The effects of orlistat on metabolic parameters and other cardiovascular risk factors

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SUMMARY
Orlistat is an antiobesity drug with a well documented efficacy in weight reduction and weight maintenance. Weight reduction with orlistat has been associated with a favourable effect on obesity-related cardiovascular risk factors. Orlistat treatment is associated with a reduction in serum insulin levels. Moreover, orlistat reduces the incidence of type 2 diabetes in patients with impaired glucose tolerance and lowers the required dose of metformin, sulfonylureas and insulin in patients with type 2 diabetes. Furthermore, orlistat can reduce total and low density lipoprotein (LDL) cholesterol levels and improve postprandial triglyceridemia, as well as the low density lipoprotein cholesterol / high density lipoprotein cholesterol ratio (LDL/HDL ratio). Moreover, orlistat appears to have a favourable effect on some inflammatory markers, such as TNF-α and interleukin-6 and has a time-depended effect on some haemostatic factors.

Key-words: Orlistat · Weight loss · Cholesterol · Metabolic parameters · Insulin · Diabetes.

Résumé
Les effets de l’orlistat sur les paramètres métaboliques et d’autres facteurs de risque cardiovasculaire
L’orlistat est une molécule antiobésité qui possède un effet bien documenté sur la réduction du poids et le maintien du poids. La réduction du poids avec l’orlistat est associée à un effet favorable sur les facteurs de risque cardiovasculaire liés à l’obésité. Le traitement par orlistat est associé à une réduction de l’insulinémie. En outre, l’orlistat réduit l’incidence de diabète de type 2 chez les patients intolérants au glucose et diminue les besoins en metformine, sulfonylurées et insuline chez les diabétiques de type 2. De plus, l’orlistat peut diminuer le cholestérol total et le cholestérol-LDL, et améliorer la triglycéridémie post-prandiale, ainsi que le rapport LDL/HDL. En outre, l’orlistat apparaît avoir un effet favorable sur certains marqueurs de l’inflammation, comme le TNF-α et l’interleukine-6 et a un effet temps-dépendant sur certains facteurs de l’hémostase.

Mots-clés : Orlistat · Perte de poids · Cholestérol · Paramètres métaboliques · Insuline · Diabète.

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Orlistat (Xenical) is a potent and specific inhibitor of intestinal lipases. In healthy volunteers, it achieved a 46.6% to 91.4% gastric lipase inhibition and a 51.2% to 81.6% pancreatic lipase inhibition [1] and had little or no activity against amylase, trypsin, chymotrypsin and phospholipases [2]. The intestinal lipases are responsible for the breakdown of dietary triglycerides into fatty acids and monoglycerides, which are then absorbed by mucosal cells. Inhibition of lipase activity with orlistat reduced fat absorption by approximately 30%, the nonabsorbed triglycerides being excreted in the faeces [2].

Orlistat works within the gut and is minimally absorbed into the systemic circulation [3]. Therefore, no systemic adverse effects have been attributed to orlistat. A meta-analysis [4] of studies in obese patients receiving orlistat 120 mg three times a day (TID) (2,038 patients) showed an increase of mild to moderate adverse gastrointestinal effects compared with placebo (1,740 patients). These effects generally decreased after 12 weeks of therapy, possibly due to dietary modification. Gastrointestinal side-effects may increase when orlistat is taken with a diet high in fat (>30% total daily calories from fat) or if the recommended daily fat intake is not distributed over three meals [5]. Absorption of fat soluble vitamins may be decreased by orlistat. During 2-year clinical studies [6, 7], plasma concentrations of fat soluble vitamins (A, D, E and beta-carotene) decreased among subjects taking orlistat but generally remained within the clinical reference range. In XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study [8] there were statistically significant decreases in the orlistat group compared with the placebo group after 4 years of treatment for all assessed fat-soluble vitamins, with the exception of 1,25-hydroxyvitamin D, but the mean level of each assessed vitamin remained well within its reference range at all times during the 4-year study for both the orlistat and placebo groups. In a short-term study [9] orlistat did not result in any change in warfarin pharmacokinetics or pharmacodynamics. However, because of a potential decrease in vitamin K absorption, patients stabilised on warfarin should be closely monitored for changes in coagulation parameters. In XENDOS study [8], in which 3,305 patients were included, the average compliance with study drug administration from first dose until treatment termination was 93.3% for orlistat patients and 92.8% for placebo patients (P = not significant). Overall, 4% of placebo patients and 8% of orlistat patients withdrew from the study because of adverse events or laboratory abnormalities. This difference was primarily due to gastrointestinal events.

