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Obesity Comorbidity/Treatment

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

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Summary

Orlistat is an effective adjunctive treatment to lifestyle modifications in the treatment of obesity. While the majority of current evidence is on the effect of orlistat in obese patients without diabetes, some studies suggest that patients who are obese and have diabetes mellitus lose more weight and have greater improvements in diabetic outcomes when treated with orlistat plus a lifestyle intervention than when treated by lifestyle interventions alone. The aim of this study was to review the evidence of the effects of orlistat on glycaemic control in overweight and obese patients with type 2 diabetes. A systematic review of randomized controlled trials of orlistat in people with type 2 diabetes reporting diabetes outcomes in studies published between January 1990 and September 2013 was conducted. We searched for articles published in English in MEDLINE and EMBASE. Inclusion criteria included all randomized controlled trials of orlistat carried out on adult participants with a body mass index of 25 kg m^{-2} or over diagnosed with type 2 diabetes, which reported weight change and at least one diabetic outcome. A total of 765 articles were identified out of which 12 fulfilled the inclusion criteria. The overall mean weight reduction (3, 6 and 12 months) in the orlistat group was –4.25 kg (95% CI: –4.5 to –3.9 kg). The mean weight difference between treatment and control groups was –2.10 kg (95% CI: –2.3 to –1.8 kg, $P < 0.001$), the mean HbA1c difference was –6.12 mmol mol^{-1} (95% CI: –10.3 to –1.9 mmol mol^{-1}, $P < 0.004$) and the mean fasting blood glucose difference was –1.16 mmol L^{-1} (95% CI: –1.4 to –0.8 mmol L^{-1}, $P < 0.001$). Treatment with orlistat plus lifestyle intervention resulted in significantly greater weight loss and improved glycaemic control in overweight and obese patients with type 2 diabetes compared with lifestyle intervention alone.

Keywords: Obesity, orlistat, randomized controlled trials, type 2 diabetes.

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Introduction

It has been estimated that by 2015, approximately 2.3 billion adults will be overweight and at least 700 million will be obese (1). Obesity is causally associated with multiple metabolic abnormalities including diabetes mellitus (2). The World Health Organization reports that more than 347 million people worldwide suffer from diabetes and most of these patients are obese. It has been estimated that in 2005, 3.4 million people died from diabetes with

predictions that this number will double by 2030 (3). Some researchers have suggested that up to two out of every three cases of type 2 diabetes can be attributed to obesity (4). In order to improve blood glucose control, it has now become a standard of care to recommend weight loss (5).

Orlistat (tetrahydrolipstatin) is a pancreatic and gastric lipase inhibitor whose primary effect is to reduce the absorption of fat and therefore calories. Long-term use is also associated with reductions in blood pressure (6). It is one of few pharmacologic treatment options available to help patients with type 2 diabetes reduce body weight and improve glycaemic control (7). There is evidence that orlistat plus lifestyle changes achieve greater weight loss than lifestyle changes alone (8). It may also reduce the risk of subsequent diabetes (9). While several randomized controlled trials have been carried out to describe changes in glycaemic control among obese patients treated with orlistat, most have been on small samples and may therefore suffer from lack of statistical power (10). To our knowledge, no attempts have been made to systematically review and synthesize the results of these trials.

The Canadian Diabetes Association clinical practice guidelines suggested that the addition of orlistat for 1 year in overweight or obese patients (body mass index [BMI] = 28–40 kg m^{-2}) with type 2 diabetes treated with other anti-hyperglycaemic agents or insulin has been shown to decrease body weight and improve HbA1c (11). In addition, a European Evidence-Based Guideline recommended in obese patients with or without impaired glucose tolerance, orlistat, in addition to lifestyle change, can be used as a second-line strategy for obese patients to prevent type 2 diabetes (12).

The aim of this paper was therefore to systematically review the evidence from randomized controlled trials (RCTs) on the effects of orlistat on glycaemic control (glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG) in overweight and obese patients with type 2 diabetes and to combine results using meta-analysis.

Materials and methods

We undertook a systematic review of RCTs published from January 1990 to September 2013. We searched EMBASE and MEDLINE databases using the following search terms: (obes* or overweight or BMI or body mass index or hyperphagia or adipose tissue or fat) and (diabet* or diabetes mellitus or NIDDM or non-insulin dependent diabetes or DM) and (orlistat or Xenical or Alli). The search was undertaken on 30 September 2013. The search was limited to humans and articles written in English.

Inclusion criteria

The inclusion criteria were as follows: adults ≥ 18 years; both sexes; participants with BMI of greater than or equal to 25 kg m^{-2}; diagnosed with type 2 diabetes; and currently using orlistat. Studies with participants with BMI of 25 kg m^{-2} or greater were included on the assumption that their weight was considered a clinical problem requiring treatment with orlistat. In addition, trials must include the following outcomes: BMI or weight (kg) and HbA1c or FPG. All completed RCTs assessed the effects of orlistat plus lifestyle intervention vs. lifestyle-control group. We included the comparison between the two groups as follows:

1. Lifestyle intervention + orlistat vs. lifestyle intervention.
2. Lifestyle intervention + orlistat vs. lifestyle intervention + placebo.

