REVIEW ARTICLE

Fatty Liver Disease and Statins – Which Discipline Does this Problem Belong To?

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SUMMARY

Šochman J.: Fatty Liver Disease and Statins – Which Discipline Does this Problem Belong To?
While fatty liver disease is a well-characterized entity, it is currently getting a completely new image. Its treatment is clearly an interdisciplinary challenge. The number of patients with fatty liver disease will be by no means negligible. The issue of fatty liver disease is not infrequently referred to in association with statin therapy instituted in an effort to treat metabolic syndrome and to reduce cardiovascular risks as part of preventive therapy. The attention focused on the increase in alanin aminotransferase levels during statin therapy is absolutely inadequate. The study includes an overview of the topic showing that the induced rise in alanin aminotransferase is merely an accompanying phenomenon, mostly of no clinical relevance. An acceptable increase in alanin aminotransferase should not provide a reason for statin withdrawal in the usual spectrum of patients with metabolic syndrome and fatty liver disease. A distinct advantage is cooperation between a hepatologist, a cardiologist, and a diabetes expert.
Key words: fatty liver disease, statin, alanin aminotransferase, cardiovascular disease. *Šo.*

Čas. Lék. čes., 2006, 145, pp. 443–447.

METABOLIC SYNDROME AND ITS INTERDISCIPLINARY POSITION

Liver steatosis without inducing alcohol effect has become a more frequent finding in the discipline of internal diseases. In accordance with its name, it should belong to the hepatology sphere; however, based on the fact that it is a virtually regular part of the metabolic syndrome, it also belongs to the sphere of the diabetology interests. Naturally, cardiology is also not out of the picture, since the patients with metabolic syndrome have at least a clear risk factor of the origin and development of cardiovascular diseases. Usually with these patients the lipid spectrum is also not in order. They may not so rarely react differently to various medicamentous procedures (in particular to hypolipidemics). The level of alanin aminotransferase (ALT) is here of key significance. These briefly mentioned problems may be combined in a different way. Regarding the liver lesion, where determining factors – among others – are the period of the disease and its progression, the transition to steatofibrosis should also not be excluded. This may already be of direct relevance for the further course of the whole complex of actions that have their origin in the simple metabolic syndrome.

FATTY LIVER DISEASE

The classically developed metabolic syndrome usually consists of hypertension, apple-like type of obesity (in particular with men), diabetes mellitus may already be present and there is a certain dislipidemy level (mostly the triglycerid level is higher and the cholesterol spectrum may be changed in a certain way). It is also possible that the bearer of this syndrome has already overcome an incidence belonging to the sphere of the cardiovascular diseases – and if not, then the patient may expect it with a high probability, if left without any treatment. Fatty Liver Disease (hereinafter referred to as " FLD") is represented in the population in a relatively high percentage. Estimates fluctuate between 16 % and 23 % (1). FLD has not been restricted either in the qualitative or in the quantitative respect and may at one extreme have only higher fat accumulation in the hepatocytes (steatosis in the closer sense of the word), while at the other liver cell lesion may already be present (in such as case steatohepatitis is the term used). The exclusion of the alcohol effect is of importance in terms of the definition. Even this condition may have the result in the alteration of the liver parenchyma with the formation of nodes and uloses (being a prerequisite for the liver cirrhosis definition). Naturally, here the consumption of a higher amount of alcohol has the role of an accelerator; however, it may be deduced that FLD preceded the alcohol consumption, so alcoholically mediated acts are not primarily involved here. A toxic effect of various medicines and viral infections affecting the liver parenchyma may also be of the inducing impact on the FLD-cirrhosis transition. As for the medicines, the group of statins in particular, being commonly indicated with the mature metabolic syndrome, has been given justified attention nowadays; on the other hand, they may cause increased liver transaminase level. Sometimes there is a concern related to the statins being exactly of the potential contribution to the adverse transition in the FLD category. Up to half of the group of patients with metabolic syndrome and diabetes mellitus is estimated to suffer from FLD. In cases of morbid obesities nearly all patients will be FLD holders, and cca 5 % may have so-called steatohepatitis (however, this will depend on the applied diagnostics method) (2).