The purpose of this study was to review the effects of orlistat treatment on lipid and metabolic parameters.

**Efficacy in weight reduction and maintenance**

The efficacy of orlistat in body weight reduction in obese patients has been demonstrated in two large (1,187 and 743 patients, respectively), multicenter, randomized, double-blind, 2-year studies [6, 7]. In the first study, during a 4-week placebo lead-in period patients lost approximately 2.3% of their initial body weight and then randomized to receive orlistat 120 mg three times a day (TID) or placebo. At the end of the first treatment year, patients adhering to a hypocaloric diet and receiving orlistat 120 mg TID lost more weight than those receiving placebo (8.8% vs 5.8% of body weight, respectively; p < 0.001). During the second year, the weight regain in patients who were treated with orlistat 120 mg during the first year and continued to receive standard-dose of orlistat (120 mg TID) was significantly less (3.2 kg, 35.2% regain) than in those who received a low-dose regimen of orlistat 60 mg TID (4.3 kg, 51% regain) or placebo (5.6 kg, 63.4% regain) [7]. Furthermore, treatment with orlistat 120 mg for 2 years produced a 7.6% weight loss from initial body weight. In contrast, subjects who received placebo for the full two years lost 4.5% of initial body weight. In the second study [6], patients randomly reassigned to receive orlistat after 1 year had only half the weight regain of those who were reassigned to placebo (p < 0.001). Those patients who had been receiving placebo and were switched to orlistat lost 0.9 kg compared with an average regain of 2.5 kg in those who continued to receive placebo (p < 0.001). Another randomized trial has shown orlistat to have similar efficacy in weight reduction and maintenance in the primary care setting [10].

**Effects on carbohydrate metabolism (Tab I)**

In the study of Davidson et al. [7], after 2 years of treatment following a 4-week placebo lead-in period, patients receiving orlistat had significantly lower plasma insulin levels, while these levels remained unchanged in the placebo group (84.02 to 64.52 pmol/L, and 86.37 to 86.32 pmol/L, respectively, p = 0.04 between treatment groups). In this study the group receiving orlistat had a lower increase in fasting serum glucose levels (+0.06 mmol/L) than patients receiving placebo for 2 years (+0.26 mmol/L, P = 0.001 between treatment groups). The minimal increase in glucose levels was probably due to the observed at the end of the second year weight regain (+35% of the first year weight loss in the orlistat group, +45% in the placebo group). Moreover, at the end of another 2-year placebo-controlled study [6], orlistat in combination with diet also resulted in significantly greater improvements in levels of fasting serum insulin and glucose after 1 and 2 years than treatment by dietary intervention alone.
Recently the XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study was published [8]. This was a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in 3,305 obese patients, which concluded that compared with lifestyle changes alone orlistat plus lifestyle changes produced greater weight loss (5.8% vs 3 kg with placebo; p < 0.001) and resulted in a greater reduction in the incidence of type 2 diabetes over 4 years (-9% vs -6.2%). In this study the difference in diabetes incidence was detectable only in the impaired glucose tolerance (IGT) subgroup, but there was a significant reduction in fasting insulin levels at the end of year 1 and year 4 in the study population (both p < 0.001 between treatment groups). Also, another study group [11] reported that in patients with impaired glucose tolerance a 2-year treatment with orlistat led to a normalization of glucose levels in a higher proportion of patients compared with placebo (71.6% vs 49.1%; p = 0.04) and reduced the rate of progression to diabetes (3.0% vs 7.6%; p = 0.04). All these studies suggest that orlistat treatment has a more favourable effect than placebo on fasting insulin and glucose levels.