All extracted journal articles were scanned in three stages by two independent authors and any disagreements were resolved by discussion. Articles were initially identified by scanning the title and abstract, if relevant the full article was then examined. All final decisions were derived by applying a standardized approach based on the study selection criteria outlined above. The risk of bias in the trials was reduced by assessing trial quality, including the quality of sequence generation and random allocation concealment, blinding of outcome assessors, incomplete outcome data and selective outcome reporting (Supporting Information Table S1) (13).

We extracted data from each study according to Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines (14). A matrix table of study characteristics was produced from which relevant information was extracted by two independent authors. The information included the author, year of publication, publication country, age and sex of participants, follow-up duration, sample size, type of intervention, baseline for outcomes, outcomes results and the difference between the baseline and results for each group of participants. Authors of the studies were contacted in some instances to provide additional information to that published in their papers. A random effects meta-analysis was undertaken to take account of the differences in study design and location. The effect size of the mean weight, HbA1c and FPG differences between orlistat and control groups was analysed. *I*-squared statistics were calculated to determine the degree of heterogeneity. The association between weight change and HbA1c change were examined by using the simple linear regression. All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, TX, USA).

Results

The search identified 765 potentially eligible citations, of which 453 were excluded as duplicates (Fig. 1). On review-

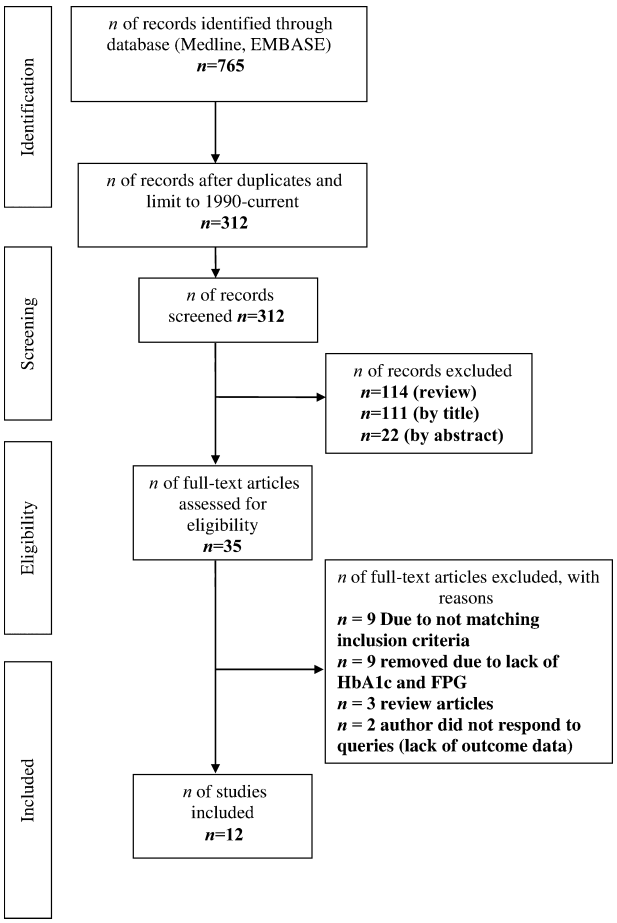

Figure 1 Search strategy for RCTs on glycaemic outcomes among overweight and obese patients treated with orlistat.

ing the titles and the abstracts of 312 articles, 35 were considered relevant and the full articles were obtained. Of the 35 articles, 14 fulfilled the inclusion criteria. Two studies (15,16) did not provide necessary information required for our meta-analysis within the publications. Contact was attempted with the corresponding authors by both email and phone to retrieve this additional information, but we received no response. One of these studies (15) had previously provided for a meta-analysis for the National Institute for Health Research (17). However, the authors of this meta-analysis no longer held these additional data (personal communication). The final 12 selected trials were published between 2002 and 2010 (Table 1). One study was conducted on only female participants (18); the remainder included both sexes.

The number of participants in each trial ranged from 36 to 550. The pooled group comprised 2,802 participants. Three (25%) of the trials were conducted in the United States (19–21), and one each in the other nine countries. The youngest participants were 18 and the oldest 75 years old, with differing age ranges in most studies. Trials varied in duration between 3 and 12 months. Ten studies (83.3%) included participants who were taking hypoglycaemic agents and two did not (19,22). Details of the interventions and outcomes can be seen in Table 2. Ten trials included a placebo control and two did not (23,24). All of the studies used hypocaloric diet and some continued with physical activity; although no specific physical activity information was provided in four of the studies (18,22,25,26). All but two studies included a reduced fat diet (18,23). Diabetes duration was not reported in the majority of the trials, except one trial, which was restricted to those with known

