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Statin induced myopathy presenting as mechanical musculoskeletal pain observed in two chiropractic patients

Robert J Rodine, BSc, DC*
Anthony C Tibbles, BSc, DC, FCCS(C)**
Peter SY Kim, BSc, DC, FCCS(C)§
Neetan Alikhan, MD, CCFP-EM†

Lipid lowering drugs, such as statins, are commonly used to treat approximately 10 million Canadians affected by hypercholesterolemia. The most commonly experienced side-effect of statin medication is muscle pain. Statin induced myopathy consists of a spectrum of myopathic disorders ranging from mild myalgia to fatal rhabdomyolysis. The following is a presentation of 2 cases of statin induced myopathy in patients presenting in a chiropractic setting. In addition, discussion will surround the mechanism, predisposing risk factors and frequency of statin induced myopathy while highlighting the role that chiropractors and other manual therapists may play in its recognition and management.
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KEY WORDS: statin, adverse events, myopathy, myalgia, myositis, rhabdomyolysis, chiropractic.

Les hypolipidémiants, tels que les statines, sont utilisés couramment pour traiter environ 10 millions de Canadiens touchés par l'hypercholestérolémie. L'effet secondaire des statines ressenti le plus souvent est la douleur musculaire. La myopathie provoquée par les statines consiste en un spectre de désordres myopathiques allant de la myalgie légère à la rhabdomyolyse mortelle. Voici une présentation de 2 cas de myopathie provoquée par les statines chez des patients d'un contexte chiropratique. En outre, la discussion portera sur le mécanisme, les facteurs de risque prédisposants, et la fréquence de la myopathie provoquée par les statines, tout en soulignant le rôle que peuvent jouer les chiropraticiens et autres thérapeutes manuels dans la reconnaissance et la gestion de celle-ci.
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MOTS CLÉS : statines, événements indésirables, myopathie, myalgie, myosite, rhabdomyolyse, chiropratique.

Introduction

Roughly 10 million Canadians and 106.7 million Americans suffer from hypercholesterolemia.[1,2] As a result, these individuals are at increased risk for atherosclerosis, stroke and heart disease.[1] Current Canadian guidelines recommend lifestyle modifications (Table 1) and statin therapy for the treatment of dyslipidemia and coronary artery disease (CAD).[3] Statins have consistently been shown to reduce cardiovascular related mortality and morbidity through the reduction of low density lipoproteins (LDL).[4–10] This has led to a trend of increased statin usage over the past two decades, represented in Canada

* Corresponding Author: Graduate Student, Graduate Education and Research Programs, Canadian Memorial Chiropractic College, 6100 Leslie Street, Toronto, Ontario, M2H 3J1. Tel: 416-482-2340. Email: rrodine@cmcc.ca
** Associate Professor, Director of Clinical Education and Patient Care, Canadian Memorial Chiropractic College, 6100 Leslie Street, Toronto, Ontario, M2H 3J1. Tel: 416-482-2340.
§ Associate Professor, Division of Clinical Education, Canadian Memorial Chiropractic College, 6100 Leslie Street, Toronto, Ontario, M2H 3J1. Tel: 416-482-2340.
† Medical Director, Markham Stouffville Urgent Care Centre, 110 Copper Creek Drive, Unit 100, Markham, Ontario, L6B 0P9. Tel: 905-472-8911.

Table 1

Current Canadian guideline recommendations for the treatment of dyslipidemia and CHD[3]

- suggest lifestyle management
- smoking cessation
- limiting the intake of saturated fats and refined carbohydrates
- maintenance of a body mass index (BMI) less than 27 kg/m^2
- participating in 30 to 60 minutes of moderate exercise at least four days per week

whereby usage rates rose from 1.6% in 1994 to 7.8% in 2002.[11] In 2004, approximately 24 million Americans were taking statin medications.[12]

