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Commentary: Does my patient have statin associated muscle symptoms (SAMS)?

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ABSTRACT

Over time, the patient cohort considered suitable for HMG-CoA reductase inhibitors (statins) has broadened considerably. Research highlights that the benefits and harms from statins can vary in different populations (e.g. the elderly, females etc.) and indicating it may be linked to an increased risk of muscle damage and myalgia in certain populations. The incidence of muscle pain and other muscle symptoms, such as weakness, cramps and loss of stamina have been reported in the literature. Studies have indicated that the prevalence of myalgia in statin therapy ranges from 1% in clinical studies to 25% in clinical reports. It is likely that osteopaths will see patients who are taking statins and present with muscle pain or loss of function. Osteopaths ought to consider how to evaluate whether or not the patient's muscular complaint is in fact caused by statins. This article reviews identified statin associated muscle symptoms (SAMS), which patients may be at risk of them and proposes a method of identifying these patients in osteopathic practice.

1. Background

Muscle symptoms (e.g. myalgia, cramps) represent the most frequent adverse events among patients treated with statins [1]. The American College of Cardiology/American Heart Association Clinical Advisory on the use and safety of statins defined 4 syndromes [2], 1) statin myopathy (any muscle complaint related to these drugs, 2) myalgia (muscle complaints without serum creatine kinase (CK) elevations), 3) myositis (muscle symptoms with CK elevations, and 4) rhabdomyolysis (markedly elevated CK levels). Musculoskeletal pain and dysfunction also occurs in the absence of statins and in patients on statins for unrelated reasons; therefore, careful assessment of patients on statins is essential to provide the most efficacious osteopathic management of musculoskeletal presentations without affecting cardiovascular risk management.

Guidelines for managing absolute cardiovascular disease (CVD) risk in the Australian population were released in 2012 [3]. These guidelines incorporate multiple risk factors and have a primary prevention goal of modifying these factors to reduce the incidence of CVD in the community [4]. In 2012, Mihaylova et al. [5] suggested prescribing guidelines for statin therapy be re-considered to expand the population treated with cholesterol lowering medications to those with a low risk of CVD (5 year risk < 10%). In the 12 months to 30 June 2017 almost 29 million prescriptions for lipid modifying agents were supplied in Australia [6], almost 23 million of these prescriptions were for three different statins. Burke et al. [7] estimate more than 17% of osteopathy patients have a cardiovascular condition, i.e. almost 1-in-6 patients, suggesting it is likely many osteopaths will encounter patients on statins.

1.1. Impact of statin associated muscle symptoms (SAMS) on patients

SAMS may present in the patient at any time after beginning statin therapy [1]. They need to be evaluated by history, physical examination and laboratory testing when appropriate. Patient presentation may include muscle discomfort (myalgia), muscle weakness (myopathy), tenderness to palpation, with or without muscle inflammation (myositis) and/or myonecrosis [1].

Many clinical trials for statins did not solicit patient information concerning muscle problems, adequately define myalgia or muscle problems or document the severity of statin-induced muscle adverse events (MAE) [8]. Two large-scale French observational post-marketing studies [9,10] documented the common muscle symptoms and the impact on quality of life (QOL). They reported the commonest terms used by participants were terms such as “stiffness”, “heaviness”, “weakness”, “cramps” and “fatigue”. Both studies report 38% of participants experienced muscle symptoms that either prevented moderate physical activity or interfered with moderate exertion [9,10].

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Rosenbaum et al. also reported 42% experienced major disruption to everyday life [10] while Bruckert et al. report that only 28% of participants with SAMS considered the symptoms “a minor disruption” to their way of life [9].

1.2. Identifying those at risk and evaluating the risk

Osteopaths perform clinical history taking and examination to consider other causes of pain such as the evaluation for trauma, infection, metabolic and hormonal factors, and drug interactions/adverse events. Osteopaths should be aware of the risk/benefit relationship of statins in a low CVD risk population and the incidence and impact of the non-cardiovascular adverse events. While adverse events can include impaired cognition, haemorrhagic stroke and diabetes mellitus [11] this paper only addresses the adverse events commonly known as Statin Associated Muscle Symptoms (SAMS).

In a randomised controlled trial, Parker et al. [12] found 9.4% on a high dose statin met their rigorous criteria of myalgia over a six-month trial compared to 4.6% of the control group. The intervention group consistently reported lower girdle symptoms with an average time to onset of 35 days (*c.f. placebo = 61 days, $p = 0.045$*). Those with myalgia demonstrated greater decreases in leg muscle strength than those without myalgia in the intervention group although this difference was not statistically significant. Statin-induced muscle symptoms also occurred more often in older persons and females [12].