Table 1 Baseline characteristics and dropout rate of included studies

Author/year	Country	Age range	Sex	Duration	*n*	Mean BMI (SD) kg m^{-2}		Dropout rate	
						Orlistat	Control	Orlistat	Control
P. Kopelman/2010 (25)	UK	18–65	M/F	3 months	250	35.0 (±4.1)	34.0 (±4.1)	23	22
C. Kuo/2006 (18)	Taiwan		F	3 months	60	27.2 (±1.1)	26.9 (±0.9)	No	No
C. Berne/2005 (30)	Sweden	30–75	M/F	12 months	220	32.6 (±3.1)	32.9 (±3.0)	15	15
T.P. Didangelos/2004 (23)	Greece	30–72	M/F	6 months	126	–	–	No	No
B. Guy-Grand/2004 (26)	France	18–65	M/F	6 months	193	33.8 (±0.3)	33.5 (±0.4)	No	No
Kelley/2004 (19)	US		M/F	6 months	52	34.0 (±5.0)	35.9 (±5.0)	9	4
M. Hanefeld/2002 (22)	Germany	18–70	M/F	12 months	383	34.5 (±5.6)	33.7 (±5.2)	6	8
J.M. Miles/2002 (20)	US	40–65	M/F	12 months	504	35.6 (±4.7)	35.2 (±3.1)	90	115
A. Halpern/2003 (31)	Brazil	18–70	M/F	6 months	338	34.6 (±0.8)	34.5 (±0.9)	25	33
D.E. Kelley/2002 (21)	USA	40–65	M/F	12 months	550	35.8 (±4.9)	35.6 (±4.1)	137	148
G. Cocco/2005 (27)	Switzerland	≥35	M/F	6 months	90	36.5 (±1.9)	36.0 (±1.8)	No	No
M.F. Pathan/2004 (24)	Bangladesh	40–65	M/F	6 months	36	31.6 (±3.5)	29.8 (±3.2)	No	No

F, female; M, male; *n*, number; SD, standard deviation.

Table 2 Studies results of weight loss by using orlistat and type 2 diabetes outcomes

Author/year	Intervention/dose			Baseline			Results (primary end point)				Difference (primary end point)		
	(a) Orlistat	(b) Control	pa	Weight (kg)	HbA1c (%) and mmol mol^{-1}	FPG mmol L^{-1}	*n*	Wt (kg)	HbA1c (%) and mmol mol^{-1}	FPG mmol L^{-1}	Wt (kg)	HbA1(%) and mmol mol^{-1}	FPG mmol L^{-1}
P. Kopelman/2009	Orlistat 360 mg + hd + rf (n = 124)	hd + rf + placebo (n = 126)	No	(a) 101 (b) 98	7.2/55 7.2/55		(a) 101 (b) 104	97.22 95.14	6.67/49 6.83/51		–3.78 –2.86	–0.53/–6 –0.37/–4	
C. Kuo/2006	Orlistat 360 mg + hd (n = 30)	hd + placebo (n = 30)	No	(a) 76.8 (b) 78.3	9.8/84 9.6/81	11.2 12.1	(a) 30 (b) 30	74.3 77.9	8.1/65 9.4/79	7.8 11.2	–2.5 –0.4	–1.7/–19 –0.2/–2	–3.40 –0.9
C. Berne/2005	Orlistat 360 mg + hd + rf + pa (n = 111)	hd + rf + pa + placebo (n = 109)	Yes	(a) 95.3 (b) 95.7	7.6/60 7.6/60	11.2 10.9	(a) 96 (b) 94	90.54 93.98	6.5/48 7.38/56	9.3 10.64	–4.76 –1.72	–1.1/–12 –0.22/–4	–1.9 –0.26
T.P. Didangelos/2004	Orlistat 360 mg + hd + pa (n = 94)	hd + pa (n = 32)	Yes	(a) 93.4 (b) 87.3	8.0/64 7.9/63	10.0 9.7	(a) 94 (b) 32	87.8 83.4	6.4/46 7.1/54	7.5 9.6	–5.6 –3.9	–1.6/–18 –0.8/–9	–2.5 –0.1
B. Guy-Grand/2004	Orlistat 360 mg + hd + rf (n = 97)	hd + rf + placebo (n = 96)	No	(a) 94.3 (b) 91.3	7.6/60 7.7/61	9.9 10.6	(a) 97 (b) 96	90.4 90.0	7.1/54 7.6/60	8.51 10.1	–3.9 –1.3	–0.54/–6 0.18/–1	–1.39 –0.50
Kelley/2004	Orlistat 360 mg + hd + rf + pa (n = 26)	hd + rf + pa + placebo (n = 26)	Yes	(a) 99.0 (b)102.0	8.13/65 7.82/62	10.87 8.77	(a) 17 (b) 22	87.0 92.0	6.48/46 6.85/51	6.82 6.99	–10.1 –9.4	–1.65/–19 –0.97/–11	–4.05 –1.78
M. Hanefeld/2002	Orlistat 360 mg + hd + rf (n = 195)	hd + rf + placebo (n = 188)	No	(a) 99.4 (b) 98.4	8.6/70 8.6/70	10.95 10.95	(a) 189 (b) 180	94.1 95.0	7.7/61 8.1/65	9.35 10.25	–5.3 –3.4	–1.1/–9 –1.0/–5	–1.6 –0.7
J.M. Miles/2002	Orlistat 360 mg + hd + rf + pa (n = 250)	hd +rf + pa + placebo (n = 254)	Yes	(a)102.1 (b)101.1	8.87/73 8.79/72	11.6 11.1	(a) 160 (b) 139	97.4 99.3	8.12/65 8.38/67	9.6 10.4	–4.7 –1.8	–0.75/–8 –0.41/–5	–2.0 –0.7
A. Halpern/2003	Orlistat 360 mg + hd + rf + pa (n = 164)	hd + rf + pa + placebo (n = 174)	Yes	(a) 89.7 (b) 89.5	8.37/67 8.49/68	11.05 11.50	(a) 139 (b) 141	84.8 86.4	7.76/61 8.27/66	10.05 11.49	–4.24 –2.58	–0.61/–6 –0.22/–2	–1.00 –0.01
D.E. Kelley/2002	Orlistat 360 mg + hd + rf + pa (n = 274)	hd + rf + pa + placebo (n = 276)	Yes	(a) 102.0 (b)101.8	9.01/75 8.99/74	10.91 11.16	(a) 137 (b) 128	98.11 100.53	8.39/67 8.72/72	9.28 10.08	–3.89 –1.27	–0.62/–8 –0.27/–2	–1.63 –1.08
G. Cocco/2005	Orlistat 360 mg + hd + rf + pa (n = 45)	hd + rf + pa + placebo (n = 45)	Yes	(a) 106.99 (b) 105.98	7.28/55 6.92/52	10.93 10.33	(a) 45 (b) 45	101.58 103.50	6.78/50 6.88/51	9.19 9.71	–5.55 –2.65	–0.5/–5 –0.04/–1	–1.74 –0.62
M.F. Pathan/2004	Orlistat 360 mg + hd + rf + pa (n = 21)	hd + rf + pa (n = 15)	Yes	(a) 76.9 (b) 73.4	8.9/74 8.0/64	9.8 10.0	(a) 21 (b) 15	73.8 72.3	6.9/52 6.9/52	7.7 7.7	–3.1 –1.1	–2.00/–22 –1.1/–12	–2.1 –2.3

