Endocrine Journal 2006, **53** (3), 401–405

HMG-CoA Reductase Inhibitors (statins) might Cause High Elevations of Creatine Phosphokinase (CK) in Patients with Unnoticed Hypothyroidism

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Abstract. Serious side effects of statins, including severe myopathy and rhabdomyolysis, are rare but important in general practice. Hypothyroidism can cause secondary hypercholesterolemia and myopathy. There have been few reports on the risk of statins in patient with unnoticed hypothyroidism. We analyzed the characteristics of 77 patients with primary hypothyroidism in our hospital. Nine patients (11%) accidentally received statins in the treatment of hypercholesterolemia without diagnosis of hypothyroidism. In such patients, free T_4 (FT_4) levels were lower, and those of LDH, CK were higher than those in patients not receiving statins. In patients accidentally receiving statins, an inverse correlation between CK and FT_4 could not be shown (which was recognized in patients not receiving them). Even after FT_4 levels were matched, levels of CK were still higher in the patients accidentally receiving statins. Patients with high CK levels over 1000 U/L were 5 times more frequent (56%) in patients accidentally receiving statins than in those not receiving statins (11%). The present study confirms that statins enhances levels of CK in patients with hypothyroidism. We must not begin and continue to use these drugs without checking the possibility of hypothyroidism.

Key words: Creatine phosphokinase (CK), HMG-CoA reductase inhibitors (statins), Hypothyroidism

(*Endocrine Journal* **53**: 401–405, 2006)

EVER since the efficacy and safety of the statins was established [1, 2], these agents have been used widely as the first choice in treatment of hypercholesterolemic patients, and their side effect are relatively infrequent. But the most important side effect is myopathy, which can cause rhabdomyolysis. Hypothyroidism is the one of the most frequent cause of the secondary hyperlipidemia. We have occasionally encountered patients accidentally receiving statins with unnoticed hypothyroidism. The reports dealing with such cases have been rare. There are several case reports on marked increases in creatine kinase (CK) in such patients [3–6]. The aim of this study was to prove the importance of excluding the possibility of primary hypothyroidism in hypercholesterolemic patients. We reported here the characteristics of patients accidentally receiving statins before diagnosis of primary hypothyroidism. We also evaluated the incidence of such cases, and the possibility that statins can cause high elevations of CK in patients with unnoticed hypothyroidism.

Received: November 9, 2004
Accepted: March 6, 2006
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Subjects and Methods

Seventy-seven primary hypothyroidism adults patients who visited our hospital to receive thyroxine replacement therapy during the period from August to October 2003 were studied. None of these patients had nephrotic syndrome or primary muscle disease. Diagnosis of primary hypothyroidism was made on the basis of increased TSH level and decreased FT_4 level. Fasting blood chemistry including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), CK, total cholesterol, HDL-cholesterol and triglyceride level were analyzed. Patients histories were reviewed for factors

that might affect CK level. We checked predisposing factors for myopathy: exercise, heavy alcohol intake, viral illness and any newly administered drugs. Use of anti-lipidemic agents was examined when the diagnosis of hypothyroidism was established.

Statistical anlysis

Differences between the groups were evaluated using Mann-Whitney U test and Wilcoxon matched pairs signed rank test. Correlations were assessed by Spearman's rank correlation test. A probability level of less than 0.05 was considered significant.

Results

Nine patients accidentally received anti-lipidemic agents at the time of diagnosis with primary hypothyroidism. All anti-lipidemic agents were statins. Characteristics of the subjects accidentally receiving statins are summarized in Table 1. Thyroid function tests were ordered for edema (patients No. 1, 5, 6), diffuse goiter (patients No. 2, 4, 9) pericardial effusion, and CK elevation (patient No. 7). But in two patients (patients No. 3, 8), the reasons for checking the thyroid functions were not clear. As for patients No. 1, 3, 5 and 6, we recognized elevated CK level, and hypothyroidism at the same time, and statins were stopped immediately and thyroxine replacement was started. In patients No. 7 and 9, moderate CK elevations were found at their visit with us, hence we stopped statins. After we checked their thyroid functions and revealed their hypothyroidism, thyroxine replacement was started and increased gradually. In patients No. 4 and 8, their CK elevations were mild. After diagnosis of hypothyroidism, statins were stopped and thyroxine replacement was started. CK fell to normal after thyroxine replacement in these 8 patients. Patient No. 2 (her CK level was normal at the time of the diagnosis of hypothyroidism) continued to receive statin together with thyroxine replacement in compliance with her wishes. Before statin treatment, the CK levels of patients were examined in 6 patients (patient No. 1, 277 U/L; patient No. 4, 124 U/L; patient No. 5, 142 U/L; patient No. 7, 330 U/L; patient No. 8, 432 U/L; patient No. 9, 110 U/L). As for these six patients, CK levels at the time of diagnosis of hypothyroidism were increased significantly compared with those before using statins (918 ± 288 vs 194 ± 36 U/L: mean ± SE, $P<0.05$).