Of considerable interest, the long-term cardiovascular benefits achieved with prolonged statin therapy may be attained without significant negative sequelae.[13–15] This observation has resulted in recommendations for the sale of statins over-the-counter in the United States.[16,17] The premise of such a move is to improve accessibility to the public, and hopefully increase usage, thereby lowering rates of cardiovascular pathology. Of concern however is that patients are unlikely to know if and when they require intervention and are not likely to receive adequate lifestyle education. In addition, un-prescribed public use reduces the ability to monitor effects, both positive and negative, of administering such a medication in the context of a broader treatment plan. These concerns have resulted in the rejection of over-the-counter (OTC) status being granted to Mevacor by the US Food and Drug Administration a total of three times.[18] Despite these concerns however statins are currently available over-the-counter in the United Kingdom.[19]

While rare, side-effects of statin therapy exist in the form of renal disease, hepatopathology, neuropathy and death.[20–29] The most common side-effect in statin users is myopathy which includes a spectrum of myogenic disorders ranging from mild myalgia to fatal rhabdomyolysis.[24] The concern regarding rhabdomyolysis resulted in a Health Canada Advisory in 2005 warning patients, physicians and pharmacists about this rare, but serious spectrum of muscle disorders.[30] From this point forward the myopathic spectrum will be referred to as statin induced myopathy (SIM).

The following is a presentation of two cases in which patients presented to a chiropractic setting complaining of diffuse and generalized muscular pain. During historical examination it was discovered that both patients were concomitantly using cholesterol lowering medication. As the initiation of statin medication coincided with the onset of musculoskeletal symptoms and pain could not be mechanically classified through clinical testing, SIM was suspected.

Case 1

A thirty-four year old female presented to a chiropractic teaching clinic with neck pain of undetermined duration, along with a seven month history of bilateral lower leg and knee pain. Health history included type 1 diabetes, progressive retinopathy, managed hypertension, previous episode of frozen shoulder, trigger finger and nephropathy. Medications included eprex, levothyroxine sodium and fluoxetine for non-specified durations and 80mg atorvastatin daily for seven years. Blood pressure was measured at 122/80 on the right arm.

Knee and lower leg pain was aggravated by lying down, with increased severity at night. Lower leg pain was described as a burning and cramping sensation, worse on the right. Subjective weakness was described in knee extension and ankle dorsiflexion bilaterally.

Lower limb pulses were palpable and symmetric bilaterally. No trophic changes were observed. Sensory testing of the lower limbs was normal with the exception of a subjective decrease in sharp and dull discrimination on the right medial malleolus. Lower limb reflexes were 2+ bilaterally. Extensor hallucis longus on the right demonstrated 4/5 strength. Vibration testing and position sense was normal in the great toe bilaterally. A bilateral straight leg raise of 90º was achieved with hamstring tightness.

Knee range of motion revealed a flexion restriction to 90º bilaterally and full extension with 'pulling' created in the popliteal fossa. Medial joint line tenderness was elicited via digital pressure within the tibio-femoral joints bilaterally. Palpation revealed tenderness in the distal iliotibial band, quadriceps tendons, tibialis anterior and peroneals. Despite these findings however the chief lower limb complaint could not be recreated with physical examination.

Neck pain was aggravated by sitting postures and relieved by massage. Cervical nerve root tension tests were negative. Cervical range of motion was decreased 25% in lateral flexion bilaterally and associated with contra-lateral tightness. Rotation to the left was decreased 25% compared to the right. Extension-rotation positions produced posterior neck pain bilaterally. A painful motion restriction was found at C2–3 on the right. Palpatory tenderness was also elicited in the trapezius and levator scapulae bilaterally. Cervical pain was recreated with range of motion and palpation. Hyperalgesia was also noted in the lumbar spine erectors and gluteal muscle group bilaterally.

The patient was diagnosed with cervical facet joint dysfunction and a possible statin induced myopathy contributing to lower leg symptoms. Treatment for the neck pain included soft tissue therapy and joint mobilization. The patient was advised to consult with her physician regarding statin medication and muscle pain.