FPG, fasting plasma glucose; hd, hypocaloric diet; pa, physical activity; rf, reduced fat.

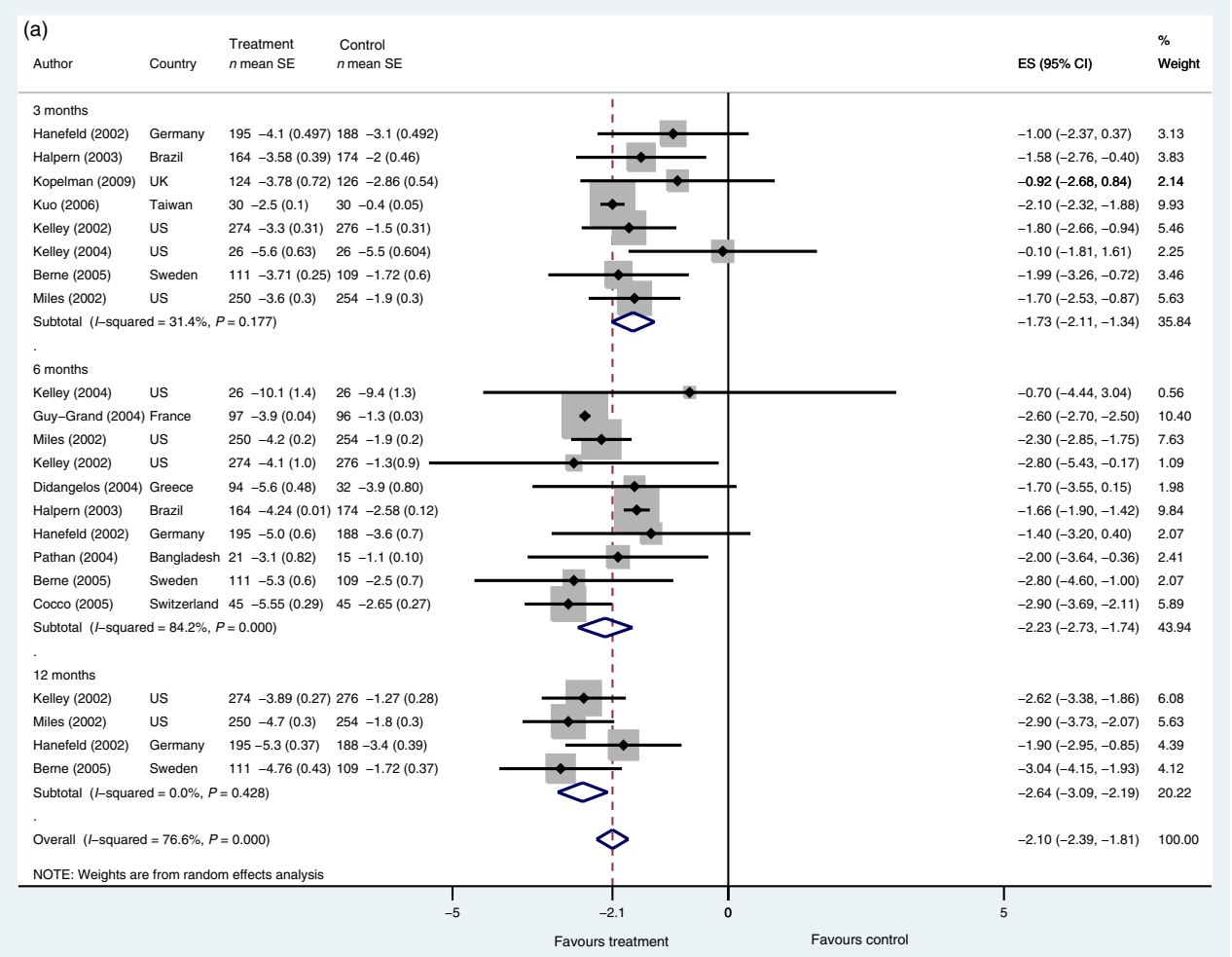

Figure 2 Forest plots of the difference between orlistat and control groups by duration. (a) Weight (kg); (b) HbA1c (mmol mol^{-1}); (c) FPG (mmol L^{-1}).

duration of type 2 diabetes of ≤5 years (19). The mean BMI values at baseline of the included trials for orlistat and control group ranged from 27.2 to 36.5 and 26.9 to 36.0 kg m^{-2}, respectively (Table 1). All the trials reported results for weight (kg), and both HbA1c and FPG except one study in which only weight and HbA1c were provided (25) (Table 2). Some of the included studies reported the outcomes for different durations of time in addition to the primary end point; these were compared in the meta-analysis. All of the included trials reported gastrointestinal side effects of orlistat such as abdominal pain, defecation urgency, diarrhoea, faecal incontinence and oily stool, except one trial, which did not report the side effects (24).

