

New antiobesity agents in type 2 diabetes: overview of clinical trials with sibutramine and orlistat

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Résumé

Nouveaux agents anti-obésité dans le traitement du diabète de type 2 : résumé des essais cliniques avec la sibutramine et avec l'orlistat.

Avec la prédisposition génétique, l'obésité est le facteur de risque le plus important pour le développement du diabète de type 2. Un amaigrissement, même modeste, peut améliorer le contrôle glycémique chez les sujets avec excès pondéral. Après échec des mesures hygiéno-diététiques, des médicaments anti-obésité comme l'orlistat, un inhibiteur sélectif puissant des lipases gastro-pancréatiques qui réduit l'absorption des lipides par l'intestin, ou la sibutramine, un inhibiteur de la recapture neuronale de la noradrénaline et de la 5-hydroxytryptamine qui module l'appétit, peuvent être envisagés pour favoriser une perte de poids et/ou consolider un amaigrissement. Plusieurs études contrôlées versus placebo ont démontré récemment que ces deux médicaments favorisent la perte de poids chez les sujets obèses avec diabète de type 2 traité par régime seul, sulfamides, metformine ou insuline. Cet amaigrissement plus marqué par rapport au placebo s'accompagne d'une réduction significative des taux d'hémoglobine glyquée et/ou des doses des agents hypoglycémiant classiques, en particulier chez les bons répondeurs qui ont perdu au moins 10 % de leur poids initial. De plus, les facteurs de risque vasculaire sont également diminués après amaigrissement, plus particulièrement les dyslipidémies avec l'orlistat. Ces agents anti-obésité peuvent aussi contribuer à retarder ou prévenir la progression de la diminution de la tolérance au glucose vers le diabète de type 2 avéré chez des individus obèses à risque (« Xenical in the prevention of diabetes in obese subjects »). De grandes études prospectives à long terme, comme l'essai « Sibutramine cardiovascular and diabetes outcome study » devraient permettre de mieux préciser la place du traitement pharmacologique anti-obésité dans la prise en charge générale du patient obèse avec diminution de la tolérance au glucose ou avec diabète de type 2.

Abstract

Besides genetic predisposition, obesity is the most important risk factor for the development of type 2 diabetes mellitus. Even modest weight reduction can improve blood glucose control in overweight subjects. After failure of lifestyle modifications, antiobesity drugs such as orlistat, a potent and selective inhibitor of gastric and pancreatic lipases that reduces lipid intestinal absorption, or sibutramine, a noradrenaline and 5-hydroxytryptamine reuptake inhibitor that regulates food intake, may be considered to favour weight loss and/or weight maintenance. Several placebo-controlled studies have recently demonstrated that both drugs are able to promote weight loss in obese type 2 diabetic patients treated with diet alone, sulphonylureas, metformin or insulin. The greater weight reduction as compared to placebo

was associated with a significant reduction of glycated haemoglobin levels and/or of the doses of classical antihyperglycaemic agents, especially in good responders who lost at least 10% of initial body weight. In addition, vascular risk factors associated to insulin resistance were also reduced after weight loss. These antiobesity agents may also contribute to delay or prevent the progression from impaired glucose tolerance to overt type 2 diabetes in at risk obese individuals (“Xenical in the prevention of diabetes in obese subjects” trial). Large long-term prospective studies, such as the “Sibutramine cardiovascular and diabetes outcome study” should better determine the place of pharmacological anti-obesity strategy in the overall management of obese patients with impaired glucose tolerance or type 2 diabetes.

Mots clés : amaigrissement , diabète de type 2 , insulino-résistance , obésité , orlistat , sibutramine

Keywords: insulin sensitivity , obesity , orlistat , sibutramine , type 2 diabetes , weight loss