A 6-month orlistat use without a concomitant hypocaloric diet in a group of severely obese young Chinese patients with type 2 diabetes mellitus [12] reduced both glycosylated haemoglobin level (-11.6%) and fasting plasma glucose levels (-18.2%). In another study [13], patients with type 2 diabetes at the end of 1-year orlistat treatment showed significant improvement in glycaemic control, with lower glycosylated haemoglobin (HbA1c) and glucose levels; in addition, they required significantly lower doses of oral sulfonylureas than did the placebo group (-23 vs -9%, p < 0.01). Similarly, in the 1-year study of Miles et al. [14] orlistat caused a greater improvement in glycaemic control than placebo, as evidenced by a greater reduction in serum HbA1c, adjusted for changes in metformin and sulfonylurea therapy (-0.9 vs -0.6, p = 0.014) and a greater reduction in fasting serum glucose (-2.0 vs -0.7 mmol/L, p = 0.001). Compared with placebo treatment, orlistat therapy was associated with reductions in both daily metformin dose (-16 vs +49 mg/day, p = 0.013) and relative sulfonylurea dose, expressed as percent change, with doses standardized to a percentage of maximum daily dose (-11.5 vs -0.9%, p = 0.027). Moreover, twice as many patients in the orlistat than in the placebo group either reduced or discontinued one or more diabetes medications (17.1 vs 8.2%). Conversely, more placebo- than orlistat-treated patients required additional or increased dosages of diabetes medication (21.7 vs 12.2%). These changes in diabetes medication usage were significantly different between treatment groups (p = 0.0004). Finally, Kelley et al. [15] reported that, after 1 year of treatment, a greater reduction in insulin dose was associated with orlistat than with placebo treatment (-8.1 vs -1.6 units/day, p = 0.007). Moreover, a greater proportion of patients achieved 5% reduction of insulin dose in the orlistat treatment group compared with placebo (41 vs 31%, p < 0.001), whereas fewer patients in the orlistat than the placebo group increased their insulin dose by 5% (12 vs 26%, p < 0.001).

### Table I

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effect vs placebo</th>
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<tbody>
<tr>
<td>Fasting insulin</td>
<td>-5% vs +19.1% ([Sjostrom et al., 1998 [6], N = 688, 2 years following a 4-week placebo lead-in period, obese patients])</td>
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<tr>
<td>&lt;21% vs -0.06% ([Davidson et al., 1999 [7], N = 892, 2 years following a 4-week placebo lead-in period, obese patients])</td>
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<tr>
<td>&lt;37.1% vs -24.6% ([Torgerson et al., 2004 [8], N = 3,305, 4 years, obese patients])</td>
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<tr>
<td>Fasting glucose</td>
<td>-0.9% vs +2.33% ([Sjostrom et al., 1998 [6], N = 688, 2 years following a 4-week placebo lead-in period, obese patients])</td>
</tr>
<tr>
<td>+0.06 mmol/L vs +0.26 mmol/L ([Davidson et al., 1999 [7], N = 892, 2 years following a 4-week placebo lead-in period, obese patients])</td>
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<tr>
<td>+0.02 vs +0.54 mmol/L ([Hollander, 1998 [13], N = 391, 1 year following a 5-week placebo lead-in period, obese diabetic patients])</td>
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<tr>
<td>-17.2% vs -6.3% ([Miles, 2002 [14], N = 503, 1 year, overweight and obese diabetic patients])</td>
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<tr>
<td>HbA1c</td>
<td>-11% vs -3.6% ([Tong et al., 2002 [12], N = 60, 6 months, obese diabetic patients])</td>
</tr>
<tr>
<td>&lt;10.1% vs -6.9% ([Miles, 2002 [14], N = 503, 1 year, overweight and obese diabetic patients])</td>
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**Effects on chylomicrons, free fatty acids, lipoprotein remnants and triglycerides**

Tan et al. [16] evaluated the acute effect of a single dose of 120 mg orlistat on postprandial lipids, lipoprotein remnants and free fatty acids (FFA) in 63 overweight patients with type 2 diabetes mellitus. The concentrations of plasma triglycerides (TG), remnant like particles-cholesterol (RLP-C) and FFA were significantly lower at 2 h after orlistat compared with placebo. Both plasma RLP-C and FFA remained lower after orlistat than placebo at 4 h. They concluded that orlistat had a beneficial effect on postprandial lipaemia in overweight type 2 diabetic patients. Reitsma et al. [17] studied the effect of orlistat on fasting plasma lipid levels and postprandial lipoproteins in