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ELEMENTARY HEPATOCYTE FAT BIOCHEMISTRY

The triglyceride condition will be decisive for the corresponding hepatocyte biochemistry. The input, being with the plus sign, is represented by the synthesis of fatty acids and of their esterification together with an increase in the triglyceride amount. The output, being with the minus sign, is with actions leading to the triglyceride decrease. This is a removal by means of the LDL or the oxidation of the fat acids. FLD originates when the input activities prevail over the output activities. Detailed procedures and primarily the role of the modulating elements shall be excluded here in the cause of simplification. In any case a longer lasting imbalance of these processes and the exhaustion of the complex preparedness of the enzymatic processes in the liver cells may result in an increase in liver transaminases (AST, and mainly ALT). And this is when it is necessary to perform careful evaluation of the selection of further hepacyte load by means of different medicines, not excluding statins. The alanin aminotransferase is a cytoplasmatic enzyme transmitting the amine group from the gluconeogenous amino acid (ALA) to the alfaceto - glutarate with the origin of the glutam acid and pyruvate. It is necessary to know that the ALT activity is in a hepacyte ca 7000 times higher than in a serum, and further that this activity is cca 10 times higher in the hepatocyte than in a cardiomyocyte (3). The ALT is among the accustomed indicators of the liver lesion and is a part of the so-called basic biochemical examination spectrum. It is becoming obvious that the ALT level is related to the body mass index. With the group of men with obesities the ALT increase may be observed more than eight times more frequently than with men of normal weight (4). An absolute majority of persons with an above-limit ALT increase which is not explainable in any other way, has a form of FLD (provided that the known causes such as viral liver inflammations, increased alcohol consumption and toxic effects have been excluded). In the category of metabolic syndrome we include in particular the people with a larger girth, lower cholesterol in the HDV fraction and patients with a tendency towards the II. stage of diabetes mellitus. On the whole, the WOSCOPS Study (West of Scotland Coronary Prevention Study) has proved this in a quite convincing way (5). In other words, FLD may nowadays also be included in the metabolic syndrome without any doubts. It must only be taken into consideration that this contention shall only be attached to the ALT, and that it shall not refer to the aspartat aminotransferase in any way, which is sometimes taken as an ALT complement. The serum gamaglutamyltransferase (6–8) is more likely to be a complement. The fact that as for the WOSCOPS study, the connection of the increased transaminase having its origin in the statin (pravastatin) (5) application is of a problematic nature. However, whether this may only be a variation within repeated measuring, the statin effect on the ALT measurement or a direct hepatotoxicity, has remained unclear. That is the reason for the bumper-like zone of triple normal ALT values having been proposed; no measure will have to be taken here. On the contrary, another piece of information from the WOSCOPS study may be mentioned as a benefit: in patients treated with statin a decrease of nearly a third in diabetes mellitus (9) development has taken place. Some patients also have an increased total bilirubin level. However, seeing this circumstance only from the FLD point of view remains unclear, because in the hepacyte biliary pole more actions are running than in the blood pole. To make the matter clearer, the biochemistry indicator spectrum should be extended (at least by the alkaline phosphate), and also by the FLD morphology knowledge; however, this might not lead to any decision related to the further treatment procedure. Unquestionably, pharmacological interventions have as a consequence further hepacyte load, the occurrence of different medicine interactions with an impact on the function (later even on the structure) of different tissues may happen. These problems are not so far from the statin induced myopathia, or from the rhabdomyolysis (10). Here, the same laboratory indicators will already have to be observed in a time axis, potential interactions clarified, an eventually the dosage of the medicine regulated. With any uncertainty, performing a liver biopsy should not be excluded.