Type 2 diabetes mellitus is strongly associated with obesity [1] [2] [3]. Over 80% of type 2 diabetic patients are overweight or obese, and the risk of developing type 2 diabetes increases in an exponential manner according to body mass index (BMI) [4]. Such a deleterious effect of weight excess on glucose metabolism is classically attributed to insulin resistance, especially in presence of visceral adiposity [5] [6] [7] [8]. Furthermore, most insulin-resistant obese diabetic patients have other vascular risk factors, especially arterial hypertension and dyslipidaemias. This segregation, known as metabolic syndrome, insulin resistance syndrome or syndrome X, explains increased cardiovascular morbidity and mortality rates in such a population [9] [10]. Conversely, numerous studies demonstrated that weight loss reduces the risk of progression from impaired glucose tolerance to overt type 2 diabetes [11] [12], markedly improves glycaemic control in individuals with type 2 diabetes [13] [14] [15] [16] [17] [18] [19], reduces the severity of vascular risk factors and comorbidities [20], and improves overall prognosis of obese diabetic patients [21]. Thus, one key issue in the management of obese patients with type 2 diabetes is to succeed in obtaining a significant and sustained weight loss [22] [23] [24]. With this objective in mind, antiobesity agents may be considered as a valuable alternative or adjunct treatment to classical antidiabetic agents in obese patients with type 2 diabetes refractory to lifestyle modifications [25] [26] [27].

A variety of pharmacological compounds can be used to promote weight loss in obese type 2 diabetic patients [22] [28] [29] [30] [31] [32] [33] [34]. Numerous studies have been published with old anorectic agents in obese non-diabetic patients [28] [29] [35] [36] [37], but only a few in obese individuals with type 2 diabetes [22] [30] [31] [32]. A majority evaluated the serotonergic compounds, fenfluramine, dexfenfluramine and fluoxetine. Most placebo-controlled, double-blind clinical trials lasted 12 weeks and only very few studies were prolonged up to 1 year or more [38]. In obese diabetic individuals, the drug-associated additional weight reduction (although rather modest in most cases) was associated with a moderate decrease (significant in about half of the studies) in fasting plasma glucose and glycated haemoglobin (HbA_{1c}) levels [22]. Interestingly, several studies showed that serotonergic agents can improve insulin sensitivity independently of weight reduction [39]. This has been demonstrated with fenfluramine, dexfenfluramine and fluoxetine, in short-term studies using various methods, especially the euglycaemic hyperinsulinaemic clamp technique [22] [30] [31]. The improvement of insulin action was associated with a significant reduction of fasting plasma glucose levels in half of the studies, as well as with an improvement of

various cardiovascular risk factors. Unfortunately, fenfluramine and dexfenfluramine, the two compounds that have been best evaluated and provided the most impressive metabolic improvement, were withdrawn from the market after the description of valvular heart disease, especially in the United States [29].

The aim of the present review is to analyse the results of controlled clinical trials performed with two recent antiobesity agents, sibutramine and orlistat, in overweight/obese individuals with impaired glucose tolerance or with type 2 diabetes.

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CLINICAL TRIALS WITH SIBUTRAMINE

Sibutramine, a new noradrenaline (NE) and 5-hydroxytryptamine (5-HT) reuptake inhibitor, has been shown to produce a dose-related weight loss in obese subjects, with optimal doses of 10-15 mg/day to be increased up to a maximal dose of 20 mg/day [40](Table I). The multicentre prospective STORM (Sibutramine Trial of Obesity Reduction and Maintenance) clinical study showed that almost all patients who persisted with the management scheme combining restricted diet and sibutramine can achieve at least a 5% weight loss, and over half can lose more than 10% weight within 6 months [41]. Furthermore, sustained weight loss was maintained in most patients continuing therapy with sibutramine for 2 years whereas weight regain was noticed in most patients randomised to placebo, thus demonstrating that sibutramine favours weight maintenance in the long-term.

