Review Article

THE EFFECT OF ORLISTAT ADMINISTRATION IN CHANGE OF GLYCEMIC CONTROL AND WEIGHT LOSS OF OBESITY OR OVERWEIGHT PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Risk of Type 2 diabetes mellitus (T2DM) increases steadily with increasing overweight and obesity, and these two-health problems are emerging epidemics worldwide. Orlistat, a lipase inhibitor for weight loss drug, is often used in T2DM medication as adjuvant therapy, but effectiveness of the drug for improving glycemic control on T2DM patients is unclear. This study was to determine the effect of orlistat on glycemic control and weight loss in overweight or obese patients with T2DM. Term "Orlistat" AND "(obesity OR overweight)" AND "(HbA1c OR A1C)" AND "diabetes" were systematically searched in Pubmed and Science Direct web databases up to March 2021. Only randomized controlled study (RCT) methods studies were included in this study. Collected final samples were presented in a table with narrative review. There were 9 RCT studies with a total 2,175 subjects that met inclusion criteria. Of the sample, 360 mg/day orlistat as an adjuvant therapy, was administered to overweight or obese T2DM patients together with hypocaloric intake (8 studies) or without hypocaloric intake (1 study) intervention. They were examined for 12-52 weeks. From 2 short-term (12 weeks) studies, one study revealed that orlistat improved HbA1c and fasting plasma glucose (FPG) level significantly, while one study showed no significant effect compared to placebo. Seven other studies (long term observation) had found that orlistat significantly improved HbA1c and FPG level. All studies found that orlistat significantly reduced body weight. As an adjuvant therapy, Orlistat improved HbA1c and FPG level in overweight and obese T2DM patients.

***Keywords**: Orlistat; type 2 diabetes mellitus; overweight; obesity; glycemic control; body weight*

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Highlights:

1. The effect of orlistat on glycemic control and weight loss in overweight or obese type 2 diabetes mellitus patients was determined.
2. HbA1c and FPG level in overweight and obese type 2 diabetes mellitus patient can improved by orlistat as an adjuvant therapy.

INTRODUCTION

The incidence and severity of metabolic disorders of type 2 diabetes mellitus are closely related to obesity and overweight (Wannamethee & Shaper 1999). The implication of the continuing increase in the prevalence of obesity and overweight for the incidence of type 2 diabetes is a serious condition (Kumanyika et al. 2002). The incidence of diabetes increased in obese people (18.0% to 20.1%), indicating that most of the increase in diabetes prevalence was due to the increase in obesity prevalence. In fact, 85.2% of people with type 2 diabetes mellitus are overweight or obese (Bhupathiraju & Hu 2016). One logical approach, but difficult to achieve in practice, to prevent or treat type 2 diabetes is the long-term management of overweight. Several studies have shown that moderate weight loss of 5–10% through diet and lifestyle interventions

substantially increase the risk profile for cardiovascular and glycemia and improves the risk of type 2 diabetes mellitus in high-risk subjects (Williamson et al. 2000).

Orlistat is a lipase inhibitor, originally developed for long-term management of obesity which selectively inhibits digestion and absorption of triglycerides in the digestive tract. At a dosage of 120 mg three times daily combined with a mildly hypocaloric diet, orlistat reduces dietary fat absorption by about 30% (Hanefield & Sachse 2002). The therapeutic application of orlistat is not just a weight-loss treatment. In combination with lifestyle intervention, orlistat reduces the development of impaired glucose tolerance and progresses to type 2 diabetes in obese patients. Besides, weight loss induced by orlistat in association with a low-calorie diet is accompanied by improved glycemic control and cardiovascular risk factors in obese patients receiving treatment for type 2 diabetes (Hanefield & Sachse 2002).

Until now, the use of orlistat as adjuvant therapy in obese patients with type 2 diabetes mellitus is still controversial. Some studies proved that giving orlistat could significantly reduce body weight, HbA1c, and GDP, but there were still studies which indicated that weight loss and HbA1c as the result of giving orlistat was less significant compared to placebo (Derosa et al. 2011, Hanefield & Sachse 2002).

Another systematic review study conducted by Aldekhail et al. (2015) showed that orlistat had a significant effect on body weight, HbA1c, and GDP in diabetic patients in the short-term (<3 months). However, this systematic review was unable to demonstrate the long-term effectiveness of orlistat (Aldekhail et al. 2015).

This study aimed to review the effect of orlistat in obese or overweight patients with diabetes in the short-term and longer-term based on several previous studies by comparing several existing studies.

