LETTERS TO THE EDITOR

Vitamin D insufficiency – a novel mechanism of statin-induced myalgia?

HMG-CoA reductase inhibitors (statins) are effective agents in both primary and secondary prevention of cardiovascular disease. However, in some patients, their clinical use is limited by side-effects, including myalgia, myositis and rhabdomyolysis in the most severe cases. Statins are not infrequently discontinued in patients at high risk of cardiovascular events because of such myopathic complications. The mechanism of statin-induced muscle injury is poorly understood, but may include a reduction in coenzyme Q10 synthesis and induction of atrogin-1 expression.[1] Patients with renal failure, obstructive liver disease and hypothyroidism appear to be most at risk.

Vitamin D deficiency is highly prevalent worldwide and is associated with similar myalgic symptoms to statin-induced muscle injury. In particular, vitamin D insufficiency is highly prevalent in patients with type 2 diabetes and may cause neuropathic pain in the moderately deficient (40–60 nmol/l) rather than severely deficient range (< 30 nmol/l).[2] However the relationship between vitamin D deficiency and statin-induced myalgia has not been investigated. We report the first case series highlighting the association between vitamin D deficiency and statin-induced myalgia.

All patients who attended the Endocrine Registrar Clinic at St Vincent's Hospital, Sydney, Australia, between February and December 2007, who discontinued statin therapy because of myalgia (Table 1), were screened for vitamin D deficiency. Patients were not receiving concurrent therapy known to increase susceptibility to myopathy. All patients were euthyroid clinically and biochemically. Mean duration of statin therapy before onset of myalgia was 3·3 ± 1·2 months. Vitamin D insufficient patients (serum 25-OH vitamin D [25-OH D] < 60 nmol/l) were supplemented with oral vitamin D_3 (initial doses between 1000 and 10 000 units/day), with a target > 60 nmol/l.

Eight of 11 patients with statin-induced myalgia were vitamin D insufficient (25-OH D < 60 nmol/l); three of these patients were severely deficient (25-OH D < 30 nmol/l) (Table 1). One patient had evidence of myositis with mildly elevated creatine kinase. Cessation of the statin with vitamin D replacement led to complete resolution of myalgia in six of the eight patients (Patients 2, 4, 5, 7, 8, 11) and significant improvement of myalgia in another two (Patients 1, 9), in over approximately 3 months. Six patients agreed to be rechallenged with statin therapy (same statin) following vitamin D repletion. In four cases (Patients 1, 2, 5, 8), statin therapy was tolerated for at least 6 months without recurrence of myalgia. Mean post-treatment serum 25-OH D concentration of the four successful cases was 84·5 ± 7·5 nmol/l. Statin therapy was successfully titrated to higher than original doses to achieve lipid-lowering goals in two of these patients. The two other patients (patients 4, 11) who initially failed rechallenge with the same statin were subsequently treated with an alternative statin (pravastatin); however, both suffered recurrence of myalgia. The three patients (patients 3, 6, 10) who were vitamin D sufficient were not rechallenged with the same statin, but all tolerated an alternative statin (pravastatin).

This is the first case series highlighting the association of vitamin D insufficiency with statin-induced myalgia, demonstrating successful rechallenge of statin therapy in a subgroup of patients following vitamin D repletion. As myalgia occurred after commencement of stain therapy in our series of patients, it argues against previously undiagnosed vitamin D deficiency as the only cause of myalgic symptoms. Although nonspecific myalgic-symptoms in some patients commenced on statin therapy may be due to undiagnosed vitamin D deficiency,[3] a direct contribution of vitamin D deficiency to the development of statin-induced muscle injury cannot be excluded. Whether vitamin D insufficiency potentiates statin-induced myalgia and whether statins contribute to vitamin D deficiency are not

Table 1. Patient characteristics

Patient	Sex	Age (year)	Statin therapy (mg/day)	Creatine kinase (0–130 U/l)	Serum 25-OH vitamin D concentration (nmol/l)		Response to vitamin D replacement	Successful rechallenge?
					Baseline	Post-treatment		
1	M	58	Atorvastatin 40	72	45	89	Improved	Yes; atorvastatin 40 mg/day
2	F	62	Simvastatin 40	65	27	75	Resolved	Yes; simvastatin 40 mg/day
3	F	79	Simvastatin 40	NA	69	Not indicated	Not replaced	Not rechallenged
4	M	43	Atorvastatin 20	84	55	NA	Resolved	Unsuccessful rechallenge
5	F	68	Atorvastatin 10	78	39	92	Resolved	Yes; atorvastatin 40 mg/day
6	F	75	Simvastatin 40	102	82	Not indicated	Not replaced	Not rechallenged
7	F	84	Atorvastatin 10	88	20	68	Resolved	Patient refused rechallenge
8	F	64	Pravastatin 20	114	< 15	82	Resolved	Yes; pravastatin 40 mg/day
9	M	73	Atorvastatin 10	83	42	98	Improved	Patient refused rechallenge
10	F	85	Simvastatin 10	92	70	Not indicated	Not replaced	Not rechallenged
11	M	70	Atorvastatin 20	135	47	62	Resolved	Unsuccessful rechallenge

NA, not available.

well-understood. The latter is less likely as atorvastatin treatment has been shown to increase serum 25-OH D concentrations.[4]

The statins most commonly associated with myalgia (simvastatin and atorvastatin) inhibit CYP3A4, which displays 25-hydroxylase activity *in vitro*.[5] Therefore, vitamin D deficient states may lead to 'preferential shunting' of CYP3A4 for hydroxylation of vitamin D, reducing availability of CYP3A4 for statin metabolism, leading to statin-induced toxicity. Higher serum 25-OH D concentrations may be protective against statin-induced myalgia, as statin rechallenge was more likely to be successful in patients who achieved higher post-treatment level (> 80 nmol/l) in our series.

