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Review Article

Effect of weight-reducing agents on glycaemic parameters and progression to Type 2 diabetes: a review

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Abstract

Weight loss is associated with improvements in glycaemic control and cardiovascular disease risk factors. However, in the diabetic population, weight management is more challenging, in part because of the weight-promoting effects of the majority of glucose-lowering therapies. This review summarizes evidence from 23 placebo-controlled randomized trials, of at least 1 year duration, on the effects of drugs promoting weight loss (orlistat, sibutramine and rimonabant) on glycaemic variables, diabetes incidence and diabetes control. Fifteen studies of non-diabetic subjects were found, eight of which included a longer treatment period. Eight studies in diabetic patients were reviewed. In non-diabetic subjects, weight loss agents led to a significant improvement in fasting glucose, fasting insulin and insulin resistance. In the diabetic population, glycated haemoglobin decreased by 0.28–1.1% with orlistat and 0.6% with sibutramine and rimonabant. Orlistat reduces progression to diabetes in patients with glucose intolerance treated for 4 years (risk reduction of 45%). In summary, despite leading to only modest weight loss after 12 months, agents promoting weight loss have beneficial effects on glycaemic parameters, glycaemic control and progression to diabetes. These additional benefits of weight loss agents need to be highlighted in order to increase their judicious use in clinical practice, although this may be limited by their well-known adverse side effects. The longer-term safety of these agents beyond a few years is yet to be established.

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Keywords diet, drugs, insulin, obesity, Type 2 diabetes

Abbreviations CB1, cannabinoid-1; HbA_{1c}, glycated haemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; UKPDS, UK Prospective Diabetes Study

Introduction

Obesity is a major public health problem worldwide and is associated with significant morbidity and mortality. Ninety per cent of patients with Type 2 diabetes are overweight or obese [1]. Obese patients who lose 5–10% of their initial body weight will have an improvement in insulin resistance and cardiovascular risk factors [2]. Weight management is more difficult in obese patients with Type 2 diabetes [3] and even more so in patients treated with sulphonylureas, thiazolidinediones or insulin therapy [4–7]. Anti-obesity medications are an underutilized adjunct to diet and lifestyle change in patients with Type 2 diabetes.

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Orlistat is a reversible inhibitor of gastric and pancreatic lipases. Its mechanism of action results in an inhibition of dietary fat absorption of 30% at the 120 mg approved dosage [8]. Sibutramine, a tertiary amine, enhances satiety by blocking the reuptake of neurotransmitters (serotonin and noradrenaline) and possibly increases thermogenesis by enhancing peripheral noradrenaline function [9]. Rimonabant is a selective cannabinoid-1 (CB1) receptor blocker that suppresses tonic endogenous activation of the endocannabinoid system centrally [10,11] and peripherally [12,13]. CB1 receptors are expressed in several areas of the brain and in peripheral organs, including the autonomic nervous system, liver, muscle, gastrointestinal tract and adipose tissue.

The aim of this report was to review data on the effect of drugs promoting weight loss on glycaemic parameters and Type 2 diabetes risk in predisposed individuals.

Methods

Data source

Relevant articles were located using computer-assisted searches of MEDLINE. The terms used for the search in the MEDLINE database were 'orlistat', 'sibutramine', 'rimonabant' and 'clinical trials'. Given the heterogeneity in study design, a meta-analysis was not appropriate; however, we conducted a systematic review of the available studies. We retrieved 210 published trials in English from November 1987 to May 2007 and selected those that satisfied the following criteria: (i) randomized double-blind placebo-controlled design; (ii) minimum duration of 1 year; (iii) inclusion of fasting blood glucose and/or glycated haemoglobin (HbA_{1c}) data. Additional publications were identified from review articles [14–22]. The doses of weight loss promoting medications used were: orlistat 120 mg three times a day, sibutramine 10 to 20 mg once daily and rimonabant 20 mg daily. When more than one dose of sibutramine was studied, data for the 20 mg dose was presented. Data were extracted by one reviewer (CLL).