Weight change

Trials included in this review reported weight losses with primary end points of 3, 6 and 12 months (Table 2). Kelley's 2004 study reported the largest weight loss for both the orlistat and placebo control groups, while Kuo and Pathan had the smallest. A greater overall (3, 6 and 12 months) mean weight reduction was reported in orlistat treatments compared with lifestyle intervention with or without placebo (–4.25 kg, 95% CI: –4.5 to –3.9 vs. –2.27 kg 95% CI: –2.6 to –1.8, $P < 0.001$). Figure 2a shows the overall effect size between orlistat treatment groups and control groups was –2.10 kg (95% CI: –2.3 to –1.8, $P < 0.001$). Results have been grouped into those that reported 3-, 6- and 12-month primary end points, respectively. Longer duration trials were associated with greater weight losses. The overall *I*-squared (test of heterogeneity) was 76.6%, $P = 0.001$, which indicates that there is substantial heterogeneity between the studies. There was no significant heterogeneity between the studies that reported weight change after 3 months (*I*-squared = 31%, $P = 0.179$).

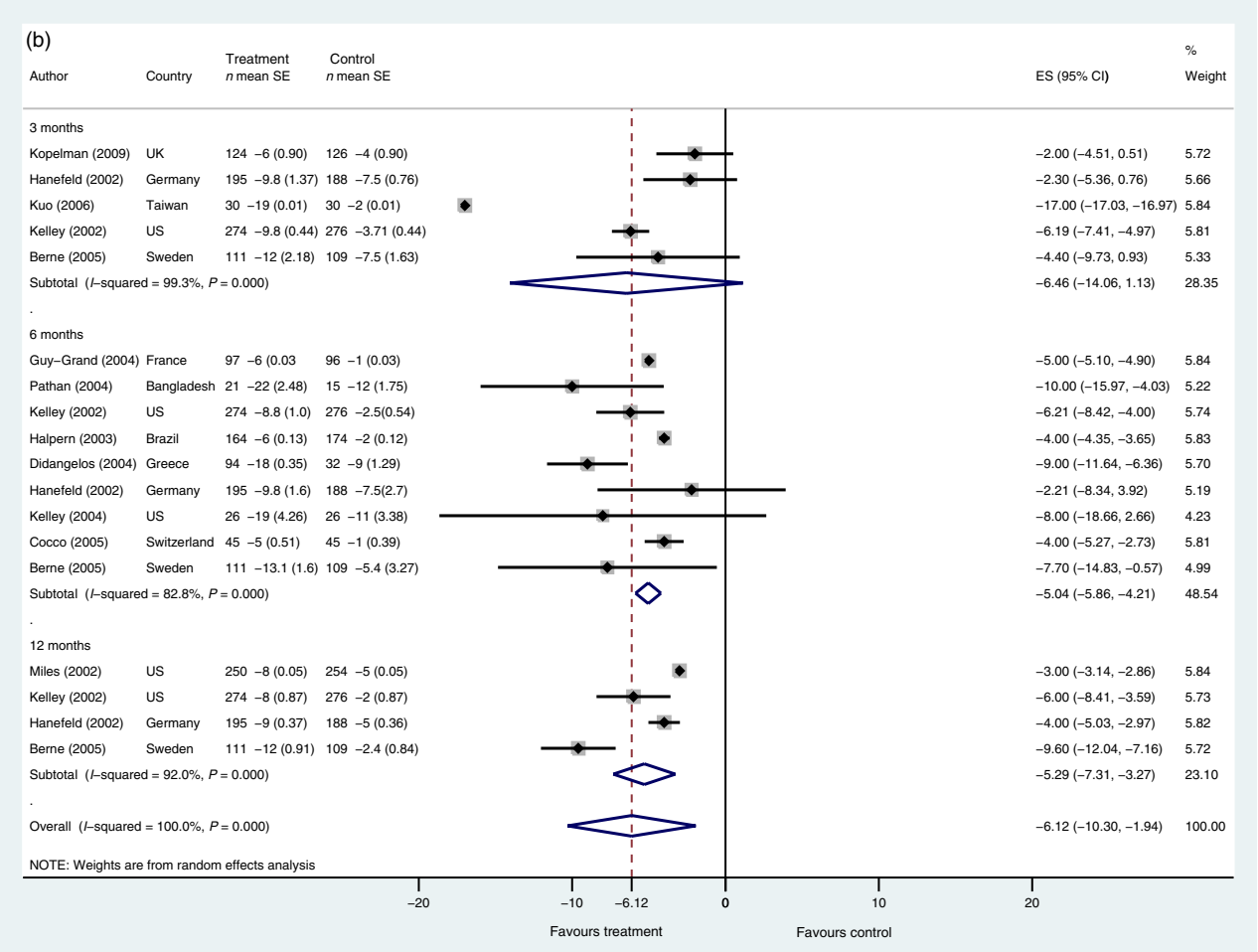

Figure 2 *Continued*

Glycaemic values

The reduction in both HbA1c and FPG in orlistat treatment groups was greater than the reduction in control groups (Table 2). Pathan reported the largest HbA1c change and Cocco the smallest. The overall mean HbA1c levels decreased more in the treatment groups than in the control groups (–11.05 mmol mol^{-1}, 95% CI: –15.0 to –7.0 vs. –4.08 mmol mol^{-1}, 95% CI: –4.8 to –3.2, $P < 0.001$) and the overall effect size difference was –6.12 mmol mol^{-1} (95% CI: –10.3 to –1.9, $P < 0.004$). Figure 2b shows that there was no significant difference in HbA1c changes between treatment and control groups at 3 months and there was considerable heterogeneity between studies ($I^2 = 99.3\%$, $P = 0.001$). Among studies reporting 6-month outcomes, the additional reduction in HbA1c in treatment groups was –5.04 mmol mol^{-1} (95% CI: –5.86 to –4.21). Heterogeneity remained considerable ($I^2 = 82.8\%$, $P < 0.001$). At 12 months, additional HbA1c reduction in orlistat treatment groups was –5.29 mmol mol^{-1} (95% CI: –7.31 to –3.27), again with considerable heterogeneity ($I^2 = 100\%$, $P < 0.001$).

Kelley's 2004 study had the largest FPG change while Halpern's had the smallest (Table 2). The mean overall FPG levels decreased more in the treatment groups than in the placebo groups (–2.05 mmol L^{-1}, 95% CI: –2.3 to –1.7 vs. –0.80 mmol L^{-1}, 95% CI: –1.0 to –0.5, $P < 0.001$) and the overall effect size difference was –1.16 mmol L^{-1} (95% CI: –1.4 to –0.8, $P < 0.001$). Figure 2c shows that the FPG difference between orlistat and control groups (–1.36 mmol L^{-1}, 95% CI: –2.59 to –0.13) within 3 months duration was larger than that at 6 and 12 months. However, there was considerable heterogeneity between studies ($I^2 = 98.9\%$, $P < 0.001$). 6- and 12-month differences in FPG were –1.12 (95% CI: –1.34 to –0.90) and –1.06 (95% CI: –1.44 to –0.68), respectively. At 12 months, heterogeneity was low and might not be important ($I^2 = 15.5\%$, $P = 0.314$).