Owing the close relationship between obesity and abnormal glucose metabolism, sibutramine may be useful in the treatment of obese diabetic patients [42], a hypothesis that was confirmed in two pilot trials [43] [44](Table I). In patients with type 2 diabetes, sibutramine-induced weight loss was accompanied by a shift towards improved metabolic control and the reduction in fasting plasma glucose was proportional to the degree of weight loss [45]. A meta-analysis of placebo-controlled studies performed in modestly hyperglycaemic obese patients showed that greater improvements in fasting plasma glucose concentrations were observed in the group receiving the active drug [46]. This difference is probably explained by the fact that more patients on sibutramine rather than on placebo achieved significant weight loss. The observation that changes in plasma glucose levels observed on sibutramine and placebo were similar for the same degree of weight loss indeed suggests an indirect rather a direct action of the drug on glucose metabolism. One study using the hyperinsulinaemic clamp demonstrated a similar improvement in insulin sensitivity in obese type 2 diabetic patients after a comparable weight loss of about 5 kg obtained with either sibutramine or placebo [44]. Thus, in contrast to the observations previously reported with dexfenfluramine and fluoxetine [30] [32] [39], no improvement of insulin sensitivity has been demonstrated with sibutramine independently of weight loss.

Favourable results were reported with sibutramine in four 6-month [47] [48] [49] [50]and two one-year [51] [52]randomised clinical trials (Table II). All studies demonstrated that, when compared to placebo, an average 3-5 kg further weight loss resulting from the prescription of sibutramine at a daily dose of 15-20 mg is sufficient to improve fasting blood glucose and HbA 1c levels, especially in patients losing \geq 10% of their baseline body weight. Interestingly, these changes were associated with improvement of other metabolic vascular risk factors, such as lipid parameters. A recent study comparing sibutramine (2 X 10 mg/day) with orlistat or metformin in obese non-diabetic female subjects reported that sibutramine was

the most effective agent in terms of weight reduction and was as effective as the two other compounds to reduce cardiovascular risk and decrease the risk of type 2 diabetes [53].

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CLINICAL TRIALS WITH ORLISTAT

Orlistat, a semisynthetic derivative of lipstatin, is a potent and selective inhibitor of gastric and pancreatic lipases [54](Table I). When administered with fat-containing foods, it partially inhibits the hydrolysis of triglycerides, thus reducing the subsequent absorption of monoglycerides and free fatty acids. Orlistat treatment results in a dose-dependent reduction in body weight in obese subjects, with an optimal dosage regimen of 120 mg tid, and is generally well tolerated besides some intestinal side-effects during the first few days-weeks of administration [55].

Several one-year and two-year trials showed that orlistat, when used with a health-promoting low-fat and moderately energy-restricted diet, confers some advantages in the long-term management of non-diabetic obese subjects [55] [56] [57] [58]. Weight loss was significantly greater in the orlistat than in the placebo group, with a specific reduction in total and LDL cholesterol serum levels of greater magnitude than that expected from weight loss [59]. Interestingly enough, orlistat-associated moderate weight loss was shown to have beneficial effects on insulin sensitivity and beta-cell function and to significantly reduce the relative risk of developing overt type 2 diabetes in obese patients with impaired glucose tolerance [60] [61]. In addition, orlistat favourably influences coronary heart disease risk profile in obese subjects [57] [62] [63] [64]. Improvement of cardiovascular risk profile was associated with a significant reduction of body weight, waist circumference, total body fat percentage, and insulin sensitivity assessed with the HOMA (HOMeostatic Model Assessment) method [63]. Two meta-analysis of five multicentre randomised placebo-controlled trials suggested that orlistat-associated weight loss resulted in a significant reduction in insulin resistance [65] and that orlistat treatment may be of particular benefit in reducing coronary heart disease risk for abdominally obese dyslipidaemic patients [66].

To test the hypothesis that orlistat combined with dietary intervention improves glucose tolerance status and prevents worsening of diabetes status more effectively than placebo, an analysis of pooled data from 3 randomised, double-blind, placebo-controlled multicentre clinical trials was performed [61]. Weight reduction was greater with orlistat (n = 359) than with placebo (n = 316): 6.72 versus 3.79 kg, $p < 0.001$. The comparison of oral glucose tolerance tests before and after 104 weeks of treatment showed that a smaller percentage of subjects with IGT at baseline progressed to diabetic status in the orlistat group (3.0% versus 7.6% in the placebo group). Conversely, among subjects with IGT at baseline, glucose levels normalized in more subjects after orlistat treatment (71.6 versus 49.1% after placebo). Thus, the addition of orlistat to a conventional weight loss regimen significantly improves oral glucose tolerance and diminishes the rate of progression to the development of IGT and type 2 diabetes [61] [67].