17 hyperlipidaemic subjects, using an oral retinyl palmitate (RP) fat load (8 hours, 50 g fat/m²). The postprandial plasma triglyceridemia, which was expressed as the area under the 8-hour triglyceride curve, improved by 27% during orlistat therapy without changes in fasting plasma TG or high-density lipoprotein (HDL) cholesterol levels. The improved postprandial triglyceridemia was accompanied by a 19% reduction in circulating levels of chylomicrons and chylomicron remnants, determined by the decreased areas under the 8-hour RP curves. The most likely mechanisms involved are decreased formation of chylomicrons by a decrease in intestinal TG absorption as a consequence of orlistat treatment as well as reduced delivery of dietary lipid and fatty acids to the liver and subsequent upregulation of hepatic LDL receptors. In agreement with the latter mechanism, the decrease in postprandial lipaemia was significantly related to the decrease in LDL cholesterol level during orlistat treatment. A study [18] comparing the effects of orlistat on postprandial triglyceridemia between BMI-matched Chinese and Caucasian subjects showed no significant interethnic differences. Finally, Tzotzas et al. [19] showed that a short-term use of orlistat in a patient with familial hyperchylomicronemia who was unable to comply with a low-fat diet decreased fasting triglycerides levels by approximately 35%, while the drug was well tolerated.

Orlistat in most trials reduced serum triglycerides. In one trial [20] triglycerides were significantly reduced (-17.4% vs baseline) after a 6-month treatment with orlistat in 50 obese female patients. Another study group [21] reported a 36% reduction in triglycerides (p < 0.01 vs baseline) after a 6-month orlistat use in 27 overweight women with mild hypercholesterolemia (total cholesterol 225 mg/dl; low-density lipoprotein cholesterol 162 mg/dl). Moreover, in the study of Derosa et al. [22] there was a 26.5% reduction in triglycerides after 1 year of orlistat treatment in obese patients with hypercholesterolemia (mean total cholesterol ² 240 mg/dl). It is important to mention that it has not been clarified if orlistat reduces triglycerides to a greater extent compared with placebo. In the 1-year study of Hollander et al. [13] triglycerides were significantly reduced compared with placebo (10% difference between orlistat and placebo groups, p = 0.036) in obese diabetic patients. On the other hand, at the end of the 2-year studies of Davidson [7] and Sjostrom [6], there was an improvement in triglyceride levels, but the reduction in triglycerides was not statistically significant between the orlistat and placebo groups. The lack of significant difference between the orlistat and placebo groups observed in most trials could not be attributed to a lack of statistical power as most of these studies included large number of patients. The most probable explanation might be the relatively small differences in weight loss between the two groups. Interestingly, the results of Lucas et al. [23] indicated that orlistat-assisted weight loss led to a significantly greater decrease in plasma triglyceride concentractions in patients with type IIB compared with those with type IA dyslipidemia.

The combination of gemfibrozil and orlistat [24] was extremely effective in reducing serum triglyceride levels in a patient with combined hyperlipidemia and predominant hypertriglyceridemia, whereas both of these agents, when used alone, were ineffective. Wierzbicki et al. [25] studied the effect of orlistat in five patients with severe hypertriglyceridemia and concluded that the addition of orlistat to fibrate — statin combination therapy resulted in a further 35% reduction in triglycerides in patients with type V hyperlipidemia.

**Effects on total and low-density lipoprotein (LDL) cholesterol (Tab II)**

Weight reduction with orlistat is associated with favourable effects on total and LDL cholesterol. Lindgarde et al. [26] assessed the effects of orlistat on cardiovascular risk among obese patients at high coronary risk. After 1 year, orlistat was associated with greater improvements than placebo in total serum cholesterol (-3.3% vs -0.5%; p < 0.05) and LDL-cholesterol (-7.0% vs -1.1%; p < 0.05). Another study group [27] also assessed the efficacy of orlistat therapy for cardiovascular risk factor reduction in obese patients with high cardiovascular risk. Orlistat was associated with greater improvements than placebo in total cholesterol (-1.31% vs +3.78%; p < 0.0001) and LDL-cholesterol (-7.09% vs -0.55%; p < 0.0001).

