CORRESPONDENCE

Treatment Options for Statin-Associated Muscle Symptoms

by Prof. Dr. med. Ulrich Laufs, Prof. Dr. rer. nat. Hubert Scharnagl, Prof. Dr. med. Martin Halle, Prof. Dr. med. Eberhard Windler, Prof. Dr. med. Matthias Endres, and Prof. Dr. med. Winfried März in issue 44/2015

Creatine Kinase Levels After Exercise

Physical exercise or strenuous sporting activities can increase blood creatine kinase (CK) levels—something to bear in mind in patients with suspected statin-associated muscle symptoms. In their article about CK increases under statin treatment, Laufs et al. have repeatedly highlighted this important aspect (1). Nevertheless, some comments are necessary to supplement the information provided.

Muscle exercise stress does not regularly "increase CK levels to 500–600 U/L" (1); in this respect, there is considerable interindividual variability. The majority of competitive athletes have raised CK level in the blood (2). In individual cases, CK levels may occur that are clearly above 1000 U/L (3). However, some athletes show only moderate or no response (non-responders) (4). Regular preventative exercise with relatively constant muscular-mechanical stress is not often associated with CK increases. On the other hand, CK levels respond to marked changes in the amount and intensity of exercise. Thus, CK levels may increase significantly after unusual and eccentric types of exercise. This primarily applies to strength and speed-strength exercise stress (4). Therefore, taking a thorough exercise history is important to resolve issues with differential diagnosis. A cut-off CK concentration of more than 4x upper limit of normal (ULN) is of little diagnostic value. One can only agree with the authors that patients with suspected exercise-induced CK increases should observe a training break of one week. Unfortunately, competitive athletes often find it quite impossible to do this.

Marked increases in CK activity in the blood are often associated with an increase in aminotransferases; here, glutamic oxaloacetic transaminase (GOT)/aspartate aminotransferase (AST)—because of its higher muscular activity—shows a stronger response compared with glutamic pyruvate transaminase (GPT)/alanine aminotransferase (ALT). Gamma-glutamyl transpeptidase (GGT) remains unchanged (3). Increases in aminotransferase levels can be expected when the creatine kinase levels exceed 3x-4x ULN.

DOI: 10.3238/arztebl.2016.0344a

REFERENCES

1. Laufs U, Scharnagl H, Halle M, Windler E, Endres M, März W: Treatment options for statin-associated muscle symptoms. Dtsch Arztebl Int 2015; 112: 748–55.
2. Meyer T, Meister S: Routine blood parameters in elite soccer players. Int J Sports Med 2011; 32: 875–81.
3. Kindermann W, Salas-Fraire O, Sroka G, Müller U: Serumenzymverhalten nach körperlicher Belastung – Abgrenzung von krankheitsbedingten Veränderungen. Herz/Kreislauf 1983; 15: 117–23.
4. Urhausen A, Kindermann W: Aktuelle Marker für die Diagnostik von Überlastungszuständen in der Trainingspraxis. Dtsch Z Sportmed 2000; 51: 226–33.

Prof. Dr. med. Wilfried Kindermann
Institut für Sport-und Präventivmedizin,
Universität des Saarlandes, Germany
w.kindermann@mx.uni-saarland.de

Conflict of interest statement
The author declares that no conflict of interest exists.

Coenzyme Q10 Deficiency

The prevalence of dyslipidemia is high. It is usually treated with statins which inhibit HMG-CoA reductase and also coenzyme Q10 synthesis. This may lead to muscle pain. The question whether coenzyme Q10 replacement treatment helps to improve these muscle symptoms has been evaluated in a prospective study.

Between April 1, 2010 and October 31, 2015, 135 patients (58 women and 77 men, mean age 61 years [41–81] and 62 years [37–87], respectively) with dyslipidemia taking doses of 20–40 mg simvastatin were treated with a dose of 100 mg coenzyme Q10 daily. All of these patients experienced muscle and joint pain. After having taken coenzyme Q10 for several weeks (at least six weeks), 74 patients reported that the symptoms had disappeared completely, 42 patients reported improvements and 19 patients no improvement at all. The latter were patients with osteoarthritis in whom the symptoms were most likely not primarily related to statin treatment. Caso et al. (1) also found a reduction in muscle pain in patients treated with 100 mg coenzyme Q10, while Young et al. (2) did not find a positive effect.