Orlistat may also be used in the treatment of obese patients with overt type 2 diabetes [67] [68]. A large multicentre, randomised double-blind, placebo-controlled group study determined the effects of orlistat 120 mg tid in obese type 2 diabetic patients treated with sulphonylurea hypoglycaemic agents [69]. After one year treatment, a mean difference of 2.4 kg greater weight loss was observed in the orlistat group versus the placebo group, which was associated with significant reductions in fasting blood glucose and HbA_{1c} levels.

Furthermore, a significant reduction in the dose of oral hypoglycaemic agents was seen in the orlistat group as well as an improvement of lipid parameters. Thus, this study showed that orlistat is well tolerated and effective in causing weight loss in obese type 2 diabetic patients with attendant improvement of glycaemic control and lipid parameters. Such positive results were confirmed in further studies in obese diabetic patients treated with diet alone [63] [67] [68], metformin [70], metformin and/or sulphonylurea [71] [72] [73] or even insulin [74] (Table III). A 1-year multicentre, randomised, double-blind, placebo-controlled trial demonstrated that orlistat 120 mg tid is a useful adjunctive treatment for producing weight loss and improving glycaemic control, serum lipid levels, and blood pressure in obese patients with type 2 diabetes who are being treated with metformin [70]. In overweight or obese patients with type 2 diabetes who had suboptimal metabolic control with insulin therapy, one-year orlistat treatment, compared to placebo, produced significantly greater decreases in body weight, HbA 1c levels, fasting serum glucose concentrations, and the required doses of insulin and other diabetic medications as well as greater reductions in total cholesterol, LDL cholesterol and LDL/HDL ratio [66]. Orlistat reduced body weight and cardiovascular disease risk factors in obese men and women with type 2 diabetes [75].

A Markov health economic model was developed to predict, over a 10-year period, the complication rates and mortality with and without a 2-year orlistat treatment, assuming a 5-year catch-up period after treatment [76]. The results suggest that orlistat is cost-effective in the management of obese type 2 diabetic patients, especially in those with the presence of hypercholesterolaemia and/or hypertension. However, evidence on longer-term benefits of orlistat (> 2 years) will be of importance for future decision-making. These results have been confirmed using a Markov state-transition model simulating diabetes-related complications in a population of 52-year old males with a BMI of 35 kg/m² and a HbA 1c of 8.5% [77].

A recent retrospective analysis of pooled data from seven multicentre, double-blind trials assessed the effect of orlistat in overweight or obese patients with type 2 diabetes. It demonstrated that orlistat has a beneficial effect on HbA 1c

- * which is, as with all other oral hypoglycaemic agents, proportional to the starting HbA 1c level [78];
- * which is best evidenced in patients with HbA 1c levels $\geq 8\%$ [79];
- * which is similar in patients receiving maximal or near maximal doses of metformin or sulphonylureas as in the overall treatment group [80];
- * which can be attributed to a significant reduction of insulin resistance as assessed with the HOMA method applied on fasting plasma glucose and insulin concentrations [81].

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COMPARISON SIBUTRAMINE VERSUS ORLISTAT

Although no direct comparative studies are available in obese type 2 diabetic patients, comparison of results of Table II (sibutramine trials) and Table III (orlistat trials) suggests that orlistat 120 mg tid may be slightly less effective than sibutramine 15-20 mg od in reducing body weight. It is noteworthy that changes in body weight were expressed as % of initial body weight in most orlistat trials whereas they were expressed as changes in kilograms in most sibutramine trials, but this difference in the mode of expression does not markedly influence the results as average body weights were around 100 kg in most clinical studies with orlistat [69] [70] [74]. In contrast, orlistat may be more powerful in improving blood glucose control