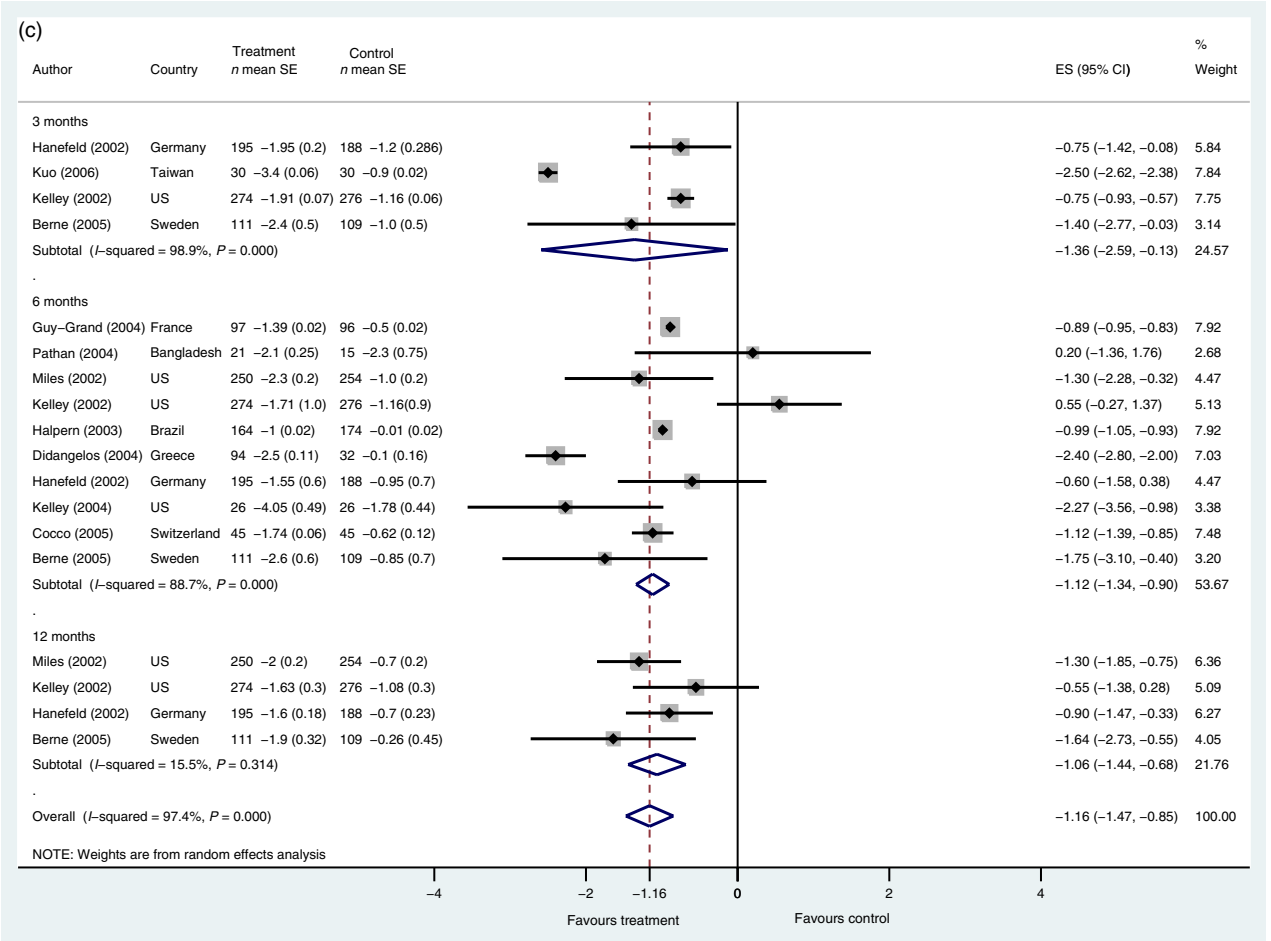

Figure 2 *Continued*

Relationship between weight and HbA1c

In order to investigate the relationship between weight differences and HbA1c differences, Fig. 3 shows the simple linear regression between weight differences and HbA1c differences. Most of the study points are clustered towards the lower left corner of the plot for the control groups and the upper middle for the treatment group. There are four outlier studies, which lie far away from the main cluster of the data where HbA1c reduction is far greater than that expected for the given weight loss (18,19,23,24). The adjusted R^2 is 19.3%, indicating that 19.3% of the variability in HbA1c difference is explained by its dependence on weight difference. The estimated coefficients is –1.25, which tells us that the average HbA1c decreases by 1.25 mmol mol^{-1} for every 1 kg decrease in weight.

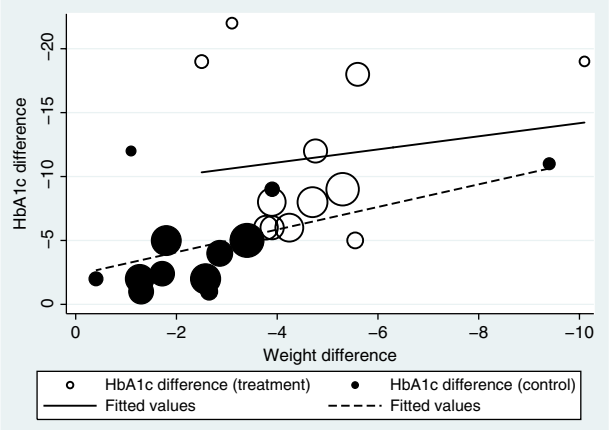

Figure 3 Simple linear regression between HbA1c difference and weight difference at the primary end point (the circles size represent the samples size).

Effects of physical activity and placebo

The effects of physical activity and placebo were considered in Table 3. There was no significant difference in weight

Table 3 Effects of physical activity and placebo in weight loss, HbA1c and FPG

	3 months			6 months			12 months			Total *P*-value (PA)
	No. of study	Results (difference between treatment and control)	*P*-value	No. of study	Results (difference between treatment and control)	*P*-value	No. of study	Results (difference between treatment and control)	*P*-value	
Weight (PA) kg										
Yes	5	–1.4	0.501	8	–2.1	0.618	3	–2.8	0.267	0.686
No	3	–1.3		2	–2.0		1	–1.9		
Placebo										
Yes	8	–1.4		8	–2.1	0.588	4	–2.6		
No	0	0		2	–1.8		0	0		
HbA1c (PA) mmol mol^{-1}										
Yes	2	–5.2	0.796	7	–6.9	0.432	3	–6.2	0.643	0.837
No	3	–7.1		2	–3.6		1	–4.0		
Placebo										
