Successful reintroduction of statin therapy after myositis: was there another cause?

Clinical record

A 43-year-old man presented with myalgia and upper respiratory tract symptoms. He had noted weight gain of 7 kg, lethargy and cold intolerance over the previous 12 months. He had no chest pain, rash or fever.

His past history included acute myocardial infarction (AMI) 12 years earlier. Subsequently, he had been taking low-dose aspirin. He commenced simvastatin 2 years after the AMI for hypercholesterolaemia (> 7 mmol/L). His sister and father have hypercholesterolaemia and his father had an AMI before 40 years of age, suggesting heterozygous familial hypercholesterolaemia. Two years before presentation, his hypolipidaemic therapy was switched from simvastatin to atorvastatin, although he denied experiencing any side effects of the former. He reported consuming 40–50 g/day of alcohol, and that he had recently quit smoking.

Examination revealed that he was hypertensive (160/90 mmHg) and obese (body mass index, 32 kg/m^2). He had marked corneal arcus, but no tendon xanthomas or xanthelasma, and no goitre. There was no muscle tenderness and power was normal. Reflexes were delayed.

The results of some of the laboratory tests performed are shown below. In addition, normal findings were recorded for full blood count, erythrocyte sedimentation rate, and C-reactive protein, electrolyte, glucose, and calcium levels. Serological tests for hepatitis, and test results for protein electrophoresis, antinuclear factor, immunoglobulin and prostate-specific antigen levels, were all normal. There was no myoglobinuria, haematuria or proteinuria. Chest x-ray findings were normal, electrocardiography showed old Q waves, and an abdominal ultrasound showed hepatic steatosis. Apart from γ-glutamyltransferase, normal results were obtained for all other liver function tests.

Statin-induced myositis was suspected and atorvastatin was stopped. Thyroid function tests instituted after endocrine review 5 days later revealed hypothyroidism (free T_4, 1.9 pmol/L [normal range, 11.0–23.0 pmol/L] and thyroid-stimulating hormone, > 100 mU/L [normal range, 0.30–5.00 mU/L]). Tests for thyroid peroxidase and thyroglobulin antibodies both gave positive results, suggesting Hashimoto's thyroiditis. The patient was prescribed thyroxine 50 μg daily, with subsequent slow-dose titration because of ischaemic heart disease.

The Box (*page 473*) shows the gradual normalisation of the creatine kinase (CK) level over time. Lipid levels remained elevated despite thyroxine therapy. Simvastatin 10 mg/d was recommenced with careful monitoring. The dose was increased progressively up to 80 mg daily for persistent hyperlipidaemia. Despite full-dose statin therapy, there was no change in the findings of liver function tests and only mild asymptomatic elevation of CK levels.

Investigation	Result (normal range)
Creatine kinase (CK) (IU/L)	4890 (< 240)
CK-MB index (%)	2.0 (< 5.0)
Total cholesterol (mmol/L)	9.0 (< 5.5)
Triglycerides (mmol/L)	2.7 (< 2.0)
High-density lipoprotein cholesterol (mmol/L)	1.2 (> 1.0)
Urea (mmol/L)	6.7 (2.3–7.6)
Creatinine (mmol/L)	0.197 (0.05–0.11)
γ-Glutamyltransferase (U/L)	196 (10–55)

STATIN-RELATED MUSCLE COMPLAINTS include myalgia, myositis and rhabdomyolysis.[1] Hypothyroidism itself can cause musculoskeletal symptoms, including myalgia, Hoffmann's syndrome (muscle stiffness, weakness and increased muscle mass, frequently with elevated creatine kinase [CK] level), Kocher–Debré–Sémélaigne syndrome (diffuse muscular hypertrophy and weakness in congenital hypothyroidism), a polymyositis-like syndrome (with proximal muscle weakness and markedly elevated CK level), and rhabdomyolysis.[2] The coexistence of hypothyroidism and statin use may increase the risk of myopathy.[3]

Statin-induced myopathies tend to resolve within a few days to 1 month after ceasing statin use.[4] Persistent elevation of CK level after stopping statin therapy has been reported, prompting further investigation and leading to the discovery of coexisting hypothyroidism.[3,5] Thyroxine replacement therapy was reported as normalising CK and total cholesterol levels in these patients. However, to the best of our knowledge, ours is the first report of a patient with treated hypothyroidism in whom statin therapy was safely reintroduced after the resolution of myositis.

While the exact aetiology of the myositis in our patient can not be proven, it seems most probable that it was precipitated by a combination of hypothyroidism and statin use. Full-dose statin therapy did not cause a recurrence of myositis once the hypothyoidism had been treated, implicating hypothyroidism as a contributing factor. However, it is uncertain whether the hypothyroidism would have resulted in myositis without coexisting statin therapy. The patient has mild asymptomatic elevation of CK level while taking simvastatin and with adequate thyroxine replacement. Such asymptomatic CK elevation is frequently seen in subjects during statin trials with both placebo and statin therapy, and continued treatment while asymptomatic and with CK levels up to 10 times the upper limit of normal has to date proven to be safe.[6]

As hypothyroidism can cause hyperlipidaemia, we suggest that thyroid function should be checked before commencing statin therapy, particularly if there are any clinical features to suggest its presence. We also suggest that patients who develop symptoms or signs suggestive of myopathy while taking statin therapy should be tested for hypothyroidism. As in our patient, it may be safe to cautiously reintroduce

Lessons from practice

- Hypothyroidism should be considered as a secondary cause of hypercholesterolaemia in all patients.
- Patients developing myopathy when taking statin therapy should be tested for hypothyroidism.
- It may be safe to cautiously reintroduce statin therapy in patients with myopathy, once coexisting hypothyroidism has been treated.

Biochemistry results and drug dosages over time

	Year 1							Year 2			Year 3	Year 4	Year 5
	20 May	25 May	22 Jun	27 Jul	22 Aug	28 Sep	1 Nov	5 Jan	12 Apr	17Aug	18 Mar	17 Jan	23 Jan
Thyroid-stimulating hormone (mU/L) (NR, 0.3–5.0)		>100	90.9	53.9	23.9	8.13	4.35	1.23		1.02	0.85	0.64	0.58
Total cholesterol (mmol/L)	9	10.2		8.9		8.2	6.2	6.5	5.7	4.4	4.9	4.0	4.4
Creatine kinase (IU/L) (NR, < 240)	4890		1839		336		196	216	209		442	320	
Creatinine (mmol/L) (NR, 0.05–0.11)	0.197		0.171	0.14		0.14	0.14	0.12	0.14	0.12	0.12	0.12	0.12
Statin (mg/d)	Stopped atorvastatin					Started simvastatin 10	10	20	40	80	80	80	80
Thyroxine (μg/d)		Started thyroxine 50	75	100	125	150	150	175	175	175	175	175	175

NR = normal range.

statin therapy in patients with a history of myopathy, once coexisting hypothyroidism has been treated.

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