(Fig. 1), with more reproducible results between different studies as compared to sibutramine (Tables II and III). One may speculate on the possible mechanisms that might be responsible for a better antihyperglycaemic effect despite a lower antiobesity effect of orlistat as compared to sibutramine. Because of its specific mechanism of action, orlistat contributes to reduce fat absorption from the gut [54]. High fat intake has been shown to be associated with decreased insulin sensitivity in both animal model and human studies [82] [83]. Because of this effect, one may hypothesize that a greater improvement of insulin sensitivity may be expected than that predicted by the modest weight loss, in a similar manner to what has been reported for the hypocholesterolaemic effect of orlistat [59]. Significant increases in insulin sensitivity index as assessed with the HOMA method have been reported in obese non-diabetic [63] [65] and diabetic [63] [81] subjects treated by orlistat 120 mg tid. In addition, lipids may also be toxic for the B cell, a process known as lipotoxicity [84] [85], and this phenomenon might also be somewhat reduced by orlistat. In contrast, sibutramine, due to its specific mechanism of action, tends to increase sympathetic drive, which is responsible of a mild, but significant, increase in thermogenesis, arterial blood pressure and heart rate [40]. Increase of sympathetic tone might contribute to decrease insulin secretion by the pancreatic islet B cells [86]. In addition, because catecholamines are counterregulatory hormones that antagonize the action of insulin [87], one may hypothesize that the improvement of insulin sensitivity associated to sibutramine might be less pronounced than what could be expected from the observed weight loss [44]. Indeed, one study failed to demonstrate any significant effect of sibutramine on insulin sensitivity [44], in contrast to what has been reported with the pure serotonergic agent dexfenfluramine [39]. These different effects on insulin sensitivity, and perhaps on insulin secretion, may explain the apparent different quantitative effects of orlistat and sibutramine on overall blood glucose control compared with weight reduction. The effects of orlistat versus sibutramine in obese type 2 diabetic patients should be verified in direct comparative clinical trials, and the specific effects of each drug, especially on insulin sensitivity, deserve further studies before drawing any definite conclusion.

Finally, neither orlistat, nor sibutramine is able to induce large weight reduction in a majority of obese patients. As the two compounds act via different mechanisms, one may speculate that their combination could increase overall weight loss. In a pilot study designed to assess whether adding orlistat to sibutramine would induce further weight loss in non-diabetic obese patients who previously had lost weight while taking sibutramine alone (– 11.6 % of initial body weight after 1 year), no additive effects was observed after 16 weeks of combined therapy with orlistat [88]. To our knowledge such combination trial has never been performed in obese patients with type 2 diabetes.

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NEW LANDMARK PROSPECTIVE CLINICAL TRIALS

Both orlistat and sibutramine have demonstrated their potential role as adjunct therapy in the treatment of obese type 2 diabetic patients. However, while some clinical trials in non-diabetic obese individuals lasted up to two years, the maximum follow-up of obese patients with type 2 diabetes was one year only. Considering type 2 diabetes as a chronic disease, long-term clinical trials should be recommended as they would allow to analyse clinical outcomes and overall prognosis rather than surrogate endpoints such as body weight and biological parameters. In addition, while the number of obese diabetic patients entering the previous placebo-controlled clinical trials with orlistat was already substantial (Table III), it was rather limited when clinical studies with sibutramine are considered (Table II). Thus, there is an urgent need for large long-term prospective controlled studies with each of this

anti-obesity agent both in the prevention and treatment of type 2 diabetes in overweight/obese individuals.

Orlistat has already demonstrated its potential to prevent the progression from impaired glucose tolerance to overt type 2 diabetes [61] [67]. A new study has been recently performed in Sweden, the XENDOS (XENical in the prevention of Diabetes in Obese Subjects) trial. XENDOS was a randomised, double-blind, placebo-controlled, prospective, multicentre trial investigating whether orlistat 120 mg tid combined with hypocaloric diet and moderate physical exercise can reduce the incidence of type 2 diabetes in obese subjects over a period of 4 years [89]. The study also evaluated a number of secondary parameters such as weight loss, risk factors, safety and tolerability. This study enrolled 3,304 obese patients (BMI ≥ 30 kg/m²) with a range of age between 30 and 60 years, and a relative priority given to men (45 % of the study population), in order to increase the risk of development of diabetes. In contrast to previous study [90], subjects were not specifically selected because they had impaired glucose tolerance (only 21 % of enrolled subjects) at baseline. The final results of this landmark study were recently presented by L. Sjöström at the 9th International Congress on Obesity. Weight loss was greater in the orlistat group (– 6.9 kg; n = 1 640) than in the placebo group (– 4.1 kg; n = 1 637; p < 0.001). Such a difference in weight reduction was sufficient to significantly reduce the cumulative incidence of type 2 diabetes (6.2% versus 9.0%; p = 0.0032; relative risk reduction of 37.3%). The difference was especially remarkable in obese patients with impaired glucose tolerance, with a reduction of conversion to diabetes from 28.8% in the placebo group to 18.8% in the orlistat group (p < 0.005) and a number needed to treat to avoid one event of 11 only. Significant and sustained reductions in cardiovascular risk factors such as arterial blood pressure and lipid levels were also observed in the orlistat group as compared to the placebo group. XENDOS is the first study demonstrating that an antiobesity agent, like orlistat, is able to reduce the progression to diabetes in obese subjects as compared with lifestyle changes alone [91].