Yes	5	–6.3		7	–5.3	0.012	4	–5.6		
No	0	0		2	–9.5		0	0		
FPG (PA) mmol L^{-1}										
Yes	2	–1.07	0.567	8	–1.1	0.603	3	–1.1	0.683	0.899
No	2	–1.62		2	–0.7		1	–0.9		
Placebo										
Yes	4	–1.3		8	–1.0	0.513	4	–1.0		
No	0	0		2	–1.1		0	0		

PA, physical activity.

differences between studies that included physical activity and those that did not at any of the time points. The effect of placebo on weight change could only be evaluated at 6 months, where no significant effect was found. Physical activity had no effect on HbA1c any of the time points. The addition of a placebo was associated with a significant difference in HbA1c at 6 months, only. FPG effects were not influenced by either physical activity or use of a placebo at any time point.

Assessment of bias

We assessed the risk of bias, using guidelines of the *Cochrane Collaboration* (13), in Supporting Information Table S1. Generally, bias was low in all included studies. However, allocation concealment and blinding of participants and personnel were not reported in Didangelos' study (23); sequence generation was unclear nor was it apparent which were primary and secondary intended outcomes in Cocco's study (27); and blinding of participants and personnel was not reported by Pathan (24). All studies reported blinding of outcome assessment and none reported missing data.

Discussion

We carried out the first systematic review and meta-analysis of RCTs that describe the effects of orlistat on glycaemic control among overweight and obese patients. We found that the addition of orlistat to lifestyle changes increased weight loss and was associated with greater reductions in both HbA1c and FPG levels that were clinically significant. The addition of physical activity to the regimen had no significant effect on overall weight loss or glycaemic control. There was little evidence that use of a placebo influenced our observed results.