Studies examined

Twenty-three studies satisfied the inclusion criteria and were analysed further. Two populations were studied: non-diabetic subjects (studies in which diabetes was an exclusion criterion or affected < 10% of the population) and subjects with diabetes. Studies with mixed populations were not included. Fifteen of the 23 studies included non-diabetic subjects (nine orlistat, three sibutramine and three rimonabant). Eight of these 15 studies included a treatment period greater than 1 year (six orlistat, one sibutramine and one rimonabant); three of the seven studies provided clinical data at 1 year (two orlistat and one rimonabant). In the diabetic population, eight studies with 1 year follow-up could be found (five orlistat, two sibutramine and one rimonabant). All trials combined pharmacological therapy with a reduced-calorie diet.

Results

Effects of drugs promoting weight loss in non-diabetic individuals

Weight loss

Orlistat led to a mean weight loss of 5.4–10.6 kg after 12 months [23–28] (Table 1). Mean weight loss in the placebo (diet alone) groups in these studies was 2.3–6.4 kg. At 12 months, 46–73% and 20–41% of patients treated with orlistat achieved a weight loss > 5% and > 10% of their initial body weight, respectively, compared with 23–49% and 11–21% in the placebo-treated groups respectively. In studies of more than 12 months' duration [23–25,28–30], mean weight loss in subjects taking orlistat was 5.0–7.4 kg. At the end of the treatment periods, 34–58% and 19–38% achieved a weight loss > 5% and > 10% of initial body weight, respectively, compared with 24–38% and 7–19% in the placebo groups, respectively. In a 52 week study of orlistat, glucose and insulin tended to decrease in both groups, although specific data are not presented [31].

In the two sibutramine studies, subjects achieved a weight loss of 6.4 and 12.1 kg [32,33] at 1 year, compared with 1.6 and 6.7 kg in the diet-alone groups, respectively (Table 1). In these studies, 57 and 73% of those treated with sibutramine achieved > 5% weight loss, compared with 20 and 53% in the placebo groups. Thirty-four per cent and 52% achieved > 10% weight loss compared with 7% and 29% in the placebo groups. In the only 2-year study of sibutramine, James *et al.* reported an average weight loss of 10.2 kg in the active group, compared with 4.7 kg in control subjects ($P < 0.001$) [34]. Forty-three per cent of patients who completed the 2-year trial maintained at least 80% of the weight lost after a 6-month low-calorie diet and sibutramine 5 mg [34].

Treatment with rimonabant 20 mg for 1 year (RIO studies) was associated with significantly greater weight loss than placebo in all studies [35–37] (Table 1). In two of these studies [35,36], the average weight loss in the rimonabant groups was 6.6 and 6.9 kg compared with 1.8 and 1.5 kg in the placebo groups, respectively. In the RIO-North America study, the additional weight lost with rimonabant compared with placebo was 4.7 kg at 1 year and 3.6 kg at 2 years ($P < 0.01$) [37]. In the active treatment groups in studies of rimonabant, 40–58% and 17–33% achieved > 5% and > 10% weight loss, respectively, compared with 19–20% and 7–9% in the control groups, respectively.

Fasting glucose and insulin and insulin resistance

Weight loss with all three agents was accompanied with a significant reduction in plasma glucose level and/or a difference compared with placebo at the end of the treated period in the majority of the studies (Table 1).

Changes in insulin levels were more inconsistent (Table 1). Of the 1-year studies of orlistat treatment, only the XENDOS study reported a significantly greater reduction in insulinaemia compared with placebo, a difference maintained at 4 years [28]. Of the other five studies lasting more than 1 year, four reported significant results.

The 2-year study of sibutramine reported a significant decrease in insulin levels compared with placebo [34]. Significant differences in the change in insulin levels between the active and placebo groups were observed in all studies of rimonabant [35–37]. Consistent with this data, rimonabant reduced HOMA-IR more than diet alone [33,35,37] (Table 2). In a 2-year study of rimonabant, the lower HOMA-IR value at 1 year was maintained at the end of the treatment period [37].

