The Dynamic Of Plasma Lipid Indices In Short Term Treatment With Statins

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ABSTRACT Statins are a class of drugs and cholesterol-lowering effect demonstrated in reducing cardiovascular mortality. Thus, an increasing number of people with increased levels of serum cholesterol achieved with statin therapy indications. The higher level of current records showing that statins prevent cardiovascular disease may be greater in patients with more pronounced vascular inflammatory process. The study included 102 hypertensive patients, with values of total cholesterol (TC) of $\geq 4.5$ mmol / L (> 200 mg / dL) and LDL-C (low molecular density lipoprotein fraction) $\geq 2.6$ mmol / L (> 135 mg / dL), which were administered simvastatin, lovastatin and pravastatin in doses of 20 mg / day and 40 mg / day for 12 weeks. He was comparing their effect on lipid indices. The dose of 20 mg / day and 40 mg / day the greatest influence on total cholesterol had a simvastatin (reduction of 21.20% and 28.10% respectively). On triglycerides, the effect varied more, the maximum decrease was caused by simvastatin (16.30%) to 20 mg / day and pravastatin (18.30%) at dose of 40 mg / day. Regarding lowering LDL-C and HDL-C (high molecular density lipoprotein fraction), three remedies have similar effects. The largest increase in HDL-C occurred under treatment with 40 mg / day of lovastatin (10.20%). The study aims to assess the effect of administration of statins is to choose a customized treatment according to individual patient characteristics.

KEY WORDS statins; hypertension; lipid indices

Introduction

Of dyslipidemia, cholesterol is the main factor that was statistically associated with the highest risk for coronary heart disease and mortality by cause. LDL cholesterol (low-molecular-density lipoprotein fraction), the lipid fraction carrying about 70% of plasma cholesterol, has a directly proportional relationship with cardiovascular risk, irrespective of race, ethnic or geographical area. Low HDL cholesterol (high molecular density lipoprotein fraction) is another factor involved in cardiovascular pathology. Involvement of triglycerides (TG) in atherogenesis remains a subject discussed, clinical and epidemiological studies failed to take a final decision on their importance in cardiovascular pathology (13, 15, 16).

One reason for the impact on the vascular system is represented by high blood pressure (hypertension), with a high prevalence (9) and with significant impact on cardiovascular morbidity and mortality, being involved in the development of atherosclerotic events. Clinical studies have shown that the therapeutic effect of blood pressure control rate was significantly reduced cardiovascular events and programs to detect and treat hypertension led to a decline in blood pressure, while reducing cardiovascular risk (4, 14).

Data from the Heart Protection Study (8) and the ASCOT study (2) have shown that statin therapy reduces the risk of stroke (stroke) and IHD (ischemic heart disease), regardless of serum cholesterol level and your value to enrollment (3). Statins can substantially reduce the risk of ischemic heart disease-IHD-(30%) and stroke (25%), as recommended by various authors as a routine therapy in patients with treated hypertension, particularly those with high cardiovascular risk because these drugs have additional effects on the primary endpoint of antihypertensive therapy.

Relationship between blood pressure and risk of cardiovascular events is continuous, constant and independent of other factors involved in this pathology. The blood pressure is higher value, the greater the risk of myocardial infarction, heart failure, stroke and kidney disease.