MATERIALS AND METHODS

This study used cross sectional study design with a systematic review method based on several randomized control trial studies. The inclusion criteria in this study were obesity (BMI >25 kg/m^2), aged >18 years, diagnosed with type 2 diabetes mellitus, and was currently on diabetes treatment or had just been given diabetes treatment at the beginning of the study. The exclusion criteria of this study were discontinuation of T2DM treatment when the study was started.

Data collection techniques in this study came from nine scientific papers published in English language international journals. The search was carried out using several search engines, such as Pubmed and ScienceDirect which focused on some keywords, namely Orlistat AND (obesity OR overweight), AND (HbA1c OR A1C), and AND diabetes conducted until March 29, 2021.

The sample used in this study were 9 RCT with a total of 2,175 research subjects from Pubmed and Science Direct regarding the effect of orlistat on changes in glycemic control and weight loss for obese or overweight patients with type 2 diabetes mellitus. The collected data were managed using PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) method and using Zotero software to manage reference sources.

RESULTS

The search identified 206 potentially eligible citations, of which one was excluded as duplicates (Figure 1). On reviewing the titles and the abstract of 205 articles, 176 were considered English language articles and the full articles were obtained. The 176 articles, and 12 fulfilled the inclusion criteria. Two studies were excluded for discarding diabetes treatment during the study (Kelley et al. 2003, Kopelman et al. 2010). One study was excluded for using both diabetic and non-diabetic patients as subjects (Hanefield & Sachse 2002). The final 9 selected RCTs were published between 1998 and 2012 (Table 1).

The number of participants in each study ranged from 60 to 503. The pooled group comprised 2,175 participants, including 1,083 participants in the orlistat treatment group and 1,092 participants in the control group. Two of the studies were conducted in China (22%) (Kuo et al. 2006, Shi et al. 2005), and one each in the other eleven countries. Studies varied in duration between 12 and 52 weeks. Studies were divided by the duration of the study. Two studies were conducted for ≤12 weeks categorized into short-term studies (Derosa et al. 2011, Kuo et al. 2006), and other studies categorized into long-term studies. All of the studies used orlistat at a dose of 360 mg/day. One study used moderate diet (Kuo et al. 2006), and the other studies used hypocaloric diet. No specific physical activity information was provided in all studies.

The mean BMI values at baseline of the included studies for orlistat and control group ranged from 26.9 (study conducted in China) to 35.2 and 27.2 (study conducted in China) to 35.6. One study did not provide BMI values at baseline, but the subjects BMI values ranged from 25 to 40 (study conducted in China) (Shi et al. 2005). All studies reported results for weight (kg), HbA1c and FPG, each baseline and changes (Table 2).

The overall mean HbA1c and FPG levels decreased more in the treatment groups than in the control group. In short-term studies, a greater mean HbA1c and FPG change was reported in lifestyle intervention with orlistat treatments compared to lifestyle intervention with placebo ($p<0.05$), although one study showed no significant changes in HbA1c and FPG (Derosa et al. 2011). In long-term studies, the reduction in HbA1c and FPG in orlistat treatment groups was greater than the reduction in control groups ($p<0.05$). Short-term studies showed a greater mean HbA1c change than long-term studies. The overall mean weight loss was greater in the treatment groups than in the control group ($p<0.05$), either in short-term group or in long-term group.