The patient returned for a follow-up visit seven days later and confirmed that she had ceased statin medication and had not felt leg cramping for four nights. Confirmatory blood tests were not obtained however as this decision was made without the aid of her family physician. Shortly thereafter, she was placed on rosuvastatin at an unidentified dosage. Symptoms returned more severely than the first episode, prompting another self-directed discontinuation of medication. The patient was seen three more times at which point lower leg cramping symptoms had discontinued and the diagnosis was shifted towards pes anserine bursitis. The patient was subsequently lost to follow-up.

Case 2

A seventy-six year old female presented to a private chiropractic office as a returning patient with a new complaint of lower thoracic paraspinal pain. No specific incident occurred at the time of onset, but the patient had been travelling, spending several hours sitting, interspersed with carrying suitcases. The pain had come on over several hours, but then remained present for several days. Morning hours were the most difficult. Initiating activity was accompanied by pain and stiffness. The intensity of the pain was significant enough to stop the patient from engaging in activities and she described the intensity as more painful than her preceding complaints.

Health history was unremarkable except for the prior back pain and one episode of angina, four years prior. The patient indicated that she was on simvastatin for the treatment of elevated cholesterol for several months. Previous complaints included low back pain and neck pain which had responded with resolution in one-to-three visits.

On physical examination, combined range of motion of the lumbo-thoracic spine was full, with pain at end range of flexion, extension and left rotation. Posterior joint provocation tests were mildly positive on the left side. Palpation revealed significant tenderness and tightness in the paraspinal muscles throughout the lower thoracic and upper lumbar regions. Pressure to the left paraspinal muscles reproduced her complaint. No abdominal tenderness was present. Lower limb neurological evaluation was within normal limits.

Plain film radiographs revealed mild osteopenia, with very mild degenerative changes.

The patient was diagnosed with mechanical back pain and treated with mobilization and interferential current for pain. Soft-tissue therapy was also incorporated. Symptoms improved for one to three days, but the pain and stiffness returned. Lack of sustained improvement raised the suspicion of statin-related myalgia. The chiropractor, with the patient's permission, discussed the issue with the woman's daughter, a nurse, who accompanied the patient on a visit. The daughter had also wondered about this possibility. The patient was referred to her Family Physician, who changed the statin to another equivalent medication, atorvastatin.

Within one week of the medication change, the symptoms were diminished to the extent that the patient could re-engage in most activities, including gardening. The complaint resolved within two weeks. The patient did have further complaints for which she returned to the chiropractor's office. However, subsequent episodes responded well to two-to-three visits with resolution of pain for several months to years.

Discussion

The mechanism of statin medication

Lovastatin (Mevacor), produced by Merck & Co. Inc. in

1987, was the first statin to be commercially marketed. To date, the statin drug family has grown to include atorvastatin (Lipitor), cerivastatin (Baycol), fluvastatin (Lescol), pravastatin (Pravachol), rosuvastatin (Crestor) and simvastatin (Zocor). Baycol was withdrawn from the market in 2001 due to its increased association with fatal rhabdomyolysis.[31]

Statins, otherwise known as HMG-CoA reductase inhibitors, decrease de novo cholesterol biosynthesis by blocking the rate-limiting step in cholesterol synthesis. By countering HMG-CoA synthase, statins block the formation of mevalonic acid, which is a precursor to all steroids, including cholesterol. This stimulates the liver to increase the number of LDL receptors and draw LDL from the blood for the purposes of bile production. [31,32]

The effectiveness of statin intervention for dyslipidemia

The Scandinavian Simvastatin Survival Study was the first major study on long term statin effectiveness. The study followed over 4000 patients for five years; it found that those receiving statin therapy demonstrated reductions in total serum cholesterol levels by 25% and LDL cholesterol levels by 35% when compared to the control group. In addition, the study group demonstrated a lower relative risk of all cause mortality (RR of 0.70) compared to controls.[33] This publication was a landmark study in the field of cardiovascular related health.

