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О. КИШКО, Ф. НЕМЕТ, Я. КМЕЦ, М. БАБЧАК, Л. ДЕРНЯРОВА  
Пряшівський університет, Пряшів, Словаччина

## ФУНКЦІЯ ПЕЧІНКИ, БІОМАРКЕР ЗАПАЛЕННЯ ТА СТАТИНИ ПРИ МЕТАБОЛІЧНОМУ СИНДРОМІ

Оскільки статини є показаними у більшості пацієнтів з метаболічним синдромом (МС), лікарі стикаються з проблемою їхнього призначення у випадку підвищених показників печінкових тестів. У даній статті обговорюються попередні висновки пілотного дослідження, присвяченого проблемі лікування статинами МС з підвищеними рівнями аланінамінотрансферази (АЛТ) та високочутливого С-реактивного протеїну (СРП-вч).

У дослідженні брало участь 50 хворих у віці 18-50 років (30 чоловіків, 60%) з МС згідно IDF критеріїв та з помірним підвищенням рівнів АЛТ і СРП-вч. Із них 25 склало досліджувану групу і отримувало аторвастатин (10-80 мг/добу), відповідно до рівня холестерину ліпопротеїнів низької густини (ЛПНГ). Контрольну групу склало 25 хворих, які не отримували статини. Вона була подібною за віком, статтю та індексом маси тіла (ІМТ) до досліджуваної групи. Показники ІМТ, ліпідів у сироватці крові, АЛТ, СРП-вч та щільність паренхіми печінки, яка оцінювалась методом ехографії, визначали на початку дослідження і через 1, 3, 6, 9 і 12 місяців лікування відповідно. Отримані показники оброблено статистичними методами.

На початку дослідження всі пацієнти мали помірно підвищені рівні АЛТ і СРП-вч. Після 6 місяців лікування вісім пацієнтів (32%) мали нормальні рівні АЛТ. Інші пацієнти продовжували лікування протягом 12 місяців, після чого 20% пацієнтів мали нормальні показники АЛТ, у той час як у решти пацієнтів даний показник знизився на 20%, у порівнянні з таким до лікування ( $p < 0,05$ ). Після 12 місяців лікування статинами у пацієнтів досліджуваної групи спостерігали достовірне зниження показника СРП-вч, у порівнянні з таким у 25 нелікованих пацієнтів, при цьому 24% лікованих пацієнтів мали нормальні показники СРП-вч, у той час як у решти пацієнтів даний показник зменшився на 25%, у порівнянні з таким на початку лікування. Після лікування спостерігалось значне зниження рівнів ЛПНГ-холестерину, у порівнянні з таким у пацієнтів контрольної групи. Отримані результати свідчать, що завдячуючи плейотропним ефектам, якими володіють статини, вони є показаними пацієнтам із МС та ознаками запалення навіть у випадках помірного підвищення печінкових амінотрансфераз.

**Ключові слова:** метаболічний синдром, аланінамінотрансфераза, високо чутливий С-реактивний протеїн, статини

A. KISKO<sup>1</sup>, F. NEMETH<sup>3</sup>, J. KMEC<sup>1</sup>, M. BABČAK<sup>2</sup>, L. DERNAROVA<sup>2</sup>

<sup>1</sup> *Cardiology Clinic, J.A.Reiman University Hospital, Presov University in Presov, Slovakia*

<sup>2</sup> *Faculty of Health, Presov University in Presov, Presov, Slovakia*

<sup>3</sup> *Geriatric Clinic, J.A.Reiman University Hospital, Presov University in Presov, Slovakia*

### HEPATIC FUNCTION, BIOMARKER OF INFLAMMATION AND STATINS IN PATIENTS WITH METABOLIC SYNDROME

Because most patients with metabolic syndrome (MS) have indications for statins, clinicians are confronted with prescribing statins to those with elevated hepatic tests.

The purpose of this study is to discuss preliminary data obtained from pilot phase of the research focused on MS associated with elevated alanine aminotransferase (ALT) and high sensitivity CRP (CRP-hs) concentrations treated with statins.

50 subjects, aged 18-50 (30 men, 60%) and meeting IDF criteria for MS with moderate elevation in ALT and CRP-hs were enrolled into the cross sectional group comparison prospective study. 25 of them in study group received atorvastatin (10-80 mg/daily) according to basal LDL-cholesterol level. 25 untreated subjects of the control group were matched by age, sex and body mass index (BMI) with the study group. BMI, serum lipids, ALT, CRP-hs and liver density assessed by echography were measured at baseline and after 1, 3, 6, 9 and 12 months of treatment. Summary outcome measures were reported as mean±SD, values of  $p < 0,05$  were considered statistically significant.

At baseline, all patients had moderately elevated ALT and CRP-hs levels. After 6 months of treatment, eight patients (32%) presented normal ALT levels. The remaining patients continued treatment for 12 months, and at that moment, 20% of patients presented normal ALT levels, while the other patients showed a 20% reduction in basal levels ( $p < 0,05$ ). After 6 months of treatment in study group there was a decline in CRP-hs levels compared with 25 untreated patients and at that moment, 24% of patients presented normal CRP-hs levels, while the other patients showed a 25% reduction in basal levels in compare with untreated patients. After treatment there was a significant reduction in mean LDL-ch levels in control group. No side effects of statin treatment were reported in our study.

Due to pleiotropic effects of the statins data support using them in patients with MS with signs of inflammation and moderate elevation in liver tests, who may be at particularly high risk for CVD.