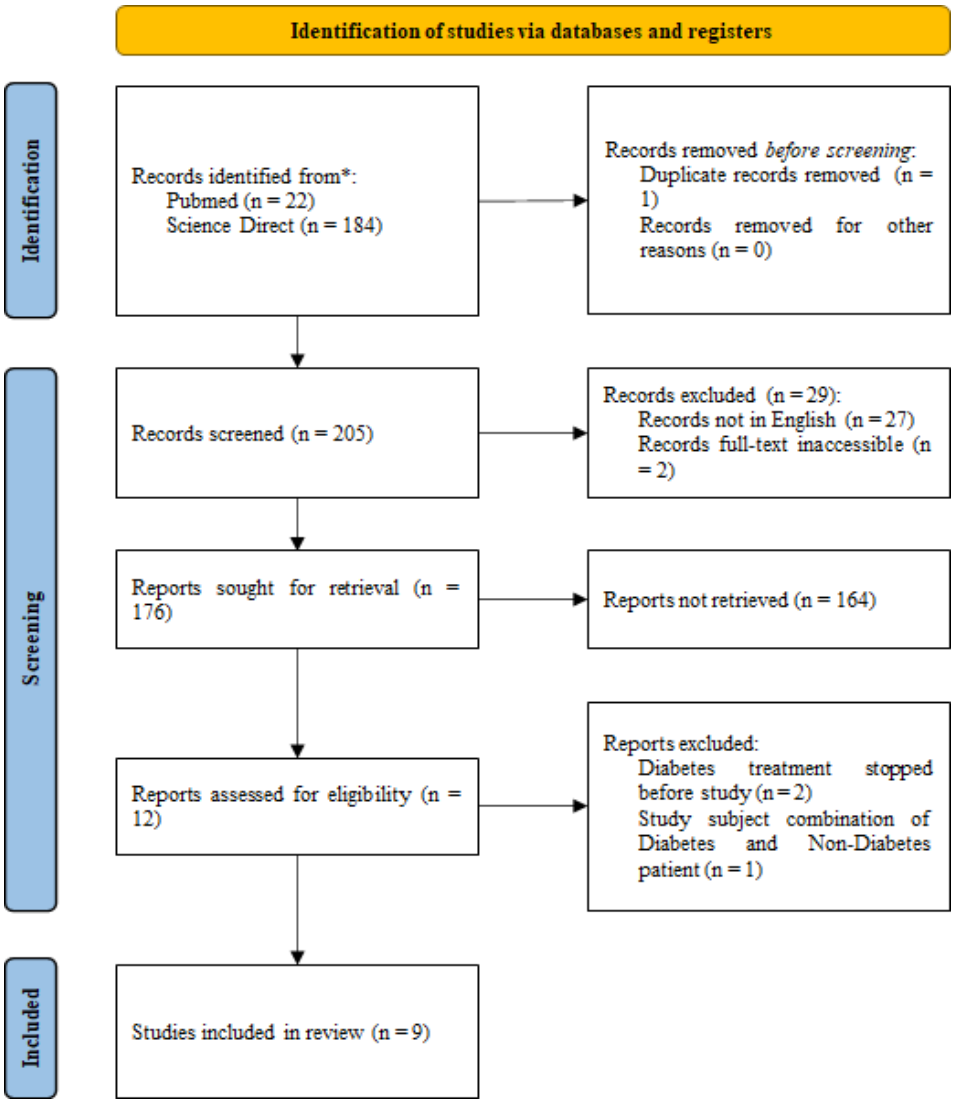

Figure 1. The PRISMA 2020 flow diagram

Table 1. Characteristics of studies included in systematic review

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

DISCUSSION

Given that the prevalence of obesity and diabetes continues to increase, more efficient treatment is needed, such as using an alternative orlistat for patients with type 2 diabetes mellitus with obesity. In general, administration of orlistat did not only reduce weight, but also improved glycemic control. Orlistat which worked to reduce fat absorption in the gastrointestinal system by inhibiting lipase had been shown to reduce body weight.

Obesity is closely related to insulin resistance. This was consistent with the mechanisms of orlistat through increased insulin sensitivity, slower and incomplete digestion of dietary fats, reduction of postprandial plasma non-esterified fatty acids, decreased visceral adipose tissue, and stimulation of peptide-1 secretion, such as glucagon in the lower small intestine (Aldekhail et al. 2015). This was proven by this review which showed the same result. Moreover, orlistat caused significant reduction in weight, BMI, waist circumference in obese adults compared to placebo (Jain et al. 2011). Orlistat also increases the proportion of people who lose 5% or more of their body weight, while on an energy deficit diet (Chauhan et al. 2011).

Our systematic review used 9 valid RCT studies. Of these studies, orlistat showed that it could decrease body weight, HbA1C, and FPG level in both short- and long-term administration. However, there were variations in outcomes between short- and long-term studies compared to placebo. This might be due to interventions not only in the form of offering orlistat, but also changing lifestyle, such as low-calorie diet and 30 minutes of exercise for 5 times a week or cycling. Low-calorie diet and exercise can increase weight loss, so that it has an impact on increasing insulin sensitivity as measured by controlled HbA1C and FPG levels.

The success of orlistat in significantly losing weight compared to placebo was found in 9 studies (100%) which included two short-term studies (100%) and seven long-term studies (100%). Meanwhile, the impact of orlistat treatment on HbA1c and FPG compared to placebo was found to be significant in one short-term study (50%) and seven long-term studies (100%), so that it seems that orlistat effected more clearly to improve glycemic control when administered in long-term (>12 weeks). This was in accordance with another study that orlistat significantly decreased FPG and HbA1C compared with placebo-treated patients (Jacob et al. 2009). In fact, orlistat still provided significantly greater decrease for both and HbA1c for patients with minimal weight loss (1% of baseline body weight). According to other research, orlistat appeared to reduce the need for concomitant diabetes medication irrespective of weight loss (Rowe et al. 2005).