Statins have consistently shown positive results in the secondary prevention of cardiovascular mortality in both meta-analysis and systematic review.[34,35] Recently, the effectiveness of statins on the primary prevention of cardiovascular mortality was addressed in a meta-analysis that included data on 65,000 patients. The authors concluded with statistical significance that statin users showed a relative risk of 0.93 for all-cause mortality, 0.89 for cardiovascular-related deaths, 0.85 for major cardiovascular events and 0.77 for myocardial infarction, when compared to controls.[36]

Canadian guidelines for the treatment of dyslipidemia

A patient's risk profile for CAD is assessed via the Framingham Heart Score (FHS) which, when combined with known comorbidities, is used to classify patients as being at either high-, moderate- or low-risk for experiencing a major cardiac event within the next 10 years. The FHS is then combined with the patient's blood-lipid profile to determine therapeutic options. Readers are encouraged to review the Canadian guidelines for the diagnosis and management of dyslipidemia for more information on this scoring system.[3]

Lifestyle modifications in the form of smoking cessation, improved dietary intake and exercise therapy should be the primary intervention tool. However, statin therapy is recommended for patients that require medical assistance to adequately reduce their risk for CAD by reaching target LDL levels. Also, an LDL reduction of at least 50% is required to prevent progression of atherosclerosis in patients with established CAD. Statin monotherapy is likely to be sufficient in achieving this reduction for most patients, however increased statin dosage, or combination therapy with other pharmaceuticals, is recommended for those not achieving target levels. [3]

The mechanism of myopathy

Many mechanisms of SIM have been proposed. Theories range from altered mitochondrial respiration and derangement of cellular membranes, to the depletion of isoprenoids which control myocyte apoptosis.[24] One theory suggests that as statins increase tyrosine phosphorylation the resulting increase in cytosolic calcium causes apoptosis.[37] Another theory surrounds ubiquinone (coenzyme Q10) which contributes to the electron transport chain and mitochondrial respiration, therefore depletion could result in aberrant cellular metabolism. Ubiquinone is also responsible for GTP activation, helping to bind regulatory proteins.[38] Additional research points to altered ratios of lactate and pyruvate in statin users, representing a decreased reliance on aerobic metabolism.[39]

It should also be considered that polypharmaceutical interactions or altered cellular pathways via defects in genetic processes could result in a higher systemic bioavailability of statins, therefore augmenting adverse events.[40]

While many theories attempt to explain the mechanism of SIM, the true pathophysiology remains unknown. Therefore, without fully understanding the physiological cause of an adverse drug reaction, it is difficult to offer adequate prevention strategies.

This being said, a thorough understanding of the mechanism is important in order to accurately grasp the clinical

picture. This is especially true for the manual therapist who simply wishes to know 'how does this result in pain?' As previously alluded, many theories involve concepts of cellular respiration and the apoptotic control pathways, which may result in chemical/ischemic nociceptive stimulus.

Risk factors for developing SIM

While difficult to determine prevention strategies, certain risk factors have been identified that may predispose an individual to developing SIM. These include older age (with a higher prevalence in females), preexisting liver or renal impairment, hepatic fatty changes (consider this in patients with a history of alcoholism), hypothyroidism, a history of drug abuse, trauma, heavy exercise, ischemic scenarios and concomitant use of fibrates or corticosteroids.[25,26,41–43] In fact, the concurrent use of gemfibrozil (Lopid), a fibric acid derivative, was associated with 1/3 of rhabdomyolysis related deaths in patients using cerivastatin.[29]

A large observational study found that the risk of a myopathic event occurring in a diabetic patient was twice that of a non-diabetic patient.[42] This may correlate with case 1, whereby the patient had type 1 diabetes. Diabetic status however has been found to have no effect on the risk of developing rhabdomyolysis. [42]

The spectrum of myopathy

Published literature offers many definitions for myopathy. As a result, an attempt at standardization by the American College of Cardiology, American Heart Association and the National Heart, Lung and Blood Institute was made, resulting in the following terminology:[44]