The German Federal Office of Consumer Protection and Food Safety (BVL, Bundesamt für Verbraucherschutz und Lebensmittelsicherheit) does not generally recommend coenzyme Q10 replacement to treat muscle symptoms associated with simvastatin intake.

Therefore, first it should be attempted to treat the coenzyme Q10 deficiency with a diet rich in liver, oily fish, nuts or pulses. In addition, it should be tried to establish an alkaline diet (vegetable, fruits). At the same time, the intake of acidic food (cereal products, pasta, hard cheese, curd cheese, fish, and meat) should be reduced. By establishing a morning pH of 7, it is possible to prevent muscle hyperacidity associated with limited blood flow as well as muscle pain (3).

Based on these data, coenzyme Q10 replacement treatment appears to be beneficial in patients who do not experience pain alleviation with these dietary measures. DOI: 10.3238/arztebl.2016.0344b

REFERENCES

1. Caso G, Kelly P, McNurlan MA, Lawson WE: Effects of coenzyme q10 on myopathic symptoms in patients treated with statins. Am J Cardiol 2007; 99: 1409–12.
2. Young Jm, Florkowski CM, Molyneux RG, Frampton CM, George PM, Scott RS: Effect of coenzyme Q (10) supplementation on simvastatin-induced myalgia. Am J Cardiol 2007; 100: 1400–3.
3. Kiesewetter H: Active Nutrient akut und aktiv zur Vorbeugung von Wadenkrämpfen. Phlebologie 2015; 44: 66–70.
4. Laufs U, Scharnagl H, Halle M, Windler E, Endres M, März W: Treatment options for statin-associated muscle symptoms. Dtsch Arztebl Int 2015; 112: 748–55.

Prof. Dr. med. Dr.-Ing. Holger Kiesewetter
kiesewetter@haemostaseologicum.com

Conflict of interest statement
The author declares that no conflict of interest exists.

Statins Impede a Healthy Lifestyle

According to the article's summary, at least 5% of patients taking statins have statin-associated muscle symptoms (1). Not much later in the body of the article, rates of 10 to 30% are mentioned. Their negative impact on quality of life is acknowledged in the introduction. It is stated that one-third of those undergoing long-term treatment with statins report difficulties under regular statin intake. Absolute values are required to assess whether taking statins helps to prevent coronary heart disease. Patients want to be able to weigh the symptoms they experience against the expected benefits.

The seven authors (only one with no conflict of interest) postulate a long-term statin compliance of 90%. Is this advisable taking into consideration the muscle symptoms and the resulting avoidance of physical exercise which leads to reduced muscle strength—especially when the body-mass index goes up?

A meta-analysis published in 2015 in the Lancet (n = 174 000, 27 studies) (2) evaluated the benefits of statin primary prevention. The study showed that statin treatment with corresponding LDL reduction over a period of 5 years per 1000 persons (male and female, respectively) prevented 9 coronary heart disease-related events in women and 12 in men. Consequently, in patients with a history of coronary heart disease, 43 severe vascular events per 1000 patients treated with statins would be prevented per mmoL LDL reduction over a period of 5 years.

A study published in 2015 (3) (n = 132 000) reported data on first heart failure hospitalization. The absolute risk of first heart failure hospitalization was 2.0% in patients treated with statins over a period of four years and 2.3% without statin therapy. A number needed to treat (NNT) of 333 was calculated; no differences in mortality were found—regardless of the history of myocardial events.