One study showed different results where there was no significance in the decrease of HbA1c and FPG compared to placebo (Derosa et al. 2011). This might be because the study population were those whose blood sugar was difficult to control even with insulin administration, because they had received antidiabetic drugs or insulin, but their blood sugar remained uncontrolled.

The comparative study between short-term and long-term administration showed that the weight loss and FPG reduction varied between two groups. However, the HbA1c reduction showed that the short-term administration provided greater results than long-term. This might be due to decreased lifestyle adherence that decreased over time and deteriorating glycemic control that occurred in long-term administration of orlistat, such as the decrease was not as optimal as during the first three months. This result was comparable with a previous study of the effect of orlistat in glycemic control conducted by Aldekhail et al. (2015) which showed the largest decrease in HbA1c levels in the first three months and was followed by a mild increase thereafter, although it was still followed by weight loss for up to 12 months.

Table 2. Effect of orlistat administration toward HbA1c, FBG, and body weight

Authors/Year of Publication	Group	HbA1c (%)		FBG (mmol/L)		Weight (kg)	
		Baseline	Changes	Baseline	Changes	Baseline	Changes
Hollander/1998	Or + hd	8.05 ± 0.98	- 0.28 ± 0.09*	8.85 ± 1.68	- 1.39 ± 0.22*	99.6 ± 14.5	- 6.19 ± 0.5*
	Pl + hd	8.2 ± 1.07	- 0.18 ± 0.11	9.09 ± 1.87	+ 0.54 ± 0.15*	99.7 ± 15.4	- 4.31 ± 0.57*
Miles/2002	Or + hd	8.87 ± 0.07	- 0.75 ± 0.08*	11.6 ± 0.2	- 2.0 ± 0.2*	102.1 ± 1.1	- 4.7 ± 0.3*
	Pl + hd	8.79 ± 0.07	- 0.41 ± 0.08	11.1 ± 0.2	- 0.7 ± 0.2	101.1 ± 1.0	- 1.8 ± 0.3
Berne/2005	Or + hd	7.6 ± 0.8	- 1.1*	11.2 ± 2.6	- 1.9*	95.3 ± 12.6	- 5%*
	Pl + hd	7.6 ± 0.8	- 0.22	10.9 ± 2.5	- 0.26	95.7	- 1.8 %
Lindgarde/2000	Or + hd	8.6 ± 1.1	- 0.9 ± 1.3*	10.95 ± 2.93	- 1.7 ± 2.1*	99.4 ± 17.5	- 6.3 ± 5.3*
	Pl + hd	8.6 ± 1.2	- 0.4 ± 1.5	10.95 ± 3.17	- 0.9 ± 2.8	98.4 ± 18.5	- 4.6 ± 5.7
Halpern/2003	Or + hd	8.37 ± 0.11	- 0.61 ± 0.15*	11.05 ± 0.27	- 1.00 ± 0.34*	89.7 ± 2.6	- 4.24 ± 0.23*
	Pl + hd	8.49 ± 0.11	- 0.22 ± 0.14	11.50 ± 0.26	- 0.01 ± 0.30*	89.5 ± 2.9	- 2.58 ± 1.46*
Guy-Grand/2004	Or + hd	7.6 ± 0.1	- 0.54 ± 0.10*	9.9 ± 0.2	- 1.39 ± 0.22*	94.3 ± 1.4	- 3.9 ± 0.4*
	Pl + hd	7.7 ± 0.1	- 0.18 ± 0.09	10.6 ± 0.3	- 0.50 ± 0.24	91.3 ± 1.3	- 1.3 ± 0.3
Shi/2005	Or + hd	7.3 ± 0.7	- 1*	8.1 ± 1.6	- 1.3*	79.4 ± 10.8	- 5.4*
	Pl +hd	7.3 ± 0.6	- 0.6	8.0 ± 1.5	- 0.5	78.7 ± 11.3	- 2.4
Kuo/2006	Or + md	9.8 ± 0.02	- 1.7 ± 0.01*	11.2 ± 0.4	- 3.40 ± 0.34*	76.8 ± 2.1	- 2.5 ± 0.6*
	Pl + md	9.6 ± 0.01	- 0.2 ± 0.01	12.1 ± 0.6	- 0.90 ± 0.12	78.3 ± 3.2	- 0.4 ± 0.3
Derosa/2012	Or + hd	8.4 ± 1.4	- 1.4 ± 0.9	7.6 ± 0.9	- 0.8 ± 0.3	94.5 ± 9.6	- 9.5 ± 3.7*
	Pl + hd	8.2 ± 1.3	- 0.3 ± 0.4	7.4 ± 0.8	- 0.7 ± 0.3	91. 7 ± 8.7	- 2.6 ± 0.9

Data are means ± SD

* Significant difference $p < 0.05$ between Or vs Pl group

Or, orlistat 360 mg/day; Pl, placebo; hd, hypocaloric diet; md, moderate-calorie, diet; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose

Although orlistat is a potent agent, the administration of orlistat should be as an adjuvant to lifestyle intervention in the form of reduced caloric intake and physical activity for maximal efficacy.

