REVIEW

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Curcumin: An effective adjunct in patients with statin-associated muscle symptoms?

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Abstract

In spite of the unequivocal efficacy of statins in reducing primary and secondary cardiovascular events, the use of these drugs in a considerable number of patients is limited because of statin intolerance, mainly statin-associated muscle symptoms (SAMS). SAMS encompass a broad spectrum of clinical presentations, including mild muscular aching and other types of myalgias, myopathy with the significant elevation of creatine kinase, and the rare but life-threatening rhabdomyolysis. Among several pathophysiologic mechanisms of SAMS, mitochondrial dysfunction is thought to be one of the main one. Curcumin is the polyphenolic ingredient of *Curcuma longa* L., which has various pharmacological properties against a vast range of diseases. Curcumin has several mechanisms of actions relevant to the treatment of SAMS. These effects include the capacity to prevent and reduce delayed onset muscle soreness by blocking the nuclear factor inflammatory pathway, attenuation of muscular atrophy, enhancement of muscle fibre regeneration following injury, and analgesic and antioxidant effects. Curcumin can also increase the levels of cyclic adenosine monophosphate, which leads to an increase in the number of mitochondrial DNA duplicates in skeletal muscle cells. Finally, owing to its essential lipid-modifying properties, curcumin might serve as an adjunct to statin therapy in patients with SAMS, allowing for effective lowering of low-density lipoprotein cholesterol and possibly for statin dose reduction. Owing to the paucity of effective treatments, and the safety of curcumin in clinical practice, proof-of-concept trials are recommended to assess the potential benefit of this phytochemical in the treatment of SAMS.

Keywords Statin; Myopathy; Curcumin; Myalgia; Mitochondria; Statin intolerance

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Statins and their side effects

Statins are the cornerstone of pharmacotherapy for dyslipidemia, and their efficacy in both primary and secondary prevention of atherosclerotic cardiovascular disease is well established.[1] There are, however, unfavourable side effects to statin therapy, sometimes leading to statin intolerance with muscular symptoms, which are the most common and of critical importance.[2] Statin-associated muscle symptoms (SAMS) comprise a diverse spectrum and encompass heterogeneous clinical presentations.[3,4] These presentations include: (i) mild forms of muscle weakness and aching, with the prevalence of even up to 29%; (ii) other forms of myopathy and myositis accompanied by the rise of creatine kinase (CK)[5] to more than 10 times the upper limit of normal, with the prevalence about 1/10 000 to 1/1000 of the consuming population per year[6]; and (iii) life-threatening rhabdomyolysis, which is fortunately very rare.[5] From this point of view, SAMS are one of the major reasons for drug non-adherence and discontinuation in even 75% of the statin users during the first 2 years of treatment.[7,8] Nonetheless, the diagnosis of SAMS is not simple because the symptoms are subjective and difficult to be judged, and also there is no gold standard diagnostic test currently available.[9] Additionally, in a relatively large percentage of patients on statin therapy we might observe the so-called *nocebo effect*, when the patients expect to have statin-associated symptoms,

what might be excluded after careful interview and physical examination in selected cases.[10] Finally, a relevant 22% of patients reporting statin-associated symptoms do not confirm their persistence after statin re-challenge, whereas up to 7% of patients still report adverse effects after placebo administration.[11] An overview of the scientific knowledge on the pathophysiology of SAMS, as well as guidance for clinicians on their management, has been recently issued.[3,4] Occurrence of SAMS is dependent on the potency, metabolism, and dose of different statins, and their interactions with other drugs.[12,13] Furthermore, patients' demographics, such as age, gender, co-morbidities (e.g. diabetes, HIV infection, severe renal failure, hypothyroidism, hepatic dysfunction, and undergoing surgery), genetic susceptibility, and race, have been proposed as other predisposing factors for SAMS.[13–17] Several pathophysiologic mechanisms have been suggested to underlie SAMS. Among these mechanisms, mitochondrial dysfunction has gained widespread attention as the main player in the etiopathogenesis of SAMS. A number of studies have indicated that physical exercise can lead to disturbances in mitochondrial function in patients on statins.[18] Analyses of muscle biopsies taken from patients with SAMS and normal CK levels have revealed mitochondrial dysfunction in muscle fibres.[19,20] On the other hand, histological findings of patients with SAMS and abnormally high CK levels showed no abnormalities in the configuration of muscle fibres.[21] In addition, mitochondrial damage by statins appears to be drug specific as muscle biopsies taken from patients treated with simvastatin 80 mg daily or atorvastatin 40 mg daily for 8 weeks showed a decline in the number of mitochondrial DNA duplicates in the simvastatin-treated group but not in the atorvastatin-treated group.[22]