Material and method

Research has been done on a number of 102 hypertensive patients. Inclusion criteria they have established: the presence in history of hypertension (HBP) 1,2,3 degree to which total cholesterol (TC) has values of $\geq 4.5$ mmol / L (> 200 mg / dL) and LDL -C $\geq 2.6$ mmol / L (> 135 mg / dl) treated with beta-blockers, ACE inhibitors, thiazide diuretics. The study also included patients with clinical manifestations following: angor pectoralis stable-functional class (FC) I-IV, heart failure (NYHA I-III FC), high level of lipid indices, cardiovascular metabolic syndrome (based on criteria established...
by the International Diabetes Federation proposed in 2005), women at least 24 months after the last menstruation, hysterectomy and use of mechanical contraceptive devices. Have not excluded patients treated with converting enzyme inhibitors or thiazide diuretics, but was formed and a subgroup of patients who will not follow treatments for hypertension. Overall cardiovascular risk was assessed according to the latest "European Guidelines on cardiovascular disease prevention in clinical practice", in 2003 and updated NCEP report - ATP III, 2004 (13). Laboratory investigations included determination of lipid spectrum: total cholesterol (TC-mg/dl), triglycerides (TG mg / dl) and high molecular density lipoprotein fraction (HDL-C mg / dL) by enzymatic method, and LDL-C was calculated using the formula (for TG less that 5 mmol / l): LDL-C = TC - (TG / 5 x 2.29 HDL-C). Atherogenic index (AI) was calculated using the formula proposed by NA Climov: AI= CT-HDL-C/HDL-C.

Statistical methods of calculation were used: t test (Student), analysis of variance (ANOVA), and Discriminant function analysis and multiple logistic regression. Additional statistical analysis included χ² test (chi square) to interpret the relationship between categorical variables. Was used as threshold for statistical significance p value <0.05. All methods were used to interpret differences in the variables observed in group of patients.

All persons included in the study were informed and encouraged to adopt a healthy lifestyle, with individualized recommendations for prevention of risk factors: moderate physical activity and continuing effort by indicating the allowed thresholds, smoking cessation, individual advice on how food (limiting food cholesterol to 300 mg / day, and easily assimilated carbohydrates). Clinical and biochemical effects of various treatment programs for patients in all groups were presented in the following terms: first, after a month of treatment, after the 3rd month of treatment with statins, three months for the control group diet hypolipemia.

Phases of the study consisted of patient identification, eligibility determination, determining the criteria for exclusion, division into groups according to therapeutic indications, investigation of patients with laboratory tests and interpretation of results. Of the 102 patients with hypertension, a number of 54 (58.74%) have set up women and 43 men (42.16%) (Figure 1). In 38 patients (49.36%), hypertension treatment was optimized (with blood pressure below 140/90 mmHg) in 42 patients (54.54%) - optimal and 1 (0.9%) - inadequate (Figure 2).

The mean age of patients was 56.3 ± 0.7 years, with limits between 43 and 60 years. For the group of women was calculated to be 55.4 years [± 45.4] and 50.6 years [± 39.7] in the group of men, age difference with statistical significance (p = 0.011). The average weight of patients reached the value of 86.1 kg, being overweight and obese patients having body mass index greater than 25 kg / m². In the group of women, the average weight is lower (80.24 kg) than male group (92.27 kg), statistically significant difference (p <0.0001), but the mean waist circumference in both groups is approximately equal (119.5 cm from 119.9 cm). Ketle index (ratio of body weight in kilograms to height in meters squared) has a mean batch of 28.8 ± 0.5 units (Table 1). Obesity abdominal (waist circumference ≥ 88 cm women and ≥ 102 cm men) presented 75 between patients (53.96%). Historically disadvantaged families were 45 patients (44.11%), active smoking 29 patients (28.43%).

Analysis of demographic data shows that the study group did not differ in respect of the anthropometric parameters, biochemical parameters of severity of hypertension (ambulatory blood pressure monitoring). Thus, we
can say that our results are not influenced by differences in known data on the distribution of masculine obesity and, consequently, its influence on defining the parameters of metabolic syndrome.