**Key words:** metabolic syndrome, alanine aminotransferase, high sensitivity C-reactive protein, statins

**Introduction.** The metabolic syndrome (MS) is a cluster of cardiometabolic risk factors associated with higher risk for atherosclerotic cardiovascular disease (CVD) and diabetes. Its prevalence is about 20% to 30% among adults worldwide and is increasing [4]. Post hoc analyses of prospective trials showed the benefit of statins in patients with the MS. Statin therapy exerts beneficial effects not only by lowering low-density lipoprotein cholesterol (LDL-ch) but also via its so-called pleiotropic effects. These effects seem particularly important for reducing risk of CV disease in patients with the MS. Thus, evidence is accumulating that statins are very effective therapeutic agents in the treatment of individuals with the MS. Statins have been repeatedly shown to decrease risk in a variety of patient groups. There are no studies directly addressing statin treatment in the MS, but post hoc analysis of several studies suggests that statins can be used to reduce CV risk in patients with this condition [3].

**Objectives.** Measurement of the serum alanine aminotransferase (ALT) level is used as an initial test for detection of liver dysfunction, and recent studies have also highlighted its potential value as a measure of overall health and survival as a marker of an increased risk of metabolic disorder. ALT is associated with MS independently of insulin resistance [1]. On the other hand the population-based study has shown that inflammation as assessed by C-reactive protein (CRP) is strongly related to all components of the MS [5]. Both CRP and MS are independent risk factors for CVD and have similar discriminatory ability with respect to subsequent CVD risk.

Because most patients with MS have indications for statins, clinicians are confronted with prescribing statins to those with elevated ALT [6].

The purpose of this study is to discuss preliminary data obtained from pilot phase of the research focused on MS associated with elevated ALT and high sensitivity CRP (CRP-hs) concentrations treated with statins.

**Materials and methods.** 50 subjects, aged 18-50 (30 men, 60%) and meeting IDF criteria for MS with moderate elevations in ALT (Cobas Intergra test system) and CRP-hs (latex test system) were enrolled into the cross sectional group comparison prospective study. All subjects were blindly randomized in to the study and control group. 25 of them in study group received atorvastatin (10-80 mg/daily) according to basal LDL-cholesterol level for 6 or 12 months until obtaining the end point of treatment. Normalization and/or improvement in ALT and CRP-hs were considered as the end point of treatment. Additionally, all patients were given standard weight-loss counselling and encouraged to follow a low fat diet. Although rare, hepatotoxicity has been reported with atorvastatin, subjects made monitoring visits to the clinic to ensure safety and adherence. 25 untreated subjects of the control

group were matched by age, sex and body mass index (BMI) with the study group. Before participating in the study each subject gave written voluntary assent and consent. BMI, serum lipids, ALT, CRP-hs and liver density assessed by echography were measured at baseline and after 1, 3, 6, 9 and 12 months of treatment. Because of the fact that all our patients were asymptomatic and without clinical or echographic signs of advanced liver disease, no biopsies were performed.

All study variables were treated as continuous variables. Summary outcome measures were reported as mean  $\pm$  SD. All analyses were performed with SAS 8.2 for Windows and 2-sided values of  $p < 0.05$  were considered statistically significant.

**Results and discussion.** At baseline, all patients had moderately elevated ALT ( $1,89 \pm 0,36$  ukat/l) and CRP-hs ( $6,42 \pm 0,86$  mg/l) levels. After 6 months of treatment, eight patients (32%) presented normal ALT levels. The remaining patients continued treatment for 12 months, and at that moment, 20% of patients presented normal ALT levels ( $0,66 \pm 0,33$  ukat/l), while the other patients showed a 20% reduction in basal levels ( $p < 0,05$ ).

After 12 months of treatment in the patients on statins group there was a decline in CRP-hs levels ( $3,21 \pm 0,64$  mg/l) compared with 25 untreated patients ( $5,88 \pm 0,40$  mg/l,  $p < 0,005$ ) and at that moment, 24% of patients presented normal CRP-hs levels ( $1,02 \pm 0,38$  mg/l), while the other patients showed a 25% reduction in basal levels in compare with untreated patients.

Mean LDL-ch levels were  $4,88 \pm 0,56$  and  $2,58 \pm 0,84$  mmol/l before and after treatment, respectively, with a significant difference between them ( $p < 0,05$ ). The mean BMI was  $37,4 \pm 3,1$  at baseline and  $36,3 \pm 2,8$  kg/cm<sup>2</sup> at the end of treatment ( $p > 0,05$ ). Liver fat measured by echography and analysed by the same gastroenterologist did not change significantly after treatment. There was no statistical difference between clinical and epidemiological variables in both groups, 6 and 12 months of treatment. No side effects were reported in our study.

As a result of the obesity epidemic in modern societies, conditions associated with MS are increasing, including CVD [2]. Inflammation is pivotal in all stages of atherosclerosis, and CRP-hs, the prototypic marker of inflammation, has emerged as a CVD marker [3, 5]. Statins reduce CRP levels, and this reduction in most studies does not correlate to reduction in cholesterol. In addition, statins have beneficial effects on endothelial function, monocyte-macrophages, and platelets [7].

Our data have emerged demonstrating that not only are statins well tolerated to use in MS patients with elevated ALT but also they may have a beneficial therapeutic effect in treating the underlying conditions predisposing for CVD. Study demonstrates that statins

decrease the levels of CRP-hs. Patients on statins were more likely to have a decline in ALT concentrations compared with untreated patients.

**Conclusions.** The results of the study support using statins in MS patients with elevated liver tests,

especially in patients with elevated levels of CRP-hs. Due to pleiotropic effects of the statins data support using them in patients with MS with signs of inflammation and moderate elevation in liver tests, who may be at particularly high risk for CVD.

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