In spite of its clinical importance, pharmacotherapy options for patients with SAMS are very limited. There is evidence showing that low vitamin D levels are associated with myalgia in patients on statin therapy[23]; in addition, a role for vitamin D supplementation in resolving SAMS has been proposed.[24] Also, statin-induced depletion in coenzyme-Q_{10} (CoQ_{10})[25] has been suggested as a causal mechanism for SAMS[18,26] and prompted several investigations on the therapeutic role of CoQ_{10}.[27–30] However, contrariwise, the results of randomized controlled trials (RCTs) have been highly ambiguous, and a recent meta-analysis concluded that treatment with CoQ_{10} does not play a significant role in lessening SAMS.[31]

Curcumin in patients with statin-associated muscle symptoms

Curcumin is a natural dietary polyphenol, extracted from *Curcuma longa* L., which has been extensively studied for the treatment of various diseases owing to its numerous pharmacological properties[32] including, but not limited to, antioxidant,[33] anti-inflammatory,[34–38] immunomodulatory,[39] anti-cancer,[40] anti-pruritic,[41] antidepressant,[42,43] and anti-arthritic[44] effects. Excessive physical pressure on skeletal muscles triggers an inflammatory cascade and rise in reactive oxygen species, which are all boosted up *via* nuclear factor kappa-B (NF-κB) pathway.[45–47] Activation of the inflammatory pathway results in delayed onset muscle soreness (DOMS).[48] One of the documented properties of curcumin, according to studies carried out in both humans and animals, is that it can prevent and reduce DOMS, which happens after unusual forceful exercise.[49–52] In a *proof-of-concept* study in C57BL/6 male mice (4–6 weeks old) with freeze injury in their masseter muscles, intraperitoneal injection of 20 μg/kg curcumin for 10 days caused regeneration of muscle fibres whereas the control group showed no signs of forming rejuvenated muscle fibres.[53] The efficacy of curcumin in diminishing DOMS has also been verified in humans, and attributed to the blockade of the NF-κB inflammatory pathway,[54,55] which consequently lowers the level of inflammatory cytokines such as interleukin 6 and tumour necrosis factor-α.[56,57] A study by Nicol *et al.* showed that oral use of curcumin (2.5 g twice daily) for 5 days can alleviate DOMS symptoms and heal muscular injuries in humans.[58] NF-κB is also involved in skeletal muscle atrophy during catabolism.[59] Therefore, inhibition of the NF-κB pathway by curcumin, which is a well-established effect of this phytochemical,[54,55] could justify the potential benefit of curcumin supplementation to attenuate muscular atrophy in catabolic conditions.[60] Moreover, curcumin can compensate for traumatized muscle fibres owing to its inflammatory suppressive features.[61]

Notably, the analgesic effect of curcumin has been shown in several RCTs and in different painful conditions including osteoarthritis,[44] rheumatoid arthritis,[62] fibromyalgia,[63] gout,[63] burning,[64] and post-surgical state.[65] Findings of a recent systematic review and meta-analysis of these RCTs implied a significant pain-relieving effect of curcumin that appeared to be independent of dose and duration of supplementation with this phytochemical.[66] Trials in osteoarthritis have shown that addition of curcumin to the treatment regimen leads to either reduction or discontinuation of the use of analgesics such as non-steroidal anti-inflammatory drugs.[67] The analgesic effects of curcumin, which can be favourable for the management of statin-induced myalgia, are thought to be because of the inhibition of cyclooxygenase-2 and prostaglandin E_2, stimulation of cortisol release, and enhancement of substance P depletion from nerve endings.[68,69]

As mentioned above, mitochondrial dysfunction has been suggested to play a key role in the development of SAMS. Mitochondrial activities are subject to oxidative stress[70–72] and are related to nuclear factor erythroid-2-related factor 2,[73–75] which acts as one of the key regulators of biological antioxidant defence.[76] Curcumin is a strong antioxidant that is known to counterbalance oxidative stress through several mechanisms including scavenging free radicals, chelating the

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Table 1 Summary of studies investigating the impact of curcumin treatment in models of muscular injury

