

# Comparison of Lipid Lowering Effect of Sibutramine in Patients Treated or not Treated with Statins – 3 month Follow-up

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**Abstract:** Older sibutramine studies showed beneficial effects on lipid profile compared to placebo. However, nowadays many obese patients are treated with lipid lowering drugs before the start of sibutramine therapy and their effects in these patients have not been investigated. Therefore we started a long term follow up of patients on sibutramine with or without previous and continuing statins. Here we present results of the first 3 months follow up of 11 patients on sibutramine 10 mg +statin group, and that of 13 patients on sibutramine 10 mg alone. Sibutramine led to the weight loss from 101.6 to 96.9 kg and in BMI from 36.35 to 34.66 kg/m<sup>2</sup>. Lipid profile changed thus: total cholesterol 4.97...5.01mmol/l (p = 0.7), LDL cholesterol 2.83...2.82 mmol/l (p = 0.9), HDL cholesterol 1.13...1.27 mmol/l (p = 0.003), triglycerides 1.98...1.91 mmol/l (p = 0.01). Comparison between the 2 groups did not show any significant differences in lipid levels, patients react to sibutramine in the same way regardless to the concomitant statin therapy. We can therefore preliminarily conclude that sibutramine therapy has significant positive effect on the lipid profile even in patients who were started on statins prior to initiation of sibutramine treatment.

## Introduction

Obesity together with its complications is rapidly becoming a significant healthcare issue. One of the important obesity complications, dyslipidemia, is characterised by an increase in triglyceride levels together with a decrease in HDL cholesterol levels [1]. Atherosclerosis in the obese is accelerated due to an increase in endogenous production of cholesterol [2], which reacts well to statin therapy [3].

Lifestyle modifications have only limited effect in treatment of obesity. Currently, the most effective treatment modality is bariatric surgery [4]. Ten years ago there was no effective anti-obesity pharmacotherapy available. Since that we have two new drugs available for administrations, sibutramine and orlistat, which are safe for prolonged period of time, without serious side effects. Until recently, their use has been limited by their price, but nowadays, sibutramine is due to its very low price accessible to everyone, with orlistat costing less than 4 times more.

Large review of sibutramine studies [5] shows its high effectiveness in three time intervals: a few weeks, about half of a year and a year of follow up. It confirms the observation proposed by many studies of the beneficial effect of sibutramine on the obesity-related dyslipidemia: a decrease in triglyceride and an increase in HDL cholesterol levels. These studies were, however, conducted in the years before large scale statin prescription, and data are sparse in the current situation, where many obese come to be prescribed sibutramine when already being treated with a statin. Therefore we initiated a long-term follow up of patients who were started on sibutramine while continuing with their established statin therapy, and comparing them to those who were not on lipid lowering drugs.

## Patients and Methods

We enrolled patients coming to our obesity clinic who were suitable for sibutramine treatment. The average age was 52.1 years, the average weight 101.6 kg and BMI 36.4 kg/m<sup>2</sup>. We measured weight, BMI, total, LDL and HDL cholesterol as well as triglycerides at baseline and at 3-months. From the total number of enrolled patients, 11 came with already established statin therapy (atorvastatin 10 mg od in 8 patients, atorvastatin 20 mg od in 3 patients) – and we continued with it, and 13 patients were not on any lipid lowering therapy, and were only prescribed sibutramine 10 mg od. In this first phase, we evaluate the first 3 months of sibutramine 10 mg od treatment. The changes in followed values were tested by nonparametric Wilcoxon's test when evaluating the 3-months development, and by the paired t-test when comparing the two groups.

## Results

The mean weight decreased from 101.6 kg to 96.9 kg and the mean BMI from 36.35 to 34.66 kg/m<sup>2</sup>. Lipid profile changed accordingly: total cholesterol 4.97...5.01 mmol/l ( $p = 0.7$ ), LDL cholesterol 2.83...2.82 mmol/l ( $p = 0.9$ ), HDL cholesterol 1.13...1.27 mmol/l ( $p = 0.003$ ), triglycerides 1.98...1.91 mmol/l ( $p = 0.01$ ). Comparing changes in the lipid profile between the 2 groups did not reveal any significant differences. Whether on or without statin, patients showed the same change in total cholesterol levels ( $p = 0.60$  – Figure 1), LDL cholesterol levels ( $p = 0.67$  – Figure 2), HDL cholesterol levels ( $p = 0.26$  – Figure 3) and triglycerides ( $p = 0.61$  – Figure 4).

Closest to significance was the difference between the groups in the case of HDL cholesterol level: without statin 1.1...1.20 mol/l, with statin 1.16...1.35 mmol/l ( $p = 0.26$ ).

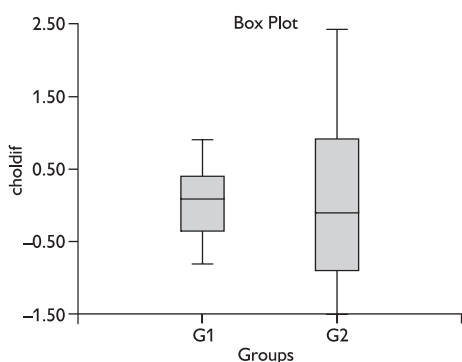


Figure 1 – Comparison of changes in total cholesterol levels in the group without statin (G1) and with statins (G2) ( $p=0.60$ ), with median horizontal line, range vertical line segment and box – 50% of cases.