- Myopathy: having to do with any disease of the muscle (non-specific)
- Myalgia: muscle ache or weakness without an elevation in blood creatine kinase (CK) levels
- Myositis: muscle symptoms that are associated with elevations in blood CK levels, upwards of ten times the normal upper laboratory limit
- Rhabdomyolysis: muscle symptoms associated with marked elevations in blood CK levels, significantly greater than 10 times the upper limit of normal and typically associated with myoglobinuria

Brought forth by similar concerns and increasing negative attention, the National Lipid Association established a Statin Safety Assessment Task Force (SSATF) charged with evaluating the effects and safety of statin therapy. One such panel, composed of muscle experts, sought to clarify definitions associated with statin myopathy as well as causative factors and management strategies.[25]

While supporting the previously mentioned definitions, the task force recommended further clarification. It was recommended that myopathy be categorized into symptomatic and asymptomatic forms (relating to elevated or non-elevated CK levels). It was also recommended that rhabdomyolysis be classified into mild (normal – <10 times normal), moderate (10 times – <50 times normal) and marked (over 50 times normal) in reference to CK elevations. Improved nomenclature based on laboratory analysis would help clinicians make more appropriate assumptions regarding the extent of muscle damage in such cases. It was also thought that new terminology would result in improved reporting of adverse events during clinical trials, including milder forms of myopathy.[25]

With regards to the presented cases, CK levels were unavailable as confirmatory blood tests were not obtained by either patient. In the example of case 1, the patient discontinued statin therapy without physician guidance and was lost to follow-up shortly thereafter. In the example of case 2, though physician guidance was sought, communication was unavailable during the time of care and the patient later became lost to follow-up.

Clinical Presentation

Unfortunately, the clinical presentation of SIM is not well described within the literature. Reports in large scale studies typically detail proximal muscle pain, weakness, myalgia, generalized aching, nocturnal cramping, diffuse or crampy pain and fatigue.[24] Case descriptions of SIM would be more valuable to manual practitioners with the inclusion of full physical examination findings such as range of motion, manual muscle testing, patient response to passive stretching, and palpatory findings. More thorough case descriptions would potentially allow clinicians to differentiate presentation and determine the likelihood of SIM in their own practice setting, though this theory is only speculative. While there has been minimal report given to physical examination findings, the timeline associated with the onset of therapy and symptom presentation has been discussed. A retrospective review of 45 SIM

patients revealed a mean onset of symptoms at 6.3 months following statin initiation, with a range between 1 week and 4 years.[45]

There is one report in the chiropractic literature of rhabdomyolysis secondary to the use of protease inhibitors for HIV infection. The patient was also taking an unidentified lipid lowering drug at 200mg/day. Rhabdomyolysis was diagnosed upon hospitalization following three days of muscle weakness and an inability to walk. This case however focuses on the link between rhabdomyolysis, medications and risk factors rather than differentiating a clinical presentation.[46]

The cases described in this report indicated that the patient history and description of pain were the most likely indicators of SIM being included in the differential diagnosis. In the first case, despite palpation revealing tenderness within the local musculature, the primary complaint was not provoked and therefore could not be classified orthopaedically. In this case, it was the patient's history and description of ischemic type pain that led to SIM as a differential diagnosis. In the second case, while palpation of local musculature did recreate the chief complaint, the patient's response did not adequately compare with treatment expectations. As a result, re-evaluation with historical consideration considered SIM as a differential diagnosis.