Diabetes incidence

Heymsfield *et al.* [14] pooled data from 316 subjects treated with placebo and 359 treated with orlistat for 2 years from three randomized, double-blind, placebo-controlled clinical trials [23,25,30]. In patients with impaired glucose tolerance at baseline (19 and 17% of subjects in the orlistat and placebo group, respectively), after average follow-up of 582 days, 72 vs. 49% had normal tolerance respectively, 25 vs. 43% had

Table 1 Double-blind placebo-controlled clinical trials of at least one year of orlistat (120 mg/day), sibutramine (10 to 20 mg/day) and rimonabant (20 mg): effect on fasting insulin and glucose levels in non-diabetic individuals

Study	Drug Placebo (*n*)	Duration (weeks)	% F	Age (years) mean (SD)	Baseline BMI (kg/m^2) mean (SD)	Weight loss (kg) mean (SD)	% who achieved		Fasting insulin (pmol/l) mean (SD)**		Fasting glucose (mmol/l) mean (SD)	
							> 5% weight loss	> 10% weight loss	Baseline	End of follow-up	Baseline	End of follow-up
ORLISTAT												
Sjostrom *et al.* (year 1) [23]	343	52	83	45.2 (—)	36.0 (—)	10.3 (—)	69	39	109 (—)	87 (—)	5.92 (—)	5.63 (—)§
	340		83	44.3 (—)	36.1 (—)	6.1 (—)	49	18	107 (—)	96 (—)	6.04 (—)	5.77 (—)
Rossner *et al.* (year 1) [24]	242	52	84	43.6 (11.4)	34.7 (3.7)	9.4 (6.4)	—	38	103 (51)	72 (54)	5.58 (0.79)	5.48 (0.86)*
	237		87	44.3 (10.8)	35.3 (4.1)	6.4 (6.7)	—	19	108 (69)	83 (74)	5.68 (0.95)	5.66 (1.01)
Hauptman *et al.* (year 1) [25]	210	52	79	43.2 (—)	36.0 (—)	7.9 (—)	51	29	90 (—)	90 (—)§	5.75 (—)	5.7 (—)
	212		78	41.6 (—)	36.1 (—)	4.1 (—)	31	11	105 (—)	120 (—)	5.66 (—)	5.8 (—)
Bakris *et al.* [26]	267	52	63	53 (0.5)	35.8 (3.9)	5.4 (6.4)	46	—	Δ: –41 (198)		—	—
	265		59	52.5 (0.5)	35.4 (4.0)	2.7 (6.4)	23	—	Δ: –27 (126)		—	—
Broom *et al.* [27]	265	52	78	46.7 (11.4)	37.1 (6.4)	5.8 (8.5)	56	20	—	—	Δ: –0.19§	
	263		78	45.3 (11.5)	37.0 (6.2)	2.3 (6.4)	24	11	—	—	Δ: +0.06	
Torgerson *et al.* (year 1) [28]	1640	52	55	43.0 (8.0)	37.3 (4.2)	10.6 (—)	73	41	86 (50)	Δ: –27§ (—)	4.6 (0.6)	Δ: +0.1§
	1637		55	43.7 (8.0)	37.4 (4.5)	6.2 (—)	45	21	84 (47)	Δ: –17 (—)	4.6 (0.6)	Δ: +0.2
Krempf *et al.* [29]	346	76	87	40 (—)	36.0 (—)	6.4 (—)	58	34	—	—	Δ: –0.86 (—)§	
	350		85	42 (—)	36.2 (—)	2.7 (—)	38	17	—	—	Δ: –0.29 (—)	
Davidson *et al.* [30]	657	104	83	43.3 (0.6)	36.2 (0.1)	—	—	34	84 (3)	67 (4)§	5.62 (0.03)	5.67 (0.05)§