### Table 1. Clinical characteristics of patients investigated.

<table>
<thead>
<tr>
<th>Parameters evaluated</th>
<th>Statins / 20 mg</th>
<th>Statins / 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Diet</td>
<td>After one month</td>
<td>After three months</td>
</tr>
<tr>
<td>Diet</td>
<td>After one month</td>
<td>After three months</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>102 102</td>
<td>43 34</td>
</tr>
<tr>
<td>Membership of sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (%)</td>
<td>43 (42.16)</td>
<td>24 (55.81)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>59 (57.84)</td>
<td>21 (61.77)</td>
</tr>
<tr>
<td>Age structure (mean, years)</td>
<td>56.3±0.7 56.3±0.7</td>
<td>55.2±0.8 55.2±0.8</td>
</tr>
<tr>
<td>Kettle index, kg/m²</td>
<td>28.8 ±0.5</td>
<td>28.2±0.6</td>
</tr>
<tr>
<td>Kettle index &gt;30 kg/m²</td>
<td>14(13.72)</td>
<td>7 (21.76)</td>
</tr>
<tr>
<td>Abdominal obesity (%)</td>
<td>75 (53.92)</td>
<td>36 (83.72)</td>
</tr>
</tbody>
</table>

### Results

In patients with hyperlipidemia treated with simvastatin at a dose of 20 mg / day (n = 20) initially observed an increased level of CT in this group (296.5 ± 23.4 mg / dL). After a month of treatment, followed a 17.2% decrease from baseline (p <0.001). In the following months, mean CT decreased by 21.2% (p <0.001).

For those treated with lovastatin (n = 13) 20 mg / day, shows that increased levels of TC (293.5 ± 22.3 mg / dl) decreased after one month of treatment, reaching 280.4 ± 20.6 mg / dL. In the following months, mean CT decreased by 20.9% (p <0.001). The same trends will be seen in patients who were given 20 mg pravastatin (n = 20).

For LDL-C levels also were obtained reduction fund - after a month of medication with lovastatin 20 mg / day is noted a 16.3% decrease from the initial rate of 218.5 ± 17.4 mg / dL (p <0.001) after the 3rd month - by 25.8% (p <0.001). Simvastatin administration, the trend was still a loss - after a month of medication to a decrease of 12.6% set the initial rate of 208.5 ± 18.4 (p <0.001) after the 3rd month - it was 177.1 ± 17.5 mg / dL (p <0.001).

Regarding changes in triglyceride levels after administration of simvastatin 20 mg / day, reached the initial level of 253.1 ± 20.1 mg / dl to 223.5 ± 19.6 mg / dl after one month (p <0.001) and 196.9 ± 19.4 mg / dl after three months (p <0.001).

Lovastatin administered the same dose caused a total reduction of TG 15.3% to 192.9 ± 19.1 mg level / dl. In the same dose of pravastatin, there was a decrease in TG concentration from 233.1 ± 20.1 mg / dl initially, to 210.5 ± 19.2 mg / dl after one month (p <0.001), because after three months of therapy value to reach 182.9 ± 18.1 mg / dL (p <0.001).

Watching developments atherogenic index, it shows a reduction of 32% at three months after starting therapy with simvastatin 20 mg / day, 30.1% to 19.7% for lovastatin and pravastatin, all three remedies causing changes statistically significant (p <0.001).

Another group was formed by patients have been given an increased dose of statin. In the study 18 patients were included (n = 18), with increased levels of LDL-C, which was administered in doses of 40 mg simvastatin. In the first test (after a month), there was slight reduction in levels of LDL-C, TG, TC. Maximum reduction of LDL-C concentration (p <0.001) occurred in the third month of treatment and up - 23.5% of baseline. In patients who received pravastatin at a dose of 40 mg / day has been the same downward trend of the concentration of LDL-C, the value of 228.5 ± 17.4 mg / dL, it was 189.9 ± 18.8 mg / dl in the first month (p <0.001), for three months after treatment to observe a 22.5% reduction from baseline (165.1 ± 17.5 mg / dl, p <0.001).