CONTRIBUTING ELEMENTS

There are genders where most of the familiar ancestors look phenotypically in the same way as the recognizable representative of today's metabolic syndrome, including the FLD. However, in most cases the FLD has been acquired as a consequence of lifestyle. A very general estimation may be made that the most of the better situated people shall have FLD with the primarily lower alcohol consumption (this will be here only of the modulating effect). The opposite poles shall be created by the people having primarily worse nutritive conditions and being with a more widely represented alcohol consumption, or already with alcoholism (here the proportion of the resulting cirrhosis may obviously be higher). With the people with the over-abundant calories consumption, this process may be more psychic and involuntary. Here, the processes have become repeated periodically leading to a habit, or dependence, the feeling of clear hunger is going to be missing. With some people, psychic tension and hurry may play their role (eating under stress, as is caused in the US by the fast food system, earlier connected with the consumption of a high amount of the non-dietary saturated drinks). Asians, however, have a similar problem (7). Gradually the stomach dilatation appears. Also in our country, an equivalent phenomenon of obligatory periodic receptions may be found that may often go together with over-abundant and thoughtless calories intake. Total physical activity level is decreasing, whereas the sometimes mentioned "mitigating" aspects of this group of patients - visiting the fitness centre, sauna, and going to play golf - may be better characterized as being nowadays a more requested activity than the actually necessary amount of the sporting activities. Thus, also the psychological component and a conscious change in the eating habits earlier than the surgical/endoscopic performances may come into consideration, being of the type of the stomach reduction.

WHICH IS TO BLAME: STATIN OR FATTY LIVER?

Principally there is consent to the mature metabolic syndrome with the FLD a certain assortment of medicines must be applied, where generally the acetylsalicyl acid, statins, inhibitors such as angiotensine of the converting enzyme, or potentially the sartans and with a high probability also the oral antibiotics may be found (11). Should ALT observance be concerned, a number of oscillations and potential ALT increase may be considered as being damage to the biochemical and metabolic hepatocyte activities within the natural progression with FLD, or as the hepatotoxic effect of the statins. However, one of the first summary analyses of year 2004 suggested that the application of the the3-hydroxy-3metylglutaryl of the coenzyme A should not lead to a statistically significant increase in the liver functions as for the biochemical point of view in comparison with the placebo group. However, a group of more than 49 000 patients were concerned and the statins of the lovastatin, pravastatin a simvastatin type were used at a low to medium dosage (12). That means that one side of the scales has to be with the positive statin effects and the other with the proved harmful ones and

