion, the meta-analysis of studies investigating the effect of orlistat administration in obesity or overweight patients with type 2 diabetes mellitus demonstrates significant reductions in HbA1c, body weight, and fasting blood glucose levels. These findings suggest that orlistat may be a beneficial intervention for managing type 2 diabetes mellitus in individuals who are obese or overweight. Further research and clinical trials are warranted to corroborate these results and explore the long-term effects and potential implications of orlistat therapy in this patient population.

DAFTAR PUSTAKA

Bansal, A.B., Al Khalili, Y. (2022). Orlistat. [Updated 2022 Dec 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542202/

Damci, T., Yalin, S., Balci, H., et al. (2004). Orlistat augments postprandial increases in glucagon-like peptide 1 in obese type 2 diabetic patients. Diabetes Care. 2004;27(5):1077-1080. doi:10.2337/diacare.27.5.1077

Ellrichmann, M., Kapelle, M., Ritter, P. R., et al. (2008). Orlistat inhibition of intestinal lipase acutely increases appetite and attenuates postprandial glucagon-like peptide-1-(7–36)-amide-1, cholecystokinin, and peptide YY Concentrations. The Journal of Clinical Endocrinology & Metabolism. 2008;93(10):3995-3998. doi:10.1210/jc.2008-0924

Enç, F.Y., Ones, T., Akin, H.L., et al. (2009). Orlistat accelerates gastric emptying and attenuates

GIP release in healthy subjects. Am J Physiol Gastrointest Liver Physiol. 2009;296(3):G482-G489. doi:10.1152/ajpgi.90209.2008

Goyal, R., Singhal, M., Jialal, I. (2023). Type 2 Diabetes. [Updated 2023 Jun 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513253/

Guerciolini, R. (1997). Mode of action of orlistat. Int J Obes Relat Metab Disord. 1997;21 Suppl 3:S12-S23.

Heck, A.M., Yanovski, J.A., Calis, K.A. (2000). Orlistat, a new lipase inhibitor for the management of obesity. Pharmacotherapy. 2000;20(3):270-279. doi:10.1592/phco.20.4.270.34882

Jacob, S., Rabbia, M., Meier, M.K., Hauptman, J. (2009). Orlistat 120 mg improves glycaemic control in type 2 diabetic patients with or without concurrent weight loss. Diabetes Obes Metab. 2009;11(4):361-371. doi:10.1111/j.1463-1326.2008.00970.x

Jain, S.S., Ramanand, S.J., Ramanand, J.B., Akat, P.B., Patwardhan, M.H., Joshi, S.R. (2011). Evaluation of efficacy and safety of orlistat in obese patients. Indian J Endocrinol Metab. 2011;15(2):99-104. doi:10.4103/2230-8210.81938

Khan, M.A.B., Hashim, M.J., King, J.K., Govender, R.D., Mustafa, H., Al Kaabi, J. (2020). Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. J Epidemiol Glob Health. 2020;10(1):107-111. doi:10.2991/jegh.k.191028.001

Kujawska-Łuczak, M., Musialik, K., Szulińska, M., et al. (2017). The effect of orlistat versus metformin on body composition and insulin resistance in obese premenopausal women: 3-month randomized prospective open-label study. Arch Med Sci. 2017;13(4):725-731. doi:10.5114/aoms.2016.62014

Lim, Y., Boster, J. (2023). Obesity and Comorbid Conditions. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK574535/

Mancini, M.C., Halpern, A. (2008). Orlistat in the prevention of diabetes in the obese patient. Vasc Health Risk Manag. 2008;4(2):325-336. doi:10.2147/vhrm.s6808

Page, M.J., McKenzie, J.E., Bossuyt, P.M., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. Published 2021 Mar 29. doi:10.1136/bmj.n71

Ruze, R., Liu, T., Zou, X., et al. (2023). Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. Front Endocrinol (Lausanne). 2023;14:1161521. Published 2023 Apr 21. doi:10.3389/fendo.2023.1161521

Schenk, S., Harber, M.P., Shrivastava, C.R., Burant, C.F., Horowitz, J.F. (2009). Improved insulin sensitivity after weight loss and exercise training is mediated by a reduction in plasma fatty acid mobilization, not enhanced oxidative capacity. J Physiol. 2009;587(Pt 20):4949-4961. doi:10.1113/jphysiol.2009.175489.