As already mentioned, sibutramine may have contrasting effects on the cardiovascular risk profile as it promotes weight loss, improves blood glucose control and lipids parameters, at least in good responders who lose at least 10% of initial body weight, whereas it tends to slightly increase heart rate and arterial blood pressure, two independent cardiovascular risk factors [40]. Consequently, the European Agency for the Evaluation of Medicinal Products (EMA) requested a large long-term prospective study to demonstrate the benefit of sibutramine treatment in obese patients, especially in those at high risk of cardiovascular complications. A randomised control trial, the “Sibutramine Cardiovascular and Diabetes Outcome Study”, has been planned to demonstrate the long-term health benefits of weight management with sibutramine plus lifestyle interventions (diet and exercise). This multinational study will recruit above 10,000 overweight/obese patients with high cardiovascular risk. Patients will be males or females, ≥ 55 years old, with a BMI ≥ 27 kg/m² or a BMI ≥ 25 kg/m² plus an increased waist circumference (> 102 cm in males and > 88 cm in females). High cardiovascular risk will be assessed by the presence of coronary, cerebral and/or peripheral arteriopathy as well as by the presence of impaired glucose tolerance or type 2 diabetes plus at least one other classical vascular risk factor. Patients with uncontrolled arterial hypertension will be excluded from the recruitment. It has been planned that half of the patients entering into the study will have type 2 diabetes mellitus, i.e. above 5,000 diabetic individuals. Lifestyle interventions and sibutramine or placebo will be given for an average of 4 years. Primary outcomes will be cardiovascular morbidity/mortality and progression to type 2 diabetes mellitus. This landmark study will combine the principles and practices of large cardiovascular outcome studies with those of obesity studies. It will attempt

to answer the two fundamental questions of whether long-term weight loss and weight maintenance result in health benefits and whether adding sibutramine to lifestyle intervention is able to delay or prevent type 2 diabetes and to improve cardiovascular prognosis in obese type 2 diabetic patients.

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CONCLUSIONS

Control of body weight appears to be crucial for both the prevention and the treatment of type 2 diabetes mellitus. Weight loss is a major target in treating obese patients with type 2 diabetes as it allows to improve both glycaemic control and various associated vascular risk factors. Lifestyle modifications should be used first in all cases. Recently available anti-obesity drugs, such as sibutramine and orlistat, can be used as an adjunctive therapy to diet since the additional weight loss, even modest on average, was able to improve blood glucose control and other risk factors. Beneficial effects essentially appear in individuals considered as good responders, i.e. reaching a weight loss above 10% of initial body weight with diet plus active drug, as compared to placebo. These two drugs may contribute to delay the progression from impaired glucose tolerance to type 2 diabetes in obese individuals, especially orlistat as recently demonstrated in the XENDOS trial. However, even if targeting weight excess rather than hyperglycaemia per se may be a valuable alternative in selected obese diabetic patients, long-term prospective studies are required to more precisely determine the place of each strategy in the overall management of patients with both obesity and type 2 diabetes. The results of the future "Sibutramine Cardiovascular and Diabetes Outcome Study" will certainly provide crucial information on the potential role of pharmacologically-induced weight reduction with long-term sibutramine treatment on the cardiovascular prognosis of obese type 2 diabetic patients.

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