Strength and limitation

According to our study, this systematic review can be developed further, considering that the number of short-term studies is less than long-term studies. The findings of this study suggest that orlistat is effective in improving glycemic control and reducing body weight in overweight or obese T2DM patients. The disadvantage of this study was that there was limited study of short-term orlistat administration as adjuvant therapy on type 2 diabetes mellitus patients with overweight or obesity, so that the effect of orlistat in the short-term use to reduce glycemic control was not convincing. The study did not consider the impact of other factors, such as lifestyle interventions or other medications, on the effectiveness of orlistat in improving glycemic control and weight loss. For long-term therapy, orlistat improved not only glycemic control, but also body weight, where normal BMI was one goal of the therapies for type 2 diabetes mellitus.

CONCLUSION

Orlistat has an effect on improving glycemic control and weight loss in overweight or obese patients with T2DM. Orlistat can significantly reduce weight both in long- and short-term administration. Based on the results of these studies, orlistat can be considered as an adjuvant therapy to lifestyle intervention in overweight or obese patients with T2DM.

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Conflict of interest

None.

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None.

Author contribution

LD and TN-conseptual idea,TN-study design, CFA-collected data, BIP, ARDJ and ANP- analysis data. LD was write the manuscript

REFERENCES

Aldekhail N, Logue J, McLoone P, et al (2015). Effect of orlistat on glycaemic control in overweight and obese patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. Obes. Rev. 16, 1071–1080.

Bhupathiraju S, Hu F (2016). Epidemiology of obesity and diabetes and their cardiovascular complications. Circ. Res. 118, 1723–1735.

Chauhan S, Arnold K, Mackenzie C, et al (2011). The influence of Orlistat (Xenical®) on weight loss in overweight and obese adults: a systematic review. In: Proceedings of the Nutrition Society. p. e18.

Derosa G, Cicero A, D'Angelo A, et al (2011). Effects of 1-year orlistat treatment compared to placebo on insulin resistance parameters in patients with type 2 diabetes. J. Clin. Pharm. Ther. 37, 187–195.

Hanefield M, Sachse G (2002). The effects of orlistat on body weight and glycaemic control in overweight patients with type 2 diabetes: A randomized, placebo-controlled trial. Diabetes, Obes. Metab. 4, 415–423.

Jacob S, Rabbia M, Meier M, et al (2009). Orlistat 120 mg improves glycaemic control in type 2 diabetic patients with or without concurrent weight loss. Diabetes, Obes. Metab. 11, 361–371.

Jain S, Ramanand S, Ramanand J, et al (2011). Evaluation of efficacy and safety of orlistat in obese patients. Indian J. Endocrinol. Metab. 15, 99–104.

Kelley D, Kuller L, McKolanis T, et al (2003). Effects of moderate weight loss and orlistat on insulin resistance, regional adiposity, and fatty acids in type 2 diabetes. Diabetes Care 27, 33–40.

Kopelman P, de Groot H, Rissanen A, et al (2010). Weight loss, HbA1c reduction, and tolerability of cetilistat in a randomized, placebo-controlled phase 2 trial in obese diabetics: Comparison with orlistat (Xenical). Obesity 18, 108–115.

Kumanyika S, Jeffery R, Morabia A, et al (2002). Obesity prevention: The case for action. Int. J. Obes. 26, 425–436.

Kuo C, Pei D, Yao C, et al (2006). Effect of orlistat in overweight poorly controlled Chinese female type 2 diabetic patients: a randomised, double-blind, placebo-controlled study. Int. J. Clin. Pract. 60, 906–910.

Rowe R, Cowx M, Poole C, et al (2005). The effects of orlistat in patients with diabetes: Improvement in glycaemic control and weight loss. Curr. Med. Res. Opin. 21, 1885–1890.

Shi Y, Pan C, Hill J, et al (2005). Orlistat in the treatment of overweight or obese Chinese patients with newly diagnosed type 2 diabetes. Diabet. Med. 22, 1737–1743.

Wannamethee S, Shaper A (1999). Weight change and duration of overweight and obesity in the incidence of type 2 diabetes. Diabetes Care 22, 1266–1272.

Williamson D, Thompson T, Thun M, et al (2000). Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care 23, 1499–1504.