The Frequency of Statin Myopathy

Prevalence estimates of SIM have been variable. One study reported 5150 cases of minor muscle pain per 100,000 patient years, 97 cases of myopathy and 4.4 cases of rhabdomyolysis.[24] The PRIMO study, which included 8,000 patients receiving high-dose statin therapy for hyperlipidemia, found that muscular symptoms were reported in 10.5% of the subjects. Symptoms developed within a median time of one month following therapy initiation and prevented moderate exertion in 38% of patients, causing 4% to become bedridden.[23] The Heart Protection Study reported mylagia in 7% of patients, though no significant difference was noted between intervention and control groups.[5] Other reports place significant myopathic symptoms occurring in less than 0.5% of statin users.[22] A more recent cross-sectional analysis of 3,580 adults found that 22% of statin users experienced musculoskeletal pain in the previous 30 days compared to 16.7% of non-statin users, placing users at an adjusted odds ratio of 1.5 for experiencing musculoskeletal pain.[47]

Given this variability, the SSATF conducted a review of twenty-one independent clinical trials, concluding that while muscular symptoms are the most prevalent side-effect of statin use they are rare.[48] The Task Force concluded that up to 3% of patients taking statins will experience myalgia and five patients per 100,000 person years will experience myositis. More serious rhabdomyolysis is estimated to be a risk in 1.6 patients per 100,000 person years with a 10% fatality rate.[48]

Patient Monitoring

Baseline testing of CK levels should be conducted in patients at high risk for SIM to establish a reference point and prevent the inappropriate discontinuation of effective therapy.[26] Asymptomatic elevations are common and often benign, therefore routine CK testing is not recommended.[25] In addition, continuation of statin therapy is suggested in those patients experiencing tolerable myalgia and no greater than a mild CK elevation, given the benefits. This being said, symptomatic patients must be monitored closely to gauge the degree of muscle damage and determine prognosis. [25]

This monitoring of myopathic symptoms is an important role that manual therapists can fulfill. One example of this role is in the higher frequency of visits typically experienced within a manual therapy treatment plan as compared to medical management. Clinicians have an increased opportunity for follow-up questioning and the assessment of signs and symptoms. In addition, if during the course of a management plan, treatment progress is not meeting expectations or fails to match the natural history of the suspected diagnosis (muscle strain, myofascial pain, etc.) an alternate cause for the myopathic symptoms should be sought. An appropriate referral can be made if myopathic symptoms become questionable in cause or appear to be progressing.

Treatment of statin myopathy

Pending the exclusion of other known causes of myopathy, such as substance abuse and hypothyroidism, the general treatment approach is statin discontinuation.[24] Patients experiencing tolerable myalgia however without CK elevation, may continue therapy at the same or reduced levels with careful monitoring. Meanwhile if CK levels increase or myalgia progresses to an intolerable level, statin use should be discontinued under the

physician supervision. Once the patient is asymptomatic, statin therapy may be reinitiated at a reduced dose. This will help to determine causation versus temporal association as well as a possible dose-dependant threshold.[25,28,38]

In the event that a patient is suffering from rhabdomyolysis, statins should be discontinued immediately and the patient should be hospitalized. Intravenous hydration and alkalinization is the primary treatment with the clinical goal in such instances being to immediately cease muscle degradation and prevent further release of myoglobin into the blood stream, limiting the extent of renal damage.[24] Given the severity of the consequences, the role of the manual therapist would be to refer the patient to the emergency room when rhabdomyolysis is suspected.

Conclusion

While the spectrum of myopathy is a rare complication of HMG-CoA reductase inhibitors, myopathic symptoms represent the most commonly experienced side effect.[48] As dyslipidemia is a highly prevalent cardiovascular disorder, many patients presenting in a chiropractic setting may be taking medication in the statin family.

As always, a thorough health history and comprehensive physical examination should be performed in all patients presenting with musculoskeletal complaints. For those patients presenting with diffuse and crampy musculoskeletal pain while concurrently taking statin medications, SIM must be considered and explored. Suspicion should increase if pain cannot be classified orthopedically/mechanically. In addition, the spectrum of myopathy represents an excellent example of how frequent re-evaluation following a trial of therapy is essential to patient care. In the event that patients are not responding as expected, or if symptoms are progressing, differential diagnoses must be explored.

When SIM is suspected, it is essential to recommend that the patient follow-up with his or her medical doctor for further laboratory analysis and to discuss the potential of modifying pharmacotherapy.

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