These findings were in accord with an observational study by Bruckert et al. [9] concerning the site of pain and prevalence (9.4% vs. 10.5%). This large-scale observational study ($n = 7954$) also identified potential triggers of SAMS such as “unusual physical exertion” or “commencing a new medication”. The study suggests that the odds ratio (OR) of experiencing muscle symptoms increases with the intensity of the regular physical activity conducted [9].

1.3. Population sub-group differences

A prospective cohort study by Smiderle et al. [13] showed the OR of an adverse drug effect (ADE) for women is 1.5–1.7 compared to men. Myalgia occurred more frequently in females compared to males (who were more likely to experience abnormal liver function). Combined use of other medications also increased the frequency of ADE. The medicine regime in this study was determined by physicians based on the participant's clinical presentation and included other medication (e.g. calcium antagonist, diuretic, anti-thrombotic etc.) as considered necessary for their cardiovascular condition. Therefore, presenting a “real world” situation of potential drug interactions.

Ito et al. [14] identified 29% of all participants in the USAGE trial experienced SAMS. 15% of all participants ceased their statin regime due to SAMS. Their analysis demonstrated the odds of new or worsened SAMS were higher in females:males (OR = 1.25–1.29); increased age (1.07–1.22) and obesity (1.07–1.27). Participants on average consumed three medicines that can interact with statins [14].

Interactions with statins are possible with colchicine (gout), some proton pump inhibitors (reflux, heartburn, ulcers), calcium channel blockers (hypertension), some anti-depressants (SSRI family) and some anti-microbial drugs [14–16]. Ito et al. [14] conclude that drug interactions are an important predictor of the occurrence of muscle pain as well as of ceasing statin therapy, and Cham et al. [17] identified patients most at risk of MAE were females and those over the age of 70.

1.4. The osteopathy patient profile and proposed SAMS risk identification

Burke et al. [7] estimate almost 1-in-6 osteopathy patients have a cardiovascular condition, suggesting it is likely osteopaths may see patients with SAMS in their practice at some time.

We propose that patients on statins presenting to an osteopath with onset of new muscle pain or complaint in one of the identified sub groups – female or over 70 or on multiple medications - should be considered at risk of SAMS. A medication review (drugs and dosages) at this point can identify patients at risk of SAMS through drug interactions. In addition, osteopaths should identify patients on statins with other risk factors, such as, a recent increase in physical activity (likely in those addressing CVD) or taking a new medication (for any reason).

Rosensen et al. [1] propose the administration of a statin myalgia clinical index questionnaire (see Appendix 1) as part of an initial screen to establish baseline muscle symptoms and periodically monitor patient symptoms. The index was assessed for content validation and inter-rater reliability and revised in 2017 (Rosensen et al. [18] - see Appendix 2). Both questionnaires document the location and pattern of muscle symptoms, the timing of symptom onset and the change in symptoms following withdrawal and re-challenge with statins. Clearly statin withdrawal and rechallenge must be under the supervision of a patient's GP. Rechallenge is defined as ‘the giving of a further dose(s) of a drug to a person who had previously taken a dose(s) of the same drug and in whom an adverse event, which might be due to that drug, had subsequently occurred’ [19]. Completing the initial section of these questionnaires can provide the patient and/or osteopath an opportunity to commence a dialogue with the patient's GP concerning statins and muscle symptoms if this has not yet occurred.

While the questionnaires are based on experience that the great majority of SAMS occur within the first month of commencing statin drug therapy it is important to remember the side effects (estimated at 15%) may occur at some time after six months [16,17] indicating that duration of statin use should not eliminate the consideration of SAMS in all patients.

A patient reported outcome (PRO) questionnaire has been developed by Jacobson et al. [20], the Statin Experience Assessment Questionnaire (SEAQ)© is a 15-item questionnaire to assess the patient experience with statin intolerance. Its aim is to foster “dialogue about statin intolerance between patients and providers” [20] (see Appendix 3).

The SEAQ is more explicit in recording the type of symptom (ache, pain, cramp, weakness etc.), symptom severity and measuring the degree of symptom interference with daily life. It also records the impact of symptoms on patient persistence with statin medication. It does not provide clinicians with a clinical index score on which to base medical decisions but does create a consistent measure of the extent and severity of patient symptoms.