(year 2 weight maintenance)	223		88	44.0 (0.7)	36.5 (0.9)	—	—	18	86 (5)	86 (7)	5.6 (0.03)	5.8 (0.06)
Sjostrom *et al.* [23]	343	104	83	45.2 (—)	36.0 (—)	—	57	—	109 (—)	83 (—)§	5.92 (—)	5.82 (—)§
(year 2 weight maintenance)	340		83	44.3 (—)	36.1 (—)	—	37	—	107 (—)	104 (—)	6.04 (—)	6.08 (—)
Rossner *et al.* [24]	242	104	84	43.6 (11.4)	34.7 (3.7)	7.4 (7.1)	—	38	103 (51)	82 (46)*	5.58 (0.79)	5.51 (1.29)
(year 2 weight maintenance)	237		87	44.3 (10.8)	35.3 (4.1)	4.3 (7.4)	—	19	108 (69)	88 (65)	5.68 (0.95)	5.54 (0.68)
Hauptman *et al.* [25]	210	104	79	43.2 (—)	36.0 (—)	5.0 (—)	34	19	90 (—)	90 (—)§	5.75 (—)	5.8 (—)
(year 2 weight maintenance)	212		78	41.6 (—)	36.1 (—)	1.7 (—)	24	7	105 (—)	104 (—)	5.66 (—)	5.9 (—)
Torgerson *et al.* [28]	1640	208	55	43.0 (8.0)	37.3 (4.2)	5.8 (—)	53	26	86 (50)	Δ: –32 (—)§	4.6 (0.6)	Δ: +0.1 (—)§
(completers)	1637		55	43.7 (8.0)	37.4 (4.5)	3.0 (—)	37	16	84 (47)	Δ: –21 (—)	4.6 (0.6)	Δ: +0.2 (—)
SIBUTRAMINE												
Smith and Goulder [32]	161	52	81	42.7 (11.7)	32.7 (3.3)	6.4 (—)	57	34	—	—	5.5 (—)	Δ: –0.19
	163		80	41.9 (11.6)	32.4 (3.5)	1.6 (—)	20	7	—	—	5.6 (—)	Δ: –0.16
Wadden *et al.* [33]	60	52	81	44.2 (10.8)	37.9 (4.2)	12.1 (9.8)	73	52	118 (66)	Δ: –43 (55)	5.26 (0.8)	Δ: –0.17 (0.63)
	55		76	43.3 (9.7)	37.8 (4.2)	6.7 (7.9)	53	29	112 (67)	Δ: –31 (46)	5.16 (0.61)	Δ: –0.23 (0.46)
James *et al.* [34]Φ	352	104	84	40.7 (10.2)	36.5 (4.1)	10.2 (9.3)	69	46	124 (90)	97 (55)*	5.2 (0.82)	5.13 (0.96)
	115		84	40.4 (9.9)	36.8 (4.1)	4.7 (7.2)	—	—	117 (85)	113 (62)	5.11 (0.56)	5.17 (0.62)
RIMONABANT												
Van Gaal *et al.* [35]	599	52	80	44.6 (11.9)	36.2 (5.8)	6.6 (7.2)	51	27	89 (67)	82 (58)§	5.28 (0.7)	5.2 (0.68)§
	305		80	45 (11.6)	35.7 (5.9)	1.8 (6.4)	19	7	87 (67)	99 (92)	5.26 (0.7)	5.29 (0.83)
Després *et al.* [36]	346	52	62	48.4 (10)	33.9 (3.3)	6.9 (6.1)	58	33	90 (86)	Δ: –12 (87)§	5.29 (0.59)	Δ: –0.08 (0.58)
	342		58	47.0 (10.1)	34.0 (3.5)	1.5 (5.0)	20	7	90 (86)	Δ: +6 (111)	5.29 (0.64)	Δ: –0.05 (0.62)
Pi-Sunyer *et al.* (year 1) [37]	1219	52	81	45.6 (11.8)	37.2 (6.2)	placebo subtracted	49	25	90 (80)	placebo subtracted	5.1 (0.61)	placebo subtracted
	607		81	44.8 (11.6)	37.6 (6.4)	Δ: 4.7 (—)	20	9	90 (69)	Δ: –20 (—)§	5.1 (0.61)	Δ: –0.04
Pi-Sunyer *et al.* [37]		104	81	45.6 (11.8)	37.2 (6.2)	placebo subtracted	40	17	94 (70)	placebo subtracted	5.1 (0.61)	placebo subtracted
			81	44.8 (11.6)	37.6 (6.4)	Δ: 3.6 (—)	19	8	90 (80)	Δ: –13 (—)§	5.1 (0.61)	Δ: –0.05