In conclusion, patients with statin-induced myalgia should be screened for vitamin D insufficiency. Vitamin D repletion may resolve myalgic symptoms and allow statin rechallenge. Future studies are required to clarify further the relationship between vitamin D insufficiency and statin-induced myopathy.

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References

1 Hanai, J., Cao, P., Tanksale, P. *et al.* (2007) The muscle-specific ubiquitin ligase atrogin-1/MAFbx mediates statin-induced muscle toxicity. *Journal of Clinical Investigation*, **117**, 3940–3951.
2 Lee, P. & Chen, R. (2008) Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain. *Archives of Internal Medicine*, **168**, 771–772.
3 Goldstein, M.R. (2007) Myopathy, statins, and vitamin D deficiency. *American Journal of Cardiology*, **100**, 1328.
4 Pérez-Castrillón, J.L., Vega, G., Abad, L. *et al.* (2007) Effects of Atorvastatin on vitamin D levels in patients with acute ischemic heart disease. *American Journal of Cardiology*, **99**, 903–905.
5 Gupta, R.P., He, Y.A., Patrick, K.S. *et al.* (2005) CYP3A4 is a vitamin D-24- and 25-hydroxylase: analysis of structure function by site-directed mutagenesis. *Journal of Clinical Endocrinology and Metabolism*, **90**, 1210–1219.

GH treatment reduces total ghrelin in Prader–Willi syndrome (PWS) and may confound ghrelin studies in young PWS children

Children with Prader–Willi syndrome (PWS) switch from a failure to thrive in early infancy to a state of insatiable appetite, leading to morbid obesity if caloric intake is not controlled. This poses many problems to parents and caregivers.[1] Understanding the mechanisms of the switch could be the key for the development of new treatment modalities. An effective treatment would relief the parents and caregivers from the constant task of withholding food from their children, and would prevent obesity and associated comorbidities. Ghrelin is elevated in individuals with PWS, suggesting a role for ghrelin in the development of food craving. An early rise of ghrelin could prime the hypothalamus to go into a state of satiety signal misinterpretation. It is therefore important to know the natural course of the ghrelin levels from birth and early infancy, when significant obesity has not yet developed. Two recent reports have addressed this issue, with conflicting results.[2,3]

Both Haqq *et al.*[2] and Feigerlová *et al.*[3] have studied ghrelin levels in young PWS children. Whereas in the PWS cohort of Feigerlová *et al.* total ghrelin concentrations were significantly increased over those in controls, no significant difference was found between PWS and control children in the study of Haqq *et al.* although plasma ghrelin concentrations were elevated in one-third of their patients. Haqq *et al.* were unable to describe a relationship between ghrelin and weight-for-height *z*-scores, and between hyperghrelinaemia and hyperphagia. They concluded that hyperghrelinaemia in young PWS infants may rather be a response to failure to thrive and to dietetic restrictions. That would not exclude the possibility that chronic hyperghrelinaemia may eventually induce hyperphagia.

The latter statements are based on the validity of two assumptions: First, it was assumed that total ghrelin is a surrogate for the active, acylated form of ghrelin. That is because in other studies the ratio of the two levels was reported to be constant under a variety of conditions. This is important since in Haqq's study, acylated ghrelin was not measured. Second, it was assumed that GH treatment has no effect on ghrelin concentrations. However, in their young PWS patient group, a considerable proportion of patients were being treated with GH, but ghrelin data before and after start of GH therapy was not provided.

There are observations indicating that their assumptions may not have been met. In an earlier publication from the same group,[4] treatment with GH of children with PWS was associated with a trend towards lower ghrelin concentrations in the GH-treated group as compared to a placebo-treated group. Intra-individual changes under GH were not reported.

Recently, we have studied the effect of GH on the response of total and acylated ghrelin to a standardized oral glucose load and insulin resistance in 28 children with PWS.[5] In this study, high fasting total ghrelin [1060 ± 292 (SD) pg/ml; $n = 12$] concentrations in GH-untreated PWS children were found to be decreased ($P = 0{\cdot}006$) in the GH-treated group (761 ± 247 pg/ml; $n = 20$). In contrast, the concentrations of acylated ghrelin were not changed by GH treatment. These findings were confirmed in eight PWS children, for whom data were available both before and after the start of treatment. BMI SDS and basal total ghrelin concentrations decreased significantly after the start of GH treatment ($P = 0{\cdot}0078$). Again, no GH-related decrease was noted for the acylated ghrelin concentrations. For the ghrelin trough concentrations after carbohydrate administration, similar results were obtained. When we reanalysed our data with regard to the ghrelin isoform ratio, in the latter situation an increased mean acylated ghrelin : total ghrelin ratio was found in GH-treated PWS children (untreated *vs.* treated: 0·18 ± 0·11 and 0·29 ± 0·14; $P < 0{\cdot}038$).

These published data may bear relevance to the interpretation of the results in the study of Haqq *et al.* In their cohort of young PWS