The Australian Guidelines for the Management of Absolute Cardiovascular Disease Risk advise that pharmacotherapy is not routinely recommended for patients at low (< 10%) risk of CVD [4]. Patients at medium (10–15%) risk of CVD should initially implement lifestyle modifications before considering pharmacotherapy. By evaluating the absolute CVD risk of a patient with SAMS, an informed discussion of the trade-off between CVD risk and the symptoms experienced can occur. The Australian absolute cardiovascular risk calculator can be found at http://www.cvdcheck.org.au/and can be readily performed during an osteopathic consultation.

Patients of low to medium risk of CVD should be encouraged to discuss their muscle symptoms with their doctors and consider their willingness to modify lifestyle risk factors in light of their possible statin induced symptoms.

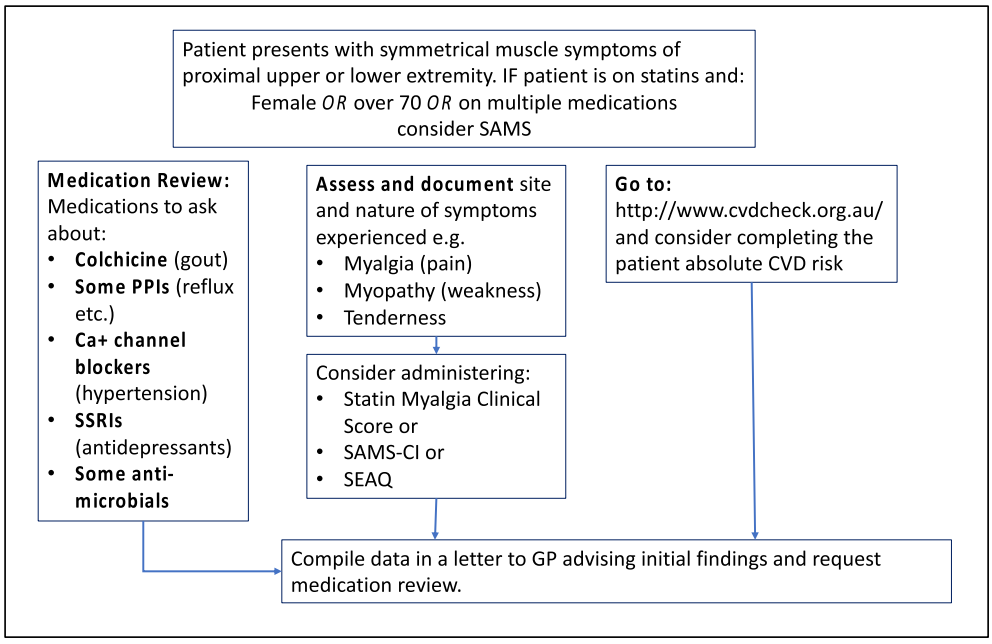
2. Conclusion

It is estimated 1-in-6 osteopathy patients in Australia have a cardiovascular condition. Women, the elderly and people on multiple medications are at greater risk of developing SAMS. Symptoms are located mainly in the lower girdle and can in some cases be attributed to unusual physical exertion or a change in medications. Most SAMS occur within one month of commencing treatment although a sizeable minority occur after six months of use, meaning duration of statin usage should not preclude consideration of SAMS. The impact of SAMS on

quality of life can be considerable.

Osteopaths should consider the possibility of SAMS in patients that meet any of the criteria identified above. Administration of a statin questionnaire as described above, combined with a medication review and a calculation of the patient's absolute CVD risk, can help inform the patient of medication issues to discuss with their doctor.

The proposed management flow chart is included below to summarise a suggested approach to manage patients suspected of SAMS



3. Recommendations

- Osteopaths should consider implementing a SAMS clinical index as a tool for screening patients who may be experiencing statin associated muscle symptoms (SAMS).
- Patients on statins who are female or over 70 or on multiple medications are at risk of SAMS.
- Patients on statins that have recently increased their physical activity or changed medication are also at risk
- Most patients experience SAMS from statins within the first 4–5 weeks however a minority (~15%) will experience SAMS after more than six months on statins.
- Australian guidelines for managing CVD risk emphasise lifestyle modification for patients of low to medium risk of CVD. Osteopaths can play a part in exercise prescription and improving patient mobility.
- Administering a clinical index score and assessing a patient's CVD risk can identify patients that may benefit from lifestyle modification instead of pharmacotherapy for CVD risk avoidance.
- Patients should discuss their symptoms and their CVD risk with their doctor when considering appropriate cardiovascular disease therapy.

Conflict of interest

LDG and MF state that there are no competing interests.

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Ethical approval

Not applicable.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ijosm.2018.05.001.

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