F, female. *Difference with baseline value $P < 0.05$; §Difference between groups $P < 0.05$; ΦSibutramine 5 mg for 6 months for all subjects followed by randomisation to sibutramine 10–20 mg or placebo and weight maintenance for 18 months.

—, missing data; Δ, change. **Some results expressed in mUI/l have been converted in pmol/l (conversion factor: ×7).

Table 2 Double-blind placebo-controlled clinical trials of at least one year of orlistat (120 mg/day), sibutramine (10 to 20 mg/day) and rimonabant (20 mg): effect on insulin resistance (HOMA-IR) in non-diabetic and diabetic individuals

		HOMA-IR mean (SD)	
	Drug Placebo (*n*)	Baseline	End of follow-up
ORLISTAT			
Berne [40]	111	8.53 (4.73)	6.39 (5.43)§
(*diabetic population*)	109	7.71 (5.89)	7.27 (5.95)
SIBUTRAMINE			
Wadden *et al.* [33]	60	3.9 (2.2)	Δ: –1.5 (1.9)
	55	3.9 (2.7)	Δ: –1.1 (1.8)
RIMONABANT			
Van Gaal *et al.* [35]	555	3.1 (2.5)	2.8 (2.3)§
	290	3.0 (2.6)	3.4 (3.5)
Scheen *et al.* [38]	339	5.9 (5.0)	Δ: –0.5 (5.7)§
(*diabetic population*)	348	5.8 (7.3)	Δ: +0.6 (8.9)
Pi-Sunyer *et al.* [37]	1219	3 (2.7)	placebo subtracted
(year 1)	607	3.1 (2.7)	Δ: –0.8§
Pi-Sunyer *et al.* [37]		3 (2.7)	placebo subtracted
(year 2)		3.1 (2.7)	Δ : –0.6§

§Difference between groups $P < 0.05$; Comparison with baseline value $P < 0.05$. Δ, change.

impaired glucose tolerance and 3 vs. 8% progressed to diabetes. The XENDOS study, a prospective study conducted to determine the effect of orlistat on reducing progression to Type 2 diabetes over 4 years in a population of patients with normal (79%) or impaired (21%) glucose tolerance, found that the cumulative incidence of Type 2 diabetes was 2.9% with orlistat vs. 4.2% for placebo (log-rank $P = 0.028$) [28]. In the subgroup of patients with impaired glucose tolerance, the incidence of diabetes was 19% in patients randomized to orlistat and 29% in those randomized to placebo (log-rank $P = 0.0024$), corresponding to a risk reduction of 45%. This was obtained despite only a moderate difference in weight loss between patients receiving orlistat and those not (5.8 vs. 3.0 kg, respectively, $P < 0.001$). No studies have examined the effect of sibutramine or rimonabant on the incidence of Type 2 diabetes.

Effects of drugs promoting weight loss in individuals with diabetes

Weight loss

In diabetic populations [39–43], orlistat reduced weight by 3.9–6.2 kg at 1 year (Table 3). Average weight loss with placebo in these studies was 1.3–4.3 kg. In contrast to studies of non-diabetic individuals, only 33–51% and 10–18% achieved a weight loss > 5% and > 10% of initial body weight, respectively, compared with 11–32% and 3–9%, respectively, in the placebo-treated groups.

With sibutramine in diabetic populations, weight loss was 8.0 kg with active drug treatment compared with 0.2 kg in the placebo group, respectively [44]. In the only study of rimonabant in Type 2 diabetes, weight loss was 5.4 and 1.4 kg in the active and placebo groups, respectively [38].

Glycaemic control

Despite more modest weight loss in diabetic compared with non-diabetic populations, orlistat led to significant improvements in HbA_{1c} of 0.28–1.1% [39–43] (Table 3). Reductions in HbA_{1c} of 0.3–0.6% were observed in studies of sibutramine [44,45] and rimonabant [38]. By comparison, improvements in HbA_{1c} with diet alone were 0.2–0.5%; in some studies, glycaemic control deteriorated. Differences in HbA_{1c} between active drug and diet groups were significant in all studies, with the exception of one sibutramine study [44].

