Effects of 1-year Orlistat treatment compared to placebo on insulin resistance parameters in patients with type 2 diabetes

BACKGROUND:

- Overweight and obesity are conditions that substantially raise the risk of morbidity from many different disease and certain cancers.
- Intensive programs aimed at reducing calorie intake and increasing physical activity has been shown to improve metabolic control in obese diabetic patients. However, the behavioral approach is usually slow and not always sufficient to reach the optimal targets of weight and metabolic control in such patients, and a pharmacological treatment is often necessary.

OBJECTIVE

- To evaluate the effects of 1-year treatment with Orlistat compared to placebo on body weight, glycemic control, insulin resistance parameters, and on inflammatory parameters in type 2 diabetic obese patients treated with different oral hypoglycemic agents or insulin.

METHODS

- **Design**: multicentre, randomized, double-blinded, parallel, placebo controlled study.
- **Duration:** 12 months

1. **Inclusion criteria**: Caucasians with type 2 diabetes, aged greater than 18, either male or female, obese with a BMI of greater tan 30 kg/m^2, had uncontrolled type 2 diabetes mellitus with an A_{1C} greater than 8%, and were on therapy with different oral hypoglycemic agents or insulin.
2. **Exclusion criteria**: history of ketoacidosis, had unstable or rapidly progressive diabetic retinopathy, nephropaty or neuropathy, had impaired hepatic function, impaired renal function, severe anemia, serious cardiovascular disease, cerebrovascular conditions within 6 months prior to study enrolment, had GI disorders, abdominal surgery within 6 months of study enrolment, were women who were pregnant or breastfeeding, or women of child-bearing potential not taking adequate contraceptive precautions.

- **Primary outcome measure**: weight, BMI, waist circumference, A_{1C}, fasting plasma glucose, post-prandial plasma glucose, fasting plasma insulin, the homeostasis model assessment insulin resistance index, retinol-binding protein-4, resistin, visfatin, high-sensitivity C-reactive protein.
- **Secondary outcome measures**: Secondary outcome measures were total cholesterol, LDL, HDL, and triglycerides
- 254 patients (126 in Orlistat group and 128 in control group) received either
    - Orlistat 60 mg TID with meals+ diet and exercise counseling
      OR
    - Placebo TID + diet and exercise counseling
- Power 80% with an alpha level of 0.05 to detect a 10% difference in the percentage change between the 2 groups. This was calculated to be sufficient for group sizes.
- Data handling method was intent-to-treat

RESULTS

- 113 patients in the Orlistat group and 121 patients in the control group completed the study
- **Primary outcome measure**: Of the primary outcomes, only weight and BMI showed that orlistat was possibly superior to diet and exercise (p.0.5). All other primary outcome measures showed that there was no significant difference between orlistat and diet and exercise alone.

1. **Secondary outcome measures**: No variations of lipid profile were recorded in the control group, whereas an improvement of TC and LDL-C was observed with orlistat vs baseline ($p<0.02$). Versus placebo orlistat also had lower TC and LDL-C values ($p<0.05$). Orlistat improve Tg ($p<0.05$) but there was no significant difference between orlistat and placebo.

2. **Author's conclusion:** orlistat improved lipid profile and led to faster glycemic control and insulin resistance parameters than the control, without any serious adverse events. They also concluded that orlistat improved RBP-4 and visfatin, which were effects not seen with placebo.

STRENGTHS

- Study duration was of a sufficient amount of time
- Inclusion and exclusion criteria allowed for extrapolation to the population of interest
- Controlled study
- Orlistat dosed appropriately

LIMITATIONS

- No data provided to account for adherence to diet, exercise, and medication regimen.
- No data provided to account for adverse effects.
- Limited number of insulin resistance biomarkers
- Lack of data regarding sustained effects after cessation of study
- No determination whether unblinding was possible
- Did not explain randomization fully
- Patients were on many different anti-diabetic therapies and changes in therapy during the 12 months of the study were not accounted for.

CONCLUSION

- On the outside this study seems strong; however, there are definitely some major flaws: lack of information regarding funding and medication acquisition, lack of data showing compliance to diet, exercise, and medication, failure to include number of adverse effects, and whether unblinding was an issue or not, all give me pause when deciding to fully trust this data or not. These reasons paired with the limitations the researchers provided, including not evaluating whether the beneficial effects on glycemic control, body weight, lipid profile and insulin resistance parameters were sustained after the cessation of therapy, lead me to believe that currently Orlistat should have an extremely limited to no place in therapy. further reputable research undoubtedly shows Orlistat as being superior to diet and exercise, we should stick to the old fashioned methods of weight loss, less calories in and more calories expended

Reference: Derosa, G., A. Cicero, et al. "Effects of 1-year Orlistat treatment compared to placebo on insulin resistance parameters in patients with type 2 diabetes." *Journal of Clinical Pharmacy and Therapeutics*. 37. (2012): 187-195. Print.

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