Reference	Model	Curcumin dose	Type of injury	Duration of treatment	Route of administration	Main result
[53]	C57BL/6 mice	20 μg/kg/day	Freeze injury in masseter muscle	Single dose	Intraperitoneal injection	Regeneration of muscle fibres
[83]	C57BL/6 mice	1500 mg/kg/day	Muscular atrophy because of streptozotocin-induced diabetes	2 weeks	Oral	Improvement of muscular atrophy
[84]	C57BL/6 mice	5% of daily diet	—	21 days	Oral	Reduced mitochondrial apoptosis No change in mitochondrial biogenesis adaptations in muscles
[85]	Wistar rats	50–100 mg/kg/day	Endurance exercise training	28 days	Intraperitoneal injection	Increase in cyclic adenosine monophosphate level and mitochondrial biogenesis in skeletal muscles
[50]	Randomized controlled trial	200 mg twice daily	Downhill running test	4 days	Oral	Reduced muscle pain and significant reduction in muscle injury in the lower limb
[58]	Randomized controlled trial	2.5 g twice daily	Eccentric single-leg press exercise	5 days	Oral	Reduced muscular pain

metal ions, up-regulation of antioxidant enzymes, and enhancement of nuclear factor erythroid-2-related factor 2 pathway.[77,78] The latter is a chief pathway through which many of the antioxidant enzymes such as superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase are up-regulated.[79]

It is known that cyclic adenosine monophosphate is dynamically involved in muscle development, adaptation, and regeneration,[80] and among different types of polyphenols, curcumin is known to be one of the most effectual ones in increasing the level of cyclic adenosine monophosphate.[81,82] Significant improvement in muscular atrophy in C57BL/6 mice suffering from streptozotocin-induced diabetes has been reported following supplementation with curcumin (1500 mg/kg/day) for a period of two weeks.[83] In another experimental study on old C57BL/6 mice (24 months), although curcumin supplementation (5% of diet) for a period of 21 days did not change mitochondrial biogenesis adaptations in muscles, it reduced mitochondrial apoptotic proteins compared with the control group.[84] While the above-mentioned findings are encouraging, more studies are still needed to be carried out in order to clarify the impact of curcumin supplementation on mitochondrial biogenesis and function in skeletal muscle fibres.[85]

Curcumin supplementation is not only believed to attenuate SAMS, but also may enhance the lipid-modifying properties of statins, and thus reduce the need for statin dose escalation (and in the consequence might allow statin dose reduction without significant risk increase), which is itself a contributing factor to myalgia and myopathies.[86] Several lines of experimental and clinical evidence have shown that curcumin can improve lipid profile by decreasing serum levels of LDL-C (by 15–20 mg/dL), total cholesterol (by about 10 mg/dL), and triglycerides (even by over 60 mg/dL in patients with metabolic syndrome).[87–89] At the molecular level, these lipid-regulating effects have been well characterized. Curcumin can down-regulate 3-hydroxy-3-methylglutaryl-coenzyme A reductase, sterol regulatory element-binding protein-1, fatty acid synthase, and apolipoprotein B100, and enhance the expression and/or activity of LDL receptor, peroxisome proliferator-activated receptor-α, and AMP-activated protein kinase as key targets involved in the regulation of lipid homeostasis.[88,90,91] Among the lipid-modifying effects of curcumin, triglyceride-lowering activity is of particular importance as statin therapy has moderate effect in correcting hypertriglyceridemia, and hypertriglyceridemia in statin-treated subjects has been suggested as an important cause of residual cardiovascular risk despite attainment of therapeutic LDL goals.[92]

Last, but not the least notable advantage of curcumin is its safety. Numerous trials have shown that curcumin is well tolerated and does not cause any serious side-effects even at high doses.[93,94] However, the safety at high-dose still needs to be affirmed in long-term uses,[87] as well as its safety in combination with statins (Table 1).

Conclusions

In conclusion, enhancement of mitochondrial biogenesis and function, along with analgesic, anti-inflammatory, antioxidant, and lipid-modifying properties jointly supports the potential benefit of curcumin supplementation as an adjunct to statin therapy in patients with SAMS, as well as in the individuals with a residual cardiovascular risk. Because accumulating clinical data has supported the safety of this polyphenol, *proof-of-concept* RCTs are recommended to unlock the potential of curcumin as a preventive and/or therapeutic strategy for SAMS.

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Conflict of interests

The authors have no competing interests to declare.

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