In some studies of orlistat, reductions in HbA_{1c} were observed even when the dosage of concurrent glucose-lowering medication(s) was decreased. For example, Miles *et al.* reported a mean reduction in HbA_{1c} of 0.75% in the orlistat group vs. 0.41% in the placebo group, despite a significantly greater reduction in dose of oral glucose-lowering agents in the former [41]. In a study of patients treated with sulphonylureas, Hollander *et al.* reported a mean decrease in HbA_{1c} of 0.28% in the orlistat-treated group (compared with an increase of 0.18% in placebo group, $P < 0.001$), with the benefits of treatment greatest when baseline HbA_{1c} was > 8.0 % (–0.53 vs. –0.05%, respectively, $P = 0.001$) [42]. These results were achieved despite the average dose of sulphonylurea medication being decreased in a greater proportion of patients in the orlistat group compared with the placebo group (23 vs. 9%, $P = 0.002$) [42]. In another population of patients with diabetes receiving sulphonylurea or diet alone at baseline, despite a placebo-subtracted reduction in HbA_{1c} of 0.5% with orlistat, intensification of therapy (an increase in dose or addition of additional glucose-lowering medication) was reported by a higher percentage of patients in the placebo group (18 vs. 14%) [43]. In a study of patients taking insulin, 52% of

Table 3 Double-blind placebo-controlled clinical trials of at least one year of orlistat (120 mg/day), sibutramine (10 to 20 mg/day) and rimonabant (20 mg): effect on HbA_{1c} in diabetic individuals

Study	Inclusion criteria (HbA_{1c}, diabetes therapy)	Drug Placebo (*n*)	Duration (weeks)	% F	Age (years) mean (SD)	Baseline BMI (kg/m^2) mean (SD)	Weight loss (kg) mean (SD)	% achieved		HbA_{1c} (%)	
								> 5% weight loss	> 10% weight loss	Baseline	Δ
ORLISTAT											
Kelley *et al.* [39]	7.5–12% + insulin	266	52	56	57.8 (—)	35.8 (—)	3.9 (—)	33	10	9.01 (—)	–0.62 (—)§
	± sulfonylurea and/or metformin	269		56	58 (—)	35.6 (—)	1.3 (—)	13	4	8.99 (—)	–0.27 (—)
Berne [40]	6.5–10% + metformin ± sulfonylurea	111	52	45	58.9 (9.1)	32.6 (3.1)	—	46	14	7.6 (0.8)	–1.1 (—)§
		109		46	59.3 (8.5)	32.9 (3.0)	—	11	3	7.6 (0.8)	–0.22 (—)
Miles *et al.* [41]	7.5–12% + metformin ± sulfonylurea	250	52	48	52.5 (—)	35.6 (—)	4.7 (—)	39	14	8.87 (—)	–0.75 (—)*
		254		48	53.7 (—)	35.2 (—)	1.8 (—)	16	4	8.79 (—)	–0.41 (—)*
Hollander *et al.* [42]	6.5–10% + sulfonylurea	162	52	51	55.4 (8.8)	34.5 (3.2)	6.2 (—)	49	18	8.05 (0.98)	–0.28 (—)§
		159		47	54.7 (9.7)	34.0 (3.4)	4.3 (—)	23	9	8.2 (1.07)	+0.18 (—)
Hanefeld and Sachse [43]	6.5–11% ± sulfonylurea	189	52	52	56.6 (8.6)	34.5 (5.6)	5.3 (5.1)	51	—	8.6 (1.1)	–0.9 (—)§
		180		50	55.8 (8.9)	33.7 (5.2)	3.4 (5.3)	32	—	8.6 (1.2)	–0.4 (—)
SIBUTRAMINE											
McNulty *et al.* [44]	metformin	62	52	56	51 (—)	37.5 (—)	8.0 (—)	65	27	9.1 (—)	–0.3 (—)
		64		66	51 (—)	36.2 (—)	0.2 (—)	11	0	9.7 (—)	–0.2 (—)
Sanchez-Reyes *et al.* [45]	glibenclamide	44	52	64	47.6 (9)	29.2 (2.6)	—	59	25	8.9 (1.2)	—*§Φ
		42		74	45.8 (8.1)	30.1 (2.5)	—	17	5	9 (1.2)	—
RIMONABANT											
Scheen *et al.* [38]	6.5–10% + metformin or sulfonylurea	339	52	50	56 (8.5)	34.1 (3.6)	5.3 (5.2)	49	16	7.3 (0.8)	–0.6 (0.8)§
		348		54	54.8 (8.6)	34.2 (3.6)	1.4 (3.6)	15	2	7.2 (0.9)	+0.1 (1.0)

F, female; —, missing data. §Difference between groups $P < 0.05$; *Comparison with baseline value $P < 0.05$; ΦChanges not stated; HbA_{1c} at 52 weeks: 8.3 (1.2)% vs 9.1 (1.3)%, drug vs placebo respectively. Δ, change.