Older patients treated with statins tend to avoid physical exercise and spend more time sitting. Physical activities are hindered by muscle pain, fatigue and weakness. This is confirmed by a prospective study (4) (n = 4.137 × 73 years). Objective data were obtained using accelerometry, and a low rate of burning calories was confirmed. The weight gain resulting from reduced physical activity contradicts the goal of lowering lipids and preventing the development of obesity. Since many patients with diabetes are treated with statins, the latter is of particular importance. A meta-analysis published in 2014 found a rate of one additional diabetes case per 255 statin users, explained by reduced insulin sensitivity and insulin secretion. DOI: 10.3238/arztebl.2016.0344c

REFERENCES

1. Laufs U, Scharnagl H, Halle M, Windler E, Endres M, März W: Treatment options for statin-associated muscle symptoms. Dtsch Arztebl Int 2015; 112: 748–55.
2. Cholesterol Treatment Trialists' (CTT) Collaboration, Fulcher J, O'Connell R, et al.: Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 2015; 385: 1397–405.
3. Lee DS, Markwardt S, Goeres L: Statins and physical activity in older men: the osteoporotic fractures in men study. JAMA Intern Med 2014; 174: 1263–70.
4. Preis D, Campbell RT, Murray HM, et al.: The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials. Eur Heart J 2015 21; 36: 1536–46.

Prof. Dr. med. Dipl.-Psych. J. Matthias Wenderlein
Universität Ulm, Germany
wenderlein@gmx.de

Conflict of interest statement
The author declares that no conflict of interest exists.

In Reply

Prof. Kindermann addresses the difficulties in interpreting creatine kinase levels when statin treatment is combined with physical activity. Interestingly, subjective symptoms poorly correlate with objective clinical parameters in many cases. Since neither the pathophysiological mechanisms nor the spectrum of potential individual signs of an excessive response have been understood as yet, further research into this question is needed (1). Especially when used for secondary prevention, statin treatment should not be too readily discontinued—by a break in exercising, the etiology of the increased CK levels can be clarified.

Prof. Kiesewetter provides additional information for the coenzyme Q10 discussion. The significance of coenzyme Q10 remains controversial, since overall the evidence from available study data is to be regarded as neutral. For example, a recent study involving 120 patients who previously experienced myalgias while being treated with statins showed that only 36% of

these patients developed symptoms at all in a study with a randomized double-blind cross-over design. The intake of coenzyme Q10 had no effect, despite a 4-fold increase in plasma levels (2). This illustrates the poor correlation between statin dose and symptoms as well as the difficulty in evaluating a supportive treatment—in this case, coenzyme Q10. As all painful conditions, statin-associated myalgias may, in principle, respond to placebo treatment.

Statins and physical activity have an additive positive effect on cardiovascular morbidity (3). However, this needs to be qualified by pointing out that in patients with type 2 diabetes the effect of physical exercise on cardiovascular events was significantly weaker than expected (4). Nevertheless, all patients with prediabetes or overt type 2 diabetes should participate in a physical exercise program. If in individual cases statins limit a patient's ability to engage in a physical exercise program in prevention or rehabilitation, as highlighted by Professor Wenderlein, special efforts should be made to determine the maximum tolerable statin dose and to improve mobility. This is related to a principal message of our article (5): Key to the management of statin-associated muscle symptoms is to make time for the patient.

DOI: 10.3238/arztebl.2016.0345

REFERENCES

1. Auer J, Sinzinger H, Franklin B, Berent R: Muscle- and skeletal-related side-effects of statins: tip of the iceberg? Eur J Prev Cardiol. 2016; 23: 88–110.
2. Taylor BA, Lorson L, White CM, Thompson PD: A randomized trial of coenzyme Q10 in patients with confirmed statin myopathy. Atherosclerosis 2015; 238: 329–35.
3. Kokkinos PF, Faselis C, Myers J, Panagiotakos D, Doumas M: Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: a cohort study. Lancet 2013; 381: 394–9.
4. Look AHEAD Research Group: Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013; 369: 145–54.
5. Laufs U, Scharnagl H, Halle M, Windler E, Endres M, März W: Treatment options for statin-associated muscle symptoms. Dtsch Arztebl Int 2015; 112: 748–55.

Prof. Dr. med Ulrich Laufs

Klinik Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Germany

ulrich@laufs.com

Conflict of interest statement

Prof. Laufs has received consultancy fees and/or lecture honoraria, study funding to a third-party account, and reimbursement of travel expenses or conference participation fees from ABDA, AkdÄ, Amgen, AstraZeneca, Bayer, Berlin-Chemie, BNK, Boehringer-Ingelheim, DACH, Daiichi-Sankyo, i-cor, Lilly, Medtronik, MSD, Pfizer, Roche, Sanofi, Servier, Synlab, UdS, and UKS.