not the concerns, or moreover, circulation of alarming news. Unequivocally, statins decrease mortality connected with the affection of the coronary vessels and decrease the incidence of the myocardium infarct incidence, vascular cerebral incidences and of the diseases of the peripheral arteries, while they also successfully decrease the necessity of any revascularization performances (13). Today's estimations are that only in the US annually more than 10 million prescriptions have been given in connection with one of the six statins available. Thus the ALT symptomatic increase has been considered to be a usual accompanying phenomenon and this problem shall be put to the recognition of a really serious liver lesion, where, without any hesitation, the statin may be blamed. This situation may seem to be exist today; however, it occurs extremely seldom. Naturally, an objection may be the fact that this statement is statistical and not allowing to distinguish an individual in advance. However, this represents a usual problem of the application of any treatment of any health problem. Nevertheless, there is also data in connection with various disasters around the rhabdomyolysis caused by the statins, which is not completely adequate. The hepatal issues are slightly different, which is because of another key organ and the biochemical tests having a different orientation, but also because of the fact that with most people there is no expression of any "preexisting muscular disease" as for the FLD analogy. It may be possible that a part of the concerns has its origin based on some experimental works carried out in the past; however, for man no hepatocellular necrosis has been observed in connection with statins. This makes the issues different from the statin rhabdomyolyse mentioned, where nowadays the already defined interaction with other "unsuitable" pharmaceutics occurring on a concrete cytochrome may mostly be detected. In addition, nowadays cerivastatin, being with problems and excluded from the market, is not mentioned in the summaries any more. Today's standpoint of the ALT elevation with the statins should be regarded as an exaggeration, being only a simple accompanying phenomenon (14–16). However, the problem of relating the achieved ALT elevation to the initial level of this indicator already before the beginning of the statin application has not been solved yet. Naturally, the input ALT level should always be known. There is an estimation that after the statins have been applied, the ALT may exceed the triple level of the normal value with ca 3 % of the patients and fewer than 1 % of the patients under the treatment shall exceed a value five times higher than the norm. Only 2 per thousand of patients will achieve the value ten times higher than the norm (17). As for these patients, there are no references related to their organic liver lesion; however, there is no notice related to an imaginary "calibration" as for the output level of the FLD. Similarly, as there are some stages of the statin safety related to the myopatia induction (10), an order may be detected, where as for the relation to the induction of more than a triple ALT elevation in comparison with the laboratory standard (thus not being in comparison with the initial value), the rosuvastatin followed by the atorvastatin might seem being the best. It may be very difficult to decide between the lovastatin, simvastatin, pravastatin and fluvastatin regarding any further positions, because here cause the fluctuating effect of the dosage (which in particular oscillates with the dosages of 40 and 80 mg) (15). To sum up, however, no really principal differences related to all statins may be detected. Similarly, nothing is known regarding the behaviour of the elevated ALT profile over a longer period of time, should the dosage of the statin remain unchanged. The indicating doctor should decrease the statin dosage after detecting the ALT increase within 2 collections following each other! Thus, nothing is known about the cell adaptation or potentially about the phenomenon that might only distantly remind of the parallel with the ischemic preconditioning, should it be existing also here. On the contrary, there is speculation related to the potential immune and allergic effect connected with the re-prescribing of the statin. One case report about atorvastatin ending in the cholestatic liver inflammation (18) has been explained by this mechanism. Completely being in the extreme position, there is a description of a case of the liver failure based on the preventive atorvastatin medication after the endarterectomy of the cervical artery (19). In that case, the patient was in a higher age with a number of associated diseases, where, among others, renal insufficiency was represented. Based on one of the theories, the statins did not have to lead to the liver lesion directly, but they might induce autoimmune processes, or unveil them, because in the time before their prescription they had been completely latent and the common biochemical tests had not been able to establish them (20). As for the cardiologist point of view, experience suggests that lovastatin applied for a long period with possible fulminant liver failure caused by the effect of the statin occurs with one in a million people taking lovastation for the period of 1 year (21). A very interesting piece of information may be found in the American liver transplantation register. In the period of 12 years ca 7700 performances of this sort were executed based on after-medicamentous liver failure. Out of this number 49 % presented a connection with the acetaminophen, with 17 % izonicotylhydrazide was to blame, with 10 % propylthiouracil and 7 % each both phenytoine and valproic acid. Out of the remaining rare agent only in 3 cases were statins represented (1 simvastatin and 2 cases with the cerivastatin taken out of the running as already mentioned above) (22). Based on this context, the statin may not seem to be to blame, with a bit of exaggeration; nevertheless, the statin remains a neither desired witness of the act and under particularly negative circumstances, and in addition quite seldom, it may be taken as an accomplice of the liver lesion. Further, a speculation may be possible that the basic problem lies with the primary liver lesion, being in the latent stage before prescribing of the statins, or clinically totally insignificant