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orlistat-treated patients vs. 40% of placebo-treated patients achieved a reduction in $HbA_{1c} > 0.5\%$ ($P = 0.008$) and 32 vs. 22%, respectively, achieved a reduction ≥ 1.0 % ($P = 0.013$) [39]. A greater improvement in HbA_{1c} was obtained in the orlistat-treated group (–0.62 vs. –0.27%), despite a statistically greater reduction in insulin dose compared with placebo (–8.1 vs. –1.6 units/day) [39].

Although a study using sibutramine in a metformin-treated population of patients with Type 2 diabetes did not demonstrate a significant change in HbA_{1c} compared with placebo [44], the percentage of weight lost significantly correlated with the fall in HbA_{1c} and patients who lost > 10% of their initial body weight showed a mean improvement in HbA_{1c} of 1.2% [44]. In a sulphonylurea-treated population receiving sibutramine, the change in HbA_{1c} was statistically different from baseline at 12 months ($P < 0.001$), whereas no statistically significant difference was found in the placebo group [45]. Nevertheless, the dose of sulphonylurea was significantly reduced in both the sibutramine and placebo groups at the end of the study, with 29 and 22% of patients, respectively, requiring no sulphonylurea treatment at 12 months (difference between the groups not statistically significant).

Scheen *et al*. reported that HbA_{1c} was improved with rimonabant 20 mg, with a decrease of 0.6%, compared with an increase of 0.1% in the placebo-treated group ($P < 0.0001$) [38]. Results were similar in patients treated with metformin and sulphonylurea [38]. Of the patients treated with rimonabant, 68 and 43% achieved $HbA_{1c} < 7.0$ % and $< 6.5\%$, respectively, compared with 48 and 21% of patients treated with placebo ($P < 0.0001$) [38]. Furthermore, more patients in the rimonabant-treated group required a reduction in the dose of their oral glucose-lowering agents compared with placebo-treated patients ($P = 0.005$).

Discussion

The treatment of obesity is particularly challenging in diabetic patients because of the obligatory weight gain induced by most glucose-lowering medications, with the exception of metformin [and some of the newer agents such as glucagon-like peptide-1 (GLP-1) analogues] [21]. The UK Prospective Diabetes Study (UKPDS) found that patients treated with insulin and sulphonylureas gained 4.0 and 2.2 kg more, respectively, than patients with diet alone [5]. However, studies in patients with Type 2 diabetes have shown that weight reduction of as little as 5–10% improves glycaemic control and cardiovascular disease risk [3].

Consistent with evidence that moderate weight loss in overweight and obese patients is accompanied by favourable changes in hepatic and peripheral insulin resistance (decreased endogenous glucose production and increased peripheral glucose uptake) [46], we observed that a significant weight loss in subjects without diabetes is associated with an improvement in fasting glucose and insulin levels and insulin resistance in the majority of the studies discussed in this review. This was particularly consistent in studies of rimonabant, despite a lesser weight loss compared with orlistat or sibutramine. This observation may be as a result of the wide distribution of CB1 receptors in peripheral tissues involved in insulin-mediated glucose uptake, including muscle, liver and adipose tissue [12,13].

Of the three available agents included in this review, to date, only orlistat has been reported to reduce the incidence of diabetes in subjects with impaired glucose tolerance. The XENDOS study demonstrated that orlistat, in combination with a lifestyle programme over 4 years, produced greater weight loss than lifestyle changes alone and decreased the incidence of diabetes in all patients, with a risk reduction of 37% [28]. However, in subjects with impaired glucose tolerance, the cumulative diabetes incidence rates were 19% with orlistat and 29% with lifestyle alone, corresponding to a 45% risk reduction (hazard ratio = 0.551) [28].

In the UKPDS cohort, a 1% reduction in HbA_{1c} was associated with a 37% risk reduction in microvascular complications and a 21% risk reduction of any diabetes-related endpoint [5]. This 1% reduction in HbA_{1c} was associated with an obligatory gain in weight, with the exception of metformin-treated patients [47]. An improvement in HbA_{1c} of up to 1.1% was observed in the studies included in this review, which is comparable with that reported for other oral glucose-lowering therapies [21]. Importantly, in many of these studies, the improvement in HbA_{1c} was achieved despite reduction in use of oral glucose-lowering medication. A reduction in sulphonylurea and insulin doses may also contribute to the reduction in weight in diabetic patients taking weight loss therapies.