Hill et al. [28] evaluated the long-term effects of orlistat on obesity-related cardiovascular disease risk factors. After a 6-month lead-in weight-loss period, total cholesterol and LDL-cholesterol concentrations decreased by 5-8% in all groups. However, at the end of the sequential 1-year treatment period, reductions in total and LDL-cholesterol concentrations from initial values were significantly greater in the 120-mg orlistat group than in the placebo group (-7.99% vs -3.89% and -7.01% vs -3.67%, respectively). Reductions in both total and LDL-cholesterol concentrations were also significantly greater after treatment with 30 and 60 mg orlistat than after treatment with placebo. Furthermore, both total and LDL-cholesterol concentrations increased in the placebo group over the sequential 1-year treatment but decreased further over this time period in the 120-mg orlistat group.

Bakris et al. [29] investigated the effect of weight reduction with orlistat plus mild caloric restriction on cardiovascular risk factors in obese individuals with inadequately controlled hypertension. They concluded that a weight-loss program with orlistat is more effective than diet alone to lower blood pressure and resulted in a tenfold greater reduction in total (-6.2% vs -0.6%, p < 0.01) and a threefold greater reduction in LDL cholesterol (-8.6% vs -2.8%, p = 0.01).
The effects of orlistat treatment in obese patients with hypercholesterolemia have been evaluated by many study groups. In obese patients with hypercholesterolemia [30], 6 months of orlistat treatment was associated with greater reductions compared with placebo in total cholesterol (-11.9% vs -4.0%, p < 0.001) and low-density lipoprotein cholesterol (-17.6% vs -7.6%, p < 0.001). Lucas et al. [23] reported a 12.8% reduction of total and a 16.8% reduction in LDL cholesterol after 1-year orlistat use in obese individuals with elevated LDL cholesterol. Similar results have been published by Micic et al. [31].

Interestingly, Muls et al. [30] reported that for comparable degree of weight loss, the decrease in LDL cholesterol was greater in the orlistat group than the placebo group, suggesting that orlistat had a direct cholesterol-lowering effect which was independent of weight reduction (p < 0.001). Moreover, in three other large trials [6, 7, 13] the impact of orlistat on total and LDL cholesterol was independent of the magnitude of weight loss and was greater in orlistat treated compared with placebo-treated patients in every category of weight loss. This independent pharmacologic lipid-lowering effect of orlistat is probably related to drug-induced reduction in the absorption of dietary fat. The findings of Mittendorfer et al. [32], who concluded that orlistat inhibits cholesterol absorption, give another possible explanation of the independent lipid-lowering effect of orlistat.

Several studies showed that the metabolic syndrome has been associated with increased cardiovascular risk [33-35]. In one study [36] orlistat treatment reduced LDL (-7.1%) cholesterol in patients with metabolic syndrome. Similar results were recently published by Bray et al. [37].

Orlistat use has favourable effects on diabetic dyslipidaemia. In diabetic patients treated with oral sulfonylureas [13] there was a significant reduction in both total and LDL cholesterol (9.1% and 12.8% difference between orlistat and placebo groups, respectively). Miles et al. [14] reported that 1-year treatment with orlistat was associated with significantly greater improvements in total and LDL cholesterol compared with placebo (-4.1% vs +2.6% and -2.8% vs +3.9%, respectively) in overweight and obese patients with type 2 diabetes treated with metformin. Another study group [15] reported a 4.7% and a 9% reduction in total and LDL cholesterol respectively after 1-year treatment in overweight and obese patients with insulin-treated type 2 diabetes.

Finally, the orlistat — fluvastatin, orlistat — simvastatin and orlistat — cerivastatin combination appeared to have additive effects on lipid profile of obese patients with hypercholesterolemia. In the studies of Derosa et al. [22, 38, 39] total and LDL cholesterol (~33% and ~41% reduction in combination groups, respectively) were lower in the combination groups than orlistat, fluvastatin, simvas-tatin and cerivastatin alone.