SPECIAL GROUP OF PATIENTS

A completely special group of patients is formed by patients not having the causal alcohol effect in the anamnesis, but who have a specific sort of metabolic syndrome and FLD. These are the patients with the lipodystrophy caused by the HIV infection, undergoing a high-effective antiretroviral treatment (HAT). The patients are of a central obesities type with a strikingly low fat layer on extremities and in the face and with fast developing laboratory changes following the prescription of the HAT (increase in the cholesterol, triglycerid and glycaemia levels, or an increase in the lactate level during the early stages). As for their restrictions, these patients should stay apart from the corticoid effects as well as from the immune-modulating agents and they should not have any serious disease in the period of the past 3 months, including those diseases usually belonging to the AIDS category. The statistics indicate that patients with HAT have a 25 % higher risk of coronary arteriosclerosis development already in the first 4 years (23). A large part of these patients have no other risk factor, and that is why the very EAT may be have been blamed with certainty to have caused the given course. There is also other evidence existing with the support in the direct measurements of the intima and media thickness in cervical arteries. In patients with a positive HIV the annual thickening of this layer is ten times faster than with patients without the HIV (24). The development of the metabolic syndrome and the FLD is completely specific; it differs from the "classical" type and has not been fully understood yet. With the patients having HAT, lipotoxicity develops gradually, being able to change the usual appearance of the patients. The recognition and composition

of the treatment of the basic disease may soon change this topic considerably, for example the application of ritonavir, nelfinavir or indinavir may lead to an induction of a various risk of inducting of dyslipidemy. This problem shall retreat with the transition of the treatment to abacavir, efavirenz or nevirapin. Primarily the stavudin in a separate application has been responsible for the induction of the lipodystrophic picture, and together in a combination with didanozin this effect has been intensified. If the statin has been added to this treatment, liver problems may occur, where the key role usually is with the cytochrome P450 3A4. Therefore, the statins, having a different metabolism, should be applied. The selection between the pravastatin, fluvastatin or rosuvastatin shall be adequate. The dosages being as low as possible (being around 10 mg/day) shall guarantee a very good service. Principally, there is consent to the fact that with these patients the combination with fibrates should not be proposed.

GLOBAL VIEWPOINT

FLD is obviously an interdisciplinary problem. It may lead to the premature arteriosclerosis of the live vital sections of the arterial bed, it may contribute to the origin and development of the diabetes mellitus of the II type and it may result in the progressing liver lesion. It should be related to the increasing number of the patients with the HIV treatment with an entirely specific importance. Statins should quite unquestionably belong to the treatment spectrum of the mentioned patients. So far, reservations relating to their potential connection with the worsening of the liver functions and even with the induction of the liver failure have been expressed sporadically. As for the common population of patients, where no extreme combination of adjoining diseases may be expected, the known liver disease at the beginning stage of the treatment and with a higher age of the patients, the risk of the statin application is fully acceptable. It is necessary to accept that with most patients statin therapy may be accompanied with the laboratory indicator increase (in particular of the ALT). This itself may not be of any significance. The fact must be taken into consideration that the desire for having the patient with ALT normal or limitary values may lead to our causing the patient harm by increasing the risk of cardiovascular incidences by the unnecessarily restricted treatment. If a connection between statin dose and ALT is found, the set statin will not have to be increased till the moment when the LDL cholesterol fraction shall be effected, but when the liver tests values will already become disproportionately high. The given problem may be solved either by the cooperation with the hepatologist (with the use of the methods from the liver sonography to the liver biopsy), or a combined course of then treatment may be selected, with the statin not being necessary to be raised, and it may be sufficient to monitor only both the cholesterol and ALT spectrums, and another chemical may be added. As for the set circumstances, the ezetimib (25) seems to be very promising.

The above-mentioned facts should not only enter cardiologic surgeries, but also the surgeries of the general practitioners, so that the intended effect of the treatment may not degrade only thanks to some superstitions, with totally rare casuistics and to the ALT meaning being read out of context . Likewise, an equal sign may be unequivocally put between the statins induced by myopatia/ rhabdomyolysis and the liver parenchyma condition. By means of statins not only a concrete dyslipidemy may be treated, but also FLD. As for a set period, an inseparable part of the treatment is naturally based on the instructions given to the patient to secure the patient's using up more calories than he or she takes in, and further aiming at achieving a balance of the general energetic terms. With regard to potential medical interactions, the individual pharmacotherapy will have to be rationally directed also at other, concurrently existing health problems. A number of well-known and unsuitable combinations of statins with other medicaments may be seen here (as for history, naturally earlier in connection with the mentioned myopathies) (26, 27) and with some food complement (grapefruit juice). The fact that this is an interdisciplinary topic may also be finally advantageous for a general practitioner as well, because in case of uncertainty at least the patient's consulting judgment between the hepatologist, cardiologist and diabetologist may be counted on.