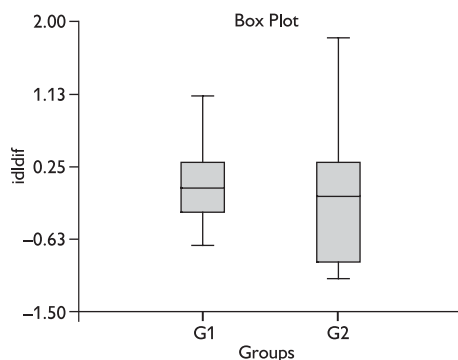


Figure 2 – Comparison of changes in LDL cholesterol levels in the group without statins (G1) and with statins (G2) ( $p=0.67$ ), with median horizontal line, range vertical line segment and box – 50% of cases.

**Discussion**

Our results confirmed the well known fact that sibutramine lowers the triglyceride level and increases the level of HDL cholesterol. Its effects on total and LDL cholesterol, according to the large metaanalysis [5] were undetectable at 3 and 12 months, with a transient decrease at 6 months of follow up. Our 3-month study confirmed that – there was no significant decrease in total or LDL cholesterol levels. This in turn was confirmed by results of the bariatric studies, where the effect of surgery on these parameters is usually lower than on other metabolic parameters [4].

In the Czech Republic, the metabolic effects of sibutramine were demonstrated by the MERIDIOS study [6]. Recently, interest has been turned to the M2 metabolite of sibutramine [7]. It seems that this compound could have a significant anti-diabetic effect and could suppress glucose production in the liver.

Patients already treated with statins exhibited a significant decrease in the lipid levels. It has been recently demonstrated that obese patients suffer from an increase in the endogenous synthesis of cholesterol, and a decrease in cholesterol absorption in the gut [8]. These are no relations to insulin resistance [9]; effect seems to be brought about by the obesity alone. Our patients have been on statins for some time and we could not establish the extent of their lipid lowering actions, but our results show that sibutramine is capable of further lowering of triglycerides and an increase in HDL cholesterol levels. In patients on statins, the effect of sibutramine was almost comparable to those without statin therapy.

Therapeutic modification of HDL levels has recently been regarded as equally important to modification of LDL levels. According to one metaanalysis on the

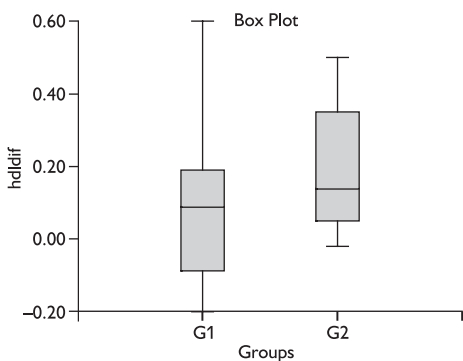


Figure 3 – Comparison of changes in HDL cholesterol levels in the group without statin (G1) and with statins (G2) ( $p=0.26$ ), with median horizontal line, range vertical line segment and box – 50% of cases.

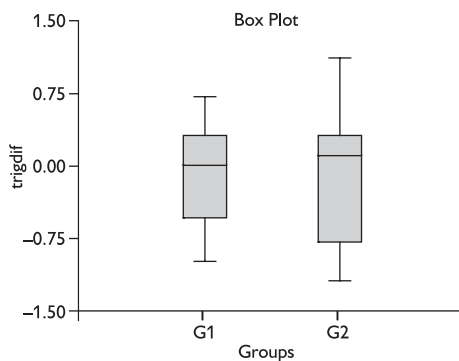


Figure 4 – Comparison of changes in triglyceride levels in the group without statin (G1) and with statins (G2) ( $p=0.61$ ), with median horizontal line, range vertical line segment and box – 50% of cases.

effects of lipid lowering drugs, both the decrease of 1% of LDL or the increase of 1% HDL cholesterol levels lead to a decrease in cardiovascular mortality by 1% [10]. Still, the possibility to increase HDL levels by therapy is not always remembered. The same metaanalysis discusses only the limited effect of statins on HDL, while a more significant effect of fibrates is noted. This is confirmed by a recent FIELD study [11]. Sibutramine could be another way how to maximise HDL levels in the obese.

Our results show that the increase in HDL cholesterol in patients on the combination of statin+sibutramine could be higher than in those treated with sibutramine alone. The increase in HDL cholesterol was almost significant when the groups treated or not treated with statin were compared. It can be expected that when this study is enlarged and of a longer duration, the effect of sibutramine in statin-treated patients becomes significantly greater than in patients not treated with statins.

Our results show that when considering treatment with sibutramine, one should always remember its documented positive effect on dyslipidemia in the obese, even in those who were already treated with statins. It is probable, that in the currently ongoing SCOUT mortality study we shall see the effect of sibutramine on the overall mortality [12]. This could be explained not only by its effects on the body weight, but also on the lipid profile.

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