### Effects on HDL and LDL/HDL ratio (Tab II)

Orlistat treatment has moderate effect on HDL cholesterol. The results of randomized placebo-controlled trials are controversial and seem to be influenced by the duration of orlistat treatment. Halpern et al. [40] reported a 1.8% reduction in HDL plasma concentrations after 6 months of orlistat use in obese, non-insulin dependent diabetic patients. On the other hand, Hanefeld et al. [41] reported a
0.6% increase of HDL plasma concentrations after 1 year of orlistat use in overweight patients with type 2 diabetes. In a 2-year study [42], there was a gradual and progressive increase in HDL cholesterol in year 1 in all treatment groups, which continued to increase during the second year of treatment, but statistical significance was only achieved at the end of year 1 in the orlistat 120 mg group. Interestingly, in the study of Lucas et al. [23], HDL cholesterol decreased with weight loss in orlistat treated patients with type IIA dyslipidaemia (-2.7 mg/dl), whereas it actually increased in subjects with type IIB dyslipidaemia (+1.5 mg/dl). This difference in response was statistically significant.

The LDL/HDL ratio improves with orlistat use. Rossner et al. [42] reported a 15.1% reduction of LDL/HDL ratio after 1 year of orlistat use combined with a hypocaloric diet and an 8% reduction at the end of the second year of orlistat use combined with a weight maintenance diet to prevent weight regain (both p < 0.002). Similarly, Sjostrom et al. [6] reported an 8.6% reduction in the ratio after the first year of orlistat use in conjunction with the hypocaloric diet (p < 0.0007 vs placebo group) and a 12.7% reduction at the end of the second year of orlistat use combined with a eucaloric diet (p < 0.0007 vs placebo group). Orlistat use in diabetic patients also led in a reduction of this ratio. Kelley et al. [15] reported a 10.1% reduction of LDL/HDL ratio after 1 year of orlistat use (p = 0.01 vs placebo group) in overweight or obese insulin-treated type 2 diabetic patients.

**Effects on apolipoproteins**

Apolipoprotein B (apoB) levels decreased in most trials in parallel with the decreases in LDL cholesterol concentrations. Gokcel et al. [20] reported an 8.4% reduction in apolipoprotein B levels after a 6 month orlistat treatment in obese female patients. A reduction (-43.7 mg/l) in apolipoprotein B levels after orlistat use for 1 year in diabetic patients was also reported by Hollander et al. [13], while there was an increase (+75.4 mg/l) in the placebo group (p < 0.01 between orlistat and placebo groups, II).

Orlistat-induced changes in apolipoprotein A1 levels seem to be influenced by the duration of orlistat treatment. Tonstad et al. [43] reported a 9.6% decrease with orlistat use (360 mg/day) for 8 weeks, while Gokcel et al. [20] reported no change (+1.2%) after a 6-month orlistat treatment (not statistically significant vs placebo).

Weight loss has a favourable effect on lipoprotein (a) [Lp(a)] levels [44, 45]. Interestingly, Muls et al. [46] and Kiortsis et al. [47] reported that a short-term weight loss in obese patients resulted in a decrease in Lp(a) levels only in individuals with pre-treatment Lp(a) above 30 mg/dl and 20 mg/dl respectively. There are few data about orlistat effects on Lp(a) levels. Gokcel et al. [20] reported a 7.1% reduction in Lp(a) levels after a 6-month orlistat treatment. In the study of Rossner et al. [42] the decrease in Lp(a) levels at the end of 1 and 2 years was significantly greater in orlistat treated (120 TID) than in placebo treated patients (p = 0.011 and p < 0.001, respectively).