Controversy exists regarding whether the reduction in weight using weight loss agents fully explains the improvement in metabolic factors. Using multiple regression analysis, Berne has shown that an improvement in glycaemic control associated with orlistat was independent of weight loss [40]. In contrast, in a study using sibutramine for 24 weeks, the improvement in glycaemic control was statistically correlated with achieved weight loss [48]. Després *et al*. reported that only 57% of the increase in adiponectin (an insulin-sensitizing adipokine) following rimonabant treatment could be attributed to weight loss [36]. *In vitro* studies have demonstrated an increase in adiponectin secretion in adipocytes isolated from animals following treatment with CB1 receptor blockers [49]. Whether this increase in adiponectin is responsible for the positive changes in insulin resistance with rimonabant treatment is yet to be determined.

Obesity is a chronic disorder associated with increased cardiovascular risk. Obese patients often require multiple medications to control obesity-associated cardiovascular risk factors, such as diabetes, hypertension and dyslipidaemia. Many of these agents could be discontinued, and cardiovascular risk improved, if effective weight loss is achieved. Indeed, weight loss > 5% at 12 weeks may be a criterion to continue drugs promoting weight loss, as in orlistat-treated patients it accurately predicted sustained improvements in weight [50].

Potential safety issues of all three weight-loss agents described in this review should be further discussed. Orlistat is generally well tolerated and adverse effects related to its mode of action, such as gastrointestinal disorders (fatty/oily stool, oily spotting), resolve within a few weeks in the majority of cases [16,51]. Nevertheless, nutrient and vitamin absorption can be affected (particularly beta-carotene, vitamins D and E) and multivitamin supplementation has been recommended for patients taking orlistat [52]. Sibutramine has been associated with a rise in diastolic and systolic blood pressure and a minor increase in heart rate [53]. In a systematic review, Aterburn *et al*. concluded that the effect of sibutramine on cardiovascular and metabolic outcomes may not be entirely positive and that there is insufficient evidence to accurately determine the long-term risk–benefit profile for sibutramine [53]. However, its safety in patients with known ischaemic heart disease is under assessment [54]. The most common adverse effects reported with rimonabant are nausea, depressed mood disorders, dizziness, arthralgia and diarrhoea, particularly during the first few months of therapy [35–38]. However, the findings of a recent meta-analysis suggested that the potential of rimonabant to induce depressive symptoms in overweight patients requires greater attention [55].

Despite the effectiveness of such agents in achieving weight loss, it is important to highlight that these agents are most effective when combined with intensive lifestyle intervention. The effectiveness of dietary changes and physical activity were highlighted by the Diabetes Prevention Program trial, which reported a lower diabetes incidence in glucose-intolerant patients in a lifestyle-intervention group compared with metformin-treated and placebo groups (4.8, 7.8 and 11.0 cases per 100 person years respectively), after an average follow-up of 2.8 years [56]. In the lifestyle intervention and metformin groups, the incidence of diabetes was reduced by 58 and 31%, respectively, as compared with placebo. This is in comparison with the 37% reduction with orlistat in the XENDOS study. In other studies, lifestyle intervention leads to significant weight loss, which is accompanied by improvement in glycaemic parameters and HbA_{1c} [57,58].

Conclusion

Weight-loss agents lead to statistically and clinically significant improvements in glycaemic parameters and glycaemic control in patients with and without diabetes. Only orlistat (XENDOS study) has been shown to reduce progression to Type 2 diabetes, particularly in individuals with impaired glucose tolerance. In contrast to the requirement for additional oral glucose-lowering agents to maintain glycaemic control over time in diabetes, the use of weight-loss agents often leads to a reduction in HbA_{1c} despite a reduction in glycaemic therapy. The many benefits of weight-loss medications above and beyond weight loss itself may lead to improved glycaemic control in obese patients with Type 2 diabetes.

Competing interests

S. Czernichow is on a scientific advisory committee for Sanofi-Aventis, France. J. Greenfield has received an honorarium from Sanofi-Aventis Australia for GP medical training.

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