Regarding the patients who received lovastatin 40 mg / day (n = 10), was observed to reduce lipid indices studied. Lowering LDL-C concentration (p <0.001) occurred in one month (269.9 ± 18.8 mg / dL) and three months, registering a 22.7% reduction from baseline.
Dynamic TC was similar decrease followed by LDL-C. Cholesterol-lowering effect occurred within 3 months after treatment, the CT values in those treated with simvastatin achieved the figure of 252.2 ± 18.2 mg/dL (p < 0.001) versus 320.5 ± 23.4 mg/dL at enrollment. And in patients who received pravastatin 40 mg/day were measured descrecătoare values of TC, from 323.5 ± 22.4 mg/dl initially, to 280.4 ± 20.6 mg/dL after one month and three months after therapy the amount of 252.2 ± 18.3 mg/dL. Also after 3 months of treatment with lovastatin 40 mg/day was recorded maximum decrease of total cholesterol values were reached by 262.2 ± 18.3 mg/dL (p < 0.001), representing a 20.4% reduction from the first measurement (329.5 ± 22.1 mg/dL).

HDL-C levels tended to increase. So the initial values of 51.1 ± 9.5 after one month of simvastatin to 40 mg/day, they rose up to 53.5 ± 9.1 mg/dL (p < 0.01). After three months of treatment with simvastatin were found further increases in levels of HDL-C: 56.4 ± 9.1 mg/dL, ie an increase of 9.3%. The same trend was preserved in the group receiving pravastatin 40 mg/day, the values of 61.8 ± 9.5 mg/dL initially, after a month of medication they increased to 68.7 ± 9.0 mg/dL (p < 0.01). After three months of treatment with statins were found further increases in HDL-C levels by 72.4 ± 9.1 mg/dL, an increase of 9.2%. HDL-C levels continued to increase during treatment with lovastatin 40 mg/day, from 58.1 ± 9.5 mg/dL initially to 68.4 ± 9.1 mg/dL at the end of records. After a month of treatment with simvastatin 40 mg/day, TG levels reached 255.5 ± 19.2 mg/dL after 3 months of treatment to 232.9 ± 18.1 mg/dL, which represented a 15.3% reduction in value 303.1 ± 22.1 initial mg/dL (p < 0.001). After administration of pravastatin 40 mg/day has been a decrease in TG levels at 253.1 ± 20.1 mg/dL to 213.5 ± 19.2 mg/dL in the first month (p < 0.001) and 172.9 ± 19.1 mg/dL after three months (p < 0.001). TG levels in patients in whom statin was given lovastatin 40 mg/day reached 192.9 ± 19.1 mg/dL after 3 months of therapy, meaning a reduction from 15.4% to 293.1 ± 20.1 initialise mg/dL (p < 0.001).

Atherogenic index was reduced from 3.96 ± 0.25 2.86 ± 0.29 at baseline (p < 0.001) for simvastatin, thus scoring a 24.7% decrease (p < 0.001).

As shown in Figure 3, there was a reduction in plasma lipid indices with three statin therapy, the dose of 20 mg/day in terms of total cholesterol, the major influence was a simvastatin (21.20%) to lovastatin and pravastatin, which led to a reduction of 20.20%. On triglycerides, the effect varied more, the maximum decrease was caused by simvastatin (16.30%), a lesser effect with pravastatin - only 12.30%. Regarding lowering LDL-C and HDL-C, three remedies have similar effects, the variation effects of these compounds showed no statistically significant differences.

Increased doses of statins, the maximal effect of simvastatin had lower total cholesterol (Figure 4), registering a decrease of 28.10% (p < 0.001) compared with pravastatin and lovastatin, which was 20.30% decrease (p < 0.001) and 20.40% respectively (p < 0.001). Effects on LDL-C were similar and there simvastatin causing the largest
decrease, from 23.50%. The largest increase in HDL-C occurred under treatment with lovastatin (10.20%). Largest decrease in triglycerides was determined by pravastatin (18.30%), simvastatin causing a decrease of 17.30% and minimum reduction was observed under treatment with lovastatin.