**Effects on other metabolic parameters**

Obese subjects tend to have higher values of fibrinogen, factor VII, factor VIII, von Willebrand factor and plasminogen activator inhibitor compared to non-obese subjects [48]. Gallistl et al. [49] determined fibrinogen levels, factor VII coagulant activity, von Willebrand factor antigen and soluble P-selectin levels before and after a 3 week programme including energy restriction and physical activity. All haemostatic risk factors measured decreased significantly during the programme and, indeed, changes in risk factors were correlated to changes in body composition. Children and adolescents with the highest initial concentrations showed the greatest decreases. Rissansen et al. [50] evaluated the effect of weight loss and subsequent weight maintenance or weight regain on the activities of plasminogen activator inhibitor 1 (PAI-1) and the concentration of fibrinogen over 12 months in obese women consuming a hypenergetic, low-fat diet with or without orlistat. The changes in body weight between orlistat and placebo groups were not significantly different and orlistat did not influence haemostatic factors beyond its effect on weight loss. Therefore, the results of the orlistat and placebo groups were pooled. No changes in the mean plasma fibrinogen concentrations were observed at any time during the trial. During the first 3 months, the activity of PAI-1 decreased. The decline depended on the magnitude of weight loss. Between months 6 and 12 the changes of PAI-1 activity paralleled the changes of body weight. The activity rose with weight rebound but remained below the 6-month values if weight loss was sustained or continued. On the other hand, in a large 4-year study [8] PAI-1 levels of obese patients with or without IGT were significantly reduced at the end of year 1 and 4 in orlistat group compared with the placebo group (both p < 0.01). Interestingly, fibrinogen levels were significantly lower in the orlistat group at the end of the fourth year compared with placebo group (p < 0.05). In this trial there was not a significant change in fibrinogen levels at the end of the first year between orlistat and placebo groups, suggesting a time-dependent orlistat effect on fibrinogen levels (Tab III).

Audikovszky et al. [51] examined in a six-month study how the orlistat treatment affected the paraoxonase activity. The serum paraoxonase activity significantly increased along with the standardised values for HDL, PON/HDL, even compared to the control diet group. From the above results it may be concluded that orlistat tends to have an antioxidiant effect.

Obesity is associated with increased levels of inflammatory mediators [52, 53]. Samuelsson et al. [54] evaluated the changes in the leukocyte derived inflammatory mediators,
Table III
Orlistat effects on haemostatic parameters.

<table>
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<tr>
<th>Parameter</th>
<th>Effect vs placebo</th>
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<tbody>
<tr>
<td>Fibrinogen*</td>
<td>No changes (Rissanen et al. [50], 2001, N = 51, 1 year, obese women) -3.4% vs -4.2% (Torgerson et al. [8], 2004, N = 3305, 4 years, obese patients)</td>
</tr>
<tr>
<td>PAI-1</td>
<td>-13% vs +0.43% (Torgerson et al. [8], 2004, N = 3305, 4 years, obese patients)</td>
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*Time-depended effect.

tumour necrosis factor alpha (TNF-alpha) and interleukin 6 (IL-6), during BMI lowering with orlistat before and after 1 year of treatment with orlistat or placebo. Weight reduction was associated with decreased levels of TNF-alpha and IL-6 in both orlistat and placebo groups. After 12 months, TNF-alpha was lower in the orlistat compared with the placebo group. Whether these results translate into reduced incidence of cardiovascular disease remains to be elucidated.

Orlistat effect on uric acid levels has not been studied in randomized placebo-controlled trials. One study group [20] reported an 8.1% reduction in uric acid levels after a 6-month orlistat treatment (p < 0.0002 vs baseline).

Pace et al. [55] assessed the orlistat effect on the physiologic balance of three macrominerals (calcium, phosphorus and magnesium) and three microminerals (iron, zinc and copper). This was a 21-day, double-blind, randomized, parallel-group, placebo-controlled mineral balance study conducted in adolescent obese volunteers. The dietary fat inhibition by orlistat caused no significant changes in mineral balance between orlistat and placebo groups. Zhi et al. [56] reported the same result two years later.

Conclusions

Orlistat is an antiobesity drug with a well documented efficacy in weight reduction. It has also favourable effects in a considerable number of cardiovascular risk factors. It reduces the incidence of type 2 diabetes in patients with IGT and lowers the required dose of oral antidiabetic drugs and insulin in patients with type 2 diabetes. Orlistat can reduce total and LDL cholesterol levels and improve the postprandial triglyceridemia, as well as the LDL/HDL ratio. Also, it seems to have a favourable effect on some inflammatory markers, such as TNF-a and IL-6, and has time-depended effects on some haemostatic factors. Although orlistat improves most of the obesity-associated cardiovascular risk factors, further studies are needed in order to assess its impact on cardiovascular morbidity and mortality. Furthermore, it must be emphasized that the long term benefits of orlistat in terms of weight reduction are modest.

References