A previous systematic review by Avenell *et al*., conducted in 2004 (17), reported a weight reduction in the first year in eight RCTs that included patients both with and without diabetes. Only one of these studies fitted the criteria for our review (15) but the published data were not sufficient for inclusion and further information was not available from either the author of the study or the authors of the systematic review. The mean weight difference after 12 months between orlistat plus diet group and placebo plus diet groups was –3.01 kg (95% CI: –3.48 to –2.54 kg, $P < 0.00001$). Out of eight RCTs, six RCTs reported the FPG outcome and three of them reported the HbA1c difference (in patients both with and without diabetes). The mean HbA1c change difference was –2.95 mmol mol^{-1} (95% CI: –4.1 to –1.6 mmol mol^{-1}, $P < 0.00001$) and the mean FPG difference was –0.24 mmol L^{-1} (95% CI: –0.34 to –0.14 mmol L^{-1}, $P < 0.00001$). Both HbA1c and FPG reductions in

Avenell's study were smaller than in our results and this is probably because the non-diabetic patients included in Avenell's analysis had less capacity for glycaemic improvements despite larger weight losses. All the results of included studies in this systematic review and meta-analysis have shown a reduction in weight and glycaemic values in orlistat and control groups but the mean reduction within the time in the orlistat group was more than the control groups. The reduction of weight, HbA1c and FPG was clinically and statistically significant after using orlistat. Reductions in HbA1c and FPG in the orlistat group occurred in the first 3 months and were followed by modest rises thereafter despite continued weight losses up to 12 months. It may be that as adherence to lifestyle lessens over time, glycaemic control deteriorates. Previous studies reported that improvement in glycaemic control occur quickly with the onset of caloric restriction, before weight loss (28). We identified outlier studies that lie far away from the main cluster of the data and the reasons for that were not clear but this is may be because of the small sample size of these studies or that they recruited different patient populations who have diabetes durations of ≤ 5 years (19). Two studies (18,24) were in Asian populations and there are several potential reasons that may result in a greater effect size with orlistat. Asian populations develop type 2 diabetes at lower BMI (22 kg m^{-2} vs. 30 kg m^{-2} in white Europeans) because of the capacity reduction for storing fat in the primary superficial subcutaneous adipose tissue compartment (29), which may mean that less absolute weight loss is required to improve insulin sensitivity. Also, differences in the diet of Asian population may help with the action of orlistat to reduce the blood glucose level. In this review, the effects of physical activity and placebo on weight loss, HbA1c and FPG were not clear because of insufficient number of studies that reported the effects without physical activity especially for 6 to 12 months duration. Likewise, low number of studies reported the outcomes in the absence of placebo, but at 6 months duration, there was a significant effect of the absence of placebo on HbA1c difference (i.e. the mean HbA1c difference in the presence and absence of placebo in 6 months duration was −5.3 and −9.5, $P = 0.012$, respectively). The reason may be that the patients in the control group did well by remembering to take their anti-diabetes medications with the placebo or were not disheartened by being blinded to their intervention.

Strengths and limitations

Previous studies on orlistat have included obese patients with and without diabetes; ours is the first systematic review to focus solely on patients with diabetes and the effect of orlistat on glycaemic control. The strengths of this review are the inclusion of randomized controlled trials, the assessment of two types of intervention and the generation of meta-analysis.

The limitations of the review are the insufficient sample sizes for some studies and the potential to overestimate the long-term effects of some studies based on inferences from short-term interventions (<6 months). In addition to this, the treatment strategies were mixed between dietary management and a variety of oral hypoglycaemic agents.

There was considerable heterogeneity between the studies that we identified. This remained after results were stratified by length of trial and was found in meta-analysis of weight, FPG and HbA1c. There are a number of ways in which the patients, the intervention and the evaluation of intervention effects might vary between studies. There were differences in the ages of patients and mean baseline weights. Dietary habits, physical environments that might promote or inhibit physical activity and seasonal variations in weight may also influence the effectiveness of weight loss interventions. Presence of other comorbidities, such as heart failure, that might affect capacity for physical activity and use of medications that may promote weight gain may also differ between patients in different studies. Details of physical activity advice given and of whether the advice was followed were lacking. Orlistat 60 mg has been available as an over-the-counter medication in the United States since 2007 and the European Union since 2009 but as our review only included studies using the prescription-only dose of 120 mg, we cannot say whether the use of the 60-mg dose by patients with obesity and diabetes improves their glycaemic control, and further research is needed to describe these patients.

Implications

Current findings show that treatment with orlistat plus lifestyle intervention provides benefits to overweight and obese individuals with type 2 diabetes. It therefore follows that orlistat should be considered as an effective adjunctive treatment to lifestyle intervention and anti-diabetes medications in improving glycaemic control among overweight and obese patients with type 2 diabetes. Future research on the effects of orlistat on glycaemic control in overweight and obese patients with diabetes would be improved by providing greater detail about physical activity interventions, objective monitoring of physical activity (e.g. by using an accelerometer), recording of comorbidities and medications, and longer follow-up periods beyond 12 months.

Conflict of interest statement

No conflict of interest statement.

Supporting information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12318

Table S1. Risk of bias assessments for included RCTs.

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