Abbreviations

AIDS – Acquired Immunodeficiency Syndrome
ALA – Alanin
ALT – Alanine Aminotransferase
AST – Aspartate Aminotransferase
HDL – lipoproteins with High- Density Lipoproteins
HIV – Human Immunodeficiency Virus
LDL – Low- Density Lipoproteins
FLD – Fatty Liver Disease
HAT – High-Efficient Anti-retroviral Treatment
WOSCOPS – West of Scotland Coronary Prevention Study

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COMMENTARY

Review of the article by J. Šochman "Non-alcoholic Liver Steatosis and Treatment by Statins"

Fatty Liver Disease and Statins – Which Discipline Does this Problem Belong To?

Non-alcoholic liver steatosis (non-alcoholic fatty liver disease – NAFLD) is a very frequent disease with an estimated prevalence of 20 % in developed countries (1). Although this disease begins first as a simple steatosis, it may proceed in a great portion of patients to the phase of steatohepatitis (non-alcoholic steatohepatitis – NASH); fibrotising steatohepatitis may evolve in up to 50 %, liver cirrhosis emerges in up to 15 % and in 3 % even hepatic insufficiency requiring liver transplantation (2, 3). Recent studies demonstrate that the cause of a significant propportion of cases of cryptogenic liver cirrhosis, representing broadly 5 % of all cases of liver cirrhosis, is NAFLD (4, 5). NAFLD is in fact the most frequent cause of chronic liver tests elevation and probably the most common liver disease (6). Considering the direct relation between obesity, with rapidly raising prevalence all around the world, and NAFLD, it is estimated that in the year 2025 more than 25 millions habitants of the USA will be affected by this disease: over ten times more than the current prevalence of hepatitis C virus infection (2). These facts have large consequences. Patients with cirrhosis on the basis of NAFLD/NASH who undergo liver transplantation have significantly worse prognosis compared with other indications of liver transplantation (2), with high risk of NASH recurrence and fibrinoid transformation of liver tissue (7).

Direct etiopatogenetic relation to NAFLD has been proved not only for obesity but also for other components of metabolic syndrome such as insulin resistance, hyperinsulinemia, hypertriglyceridemia and systemic hypertension (8). Inhibitors of HMG-CoA reductase, statins, are among the pharmacotherapeutic equipment used in the treatment of metabolic syndrome (9). For these reasons their application in the treatment of NAFLD/NASH seems to be reasonable. In consensus with the opinion of Dr. Šochman as presented in his article, statins may be considered very dangerous drugs regarding the possible hepatotoxicity. This, among other things, was very summarised in very complex fashion in the recent article by Chalasani (10). This fact is also supported by the results of several recent studies where statins were successfully applied in the treatment of NAFLD despite certain risk of hepatotoxicity in some studies. In the study of Turkish authors (11) 27 patients with NAFLD were treated with atorvastatin for 6 months. After this treatment transaminases normalised and even liver steatosis improved in these patients. Improvement of liver ultrasound picture also appeared after treatment with atorvastatinu for 24 months in a small group of patients with NAFLD as reported by Greek authors (12), as well as in the study by Horlander and Kwo (13). Normalisation of liver tests and improvement of histological picture of NASH were described in 5 patients treated with pravastatin for 6 months in another study (14). In this context is appropriate to add that considering the last studies, even a low risk of hepatotoxicity induced by statins is not increased in patients with liver test elevation (15), and administration of statins to patients with NAFLD is not considered as contraindicated (16) but probably useful, according to the above facts. This question will be definitively proved only by larger controlled studies, the execution of which is to be expected in the near future.

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Supported by Grant of the Ministry of Education, Youth and Sport MSM 0021620807.

Translation: P. Peisker