Discussions

In 2001, NCEP-ATPIII (National Cholesterol Education Program - Adult Treatment Panel III) updates a guide that makes changes in detection, evaluation and treatment of adult dyslipidemia and other risk factors in the interpretation. This guide continues to consider the primary target of LDL cholesterol treatment, but at the same time, the management was changed, to include the lower target LDL below 100 mg / dL and those patients who are at high risk for coronary heart disease but not yet clinical evidence for this disease.

It is estimated that a standard treatment with statins reduced LDL cholesterol by 25-40%, reduce triglycerides by 10-20%, probably by decreasing VLDL and increase HDL cholesterol by 5-10% (5). Our results showing a maximum reduction of LDL cholesterol by 23.5% after administration of 40 mg / day of simvastatin. Effectiveness of the various statins is comparable, but there are authors who do a ranking of statins in terms of effectiveness. Thus, Goodman and Gilman (2006) (7) states that simvastatin is 2 times more effective than lovastatin, which is as effective as fluvastatin or, in other words, to lower LDL cholesterol by at least 25%, are necessary dose of 5 mg simvastatin, lovastatin or pravastatin 10-20 mg and 20-40 mg of fluvastatin. Hierarchy is maintained for higher doses. Although there was a decrease of 25% of LDL cholesterol in our case study was not to demonstrate the effectiveness of compounds or to establish a minimum level of this parameter (which could require a larger period of administration of statins) but dynamic indices tracking lipid indices.

The ALLHAT study (1), administration of 40 mg / day of pravastatin to 10,000 hypertensive patients (of which approximately two thirds had known vascular disease) resulted in reducing total cholesterol and LDL cholesterol (by 11% and 17% respectively) compared usual therapy. In our study, the effect of pravastatin administration was even more pronounced, so the decrease in total cholesterol (reduction of 20.30%) and the LDL-C (22.5% reduction). One result has been great on triglycerides, which decreased at low doses was 12.3% and 18.3% at high doses. According ASCOT study (2), administration of 10 mg / day atorvastatin in over 10,000 hypertensive patients with additional cardiovascular risk factors and a total cholesterol <6.5 mmol / l, total serum cholesterol reduction resulted in 19.9%, compared placebo. Perhaps variations of values of total cholesterol and LDL cholesterol recorded in patients who received the active substance compared with those receiving placebo, explains differences in results between the two trials.

The REVERSAL study presents great interest, in which it was intended effect of treatment versus standard hipolipidemiant pravastatin 40 mg, each dose vs. aggressive Atorvastatin 80 mg (10). Relatively recent publication of study results pravastatin atorvastatin The Evaluation and Infection Therapy (PROV-IT) saw a turning point in the prevention and treatment of atherosclerotic disease, marking a new era in the intensive treatment with statins (12). This study compared the effects of intensive therapy (80mg of atorvastatin) and moderate (pravastatin 40 mg) in a total of 4162 patients. We have obtained significant results, after taking 40 mg of pravastatin, all parameters studied. Significant reduction (over 16%) of major cardiovascular events among those receiving intensive confirms, that the effect of decreasing the LDL-C translates to a reduction in major cardiovascular diseases.

Conclusions

1. Our study confirmed the effectiveness of statins in reducing total cholesterol, LDL-C and triglycerides.
2. Lowering LDL-C did not reach 25% of other studies, but was statistically significant for all three statins whose effect was compared, the most effective is determined by taking 40 mg of simvastatin.
3. Lovastatin produced the same dose, the greatest increase in HDL-L, for lower doses the effects are similar to those caused by simvastatin and pravastatin.
4. If both dose effects on total cholesterol are of statistical significance for all compounds studied, is more effective at higher doses I found to simvastatin.
5. Triglyceride values are in direct correlation with the atherogenic index, the indirect correlation with HDL cholesterol but independent of LDL-cholesterol. Pravastatin was with striking effect on them, at doses of 40 mg / day.
6. Mean atherogenic index (total cholesterol / HDL-cholesterol) exceeds the permitted limit, confirming endothelial aggression risk,
particularly in the context of the existence of other risk factors.

References

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