We divided subjects into two groups: those receiving statins (statin group: n = 9) and those who did not receive statins (non-statin group: n = 68). The characteristics of the patients are summarized in Table 2. FT_4 levels in the statin group (0.22 ± 0.06 ng/dL) were lower than those in the non-statin group (0.47 ± 0.06 ng/dL). LDH levels in the statin group (599 ± 86 U/L) were higher than those in non-statin group (408 ± 27 U/L) (normal 205–434). CK levels in the statin group 1095 ± 338 U/L) were higher than those in non-statin group (338 ± 70 U/L) (normal<187 U/L).

The relationship between FT_4 levels and CK levels was analyzed in the non-statin group. There was an inverse correlation between CK levels and FT_4 levels in the non-statin group ($r = –0.53$, $P<0.01$) (Fig. 1). Interestingly, there was no significant correlation between CK levels and FT_4 levels in statin group ($r = –0.23$, not significant) (Fig. 2). These results seem to indicate that prior use of statins in unrecognized hypothyroidism affects the CK level.

After FT_4 levels were matched between statin group and non-statin group, AST, ALT, LDH and CK levels were examined. As shown in Table 3, CK levels were still higher in patients receiving statins. The frequencies of patients who revealed high CK levels over 1000 U/L were examined. There was a significantly higher number of patients with high CK levels over 1000 U/L (56%, $p = 0.023$) in statin group than in non-statin group (11%).

Discussion

Statins have been found to be effective in primary prevention as well as secondary prevention of coronary disease [1, 2, 7]. In addition, they are well tolerated by most patients. Statins are used overwhelmingly as the first choice treatment of hypercholesterolemia. But statins can cause a variety of skeletal muscle problems, including clinically important myositis and rhabdomyolysis [8–11]. It is known that risk of statin-associated myopathy, including rhabdomyolysis, can be exacerbated by renal failure [12, 13]. Medications that inhibit cytochrome P-450 (CYP) 3A4, such as macrolide antibiotics, azole antifungals, and cyclosporine, increase serum concentrations of statins and risk of rhabdomyolysis [14].

Hypothyroidism frequently leads to skeletal muscle

Table 1. Characteristics of the patients receiving statins with unnoticed hypothyroidism

Patients	AGE at diagnosis (year)	SEX	TSH (μU/mL)	FT_4 (ng/dL)	AST (U/L)	ALT (U/L)	LDH (U/L)	CPK (U/L)	T-Cho (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)	Lipid lowering drugs (Statins)
1	65	M	100<	0.13	81	90	392	2131	197	61	79	Sinvastatin
2	53	F	40<	0.37	26	22	345	98	210	53	187	Pravastatin
3	54	M	100<	0.08	52	40	736	1025	317	97	134	Pravastatin
4	49	F	40<	0.21	40	36	419	205	187	58	147	Pravastatin
5	67	F	40<	0.59	33	22	972	1052	242	69	178	Pravastatin
6	55	F	100<	0.09	93	50	839	3231	197	88	142	Atorvastatin
7	63	F	40<	0.11	n.d.	n.d.	876	708	n.d.	n.d.	n.d.	Pravastatin
8	69	F	40<	0.14	24	26	518	286	415	54	519	Pravastatin
9	53	F	123.2	0.3	45	45	296	1125	362	46	337	Atorvastatin

Table 2. Characteristics of patients receiving and not receiving statins with hypothyroidism

Patient profiles	Statin group (n = 9)	Non-Statin group (n = 68)	P-value
Age at diagnosis (year)	59 ± 7.3	55 ± 7.3	NS
FT_4 (ng/dl)	0.23 ± 0.06	0.47 ± 0.04	<0.05
AST (U/l)	49 ± 8.9	43 ± 4.2	NS
ALT (U/l)	40 ± 7.9	30 ± 4.4	NS
LDH (U/l)	599 ± 86	408 ± 7.3	<0.05
CPK (U/l)	1095 ± 338	338 ± 70	<0.01
Total cholesterol (mg/dl)	266 ± 30.9	249 ± 8.4	NS
HDL cholesterol (mg/dl)	66 ± 6.4	75 ± 9.9	NS
Triglyceride (mg/dl)	215 ± 50.8	157 ± 16.5	NS

Values are mean ± SE. Statistical significance was determined by Mann-Whitney U test.

Table 3. Characteristics of patients receiving and not receiving statins with hypothyroidism (FT_4 levels were matched in each group)

Patient profiles	Statin group (n = 9)	Non-Statin group (n = 18)	P-value
FT_4 (ng/dl)	0.23 ± 0.06	0.23 ± 0.05	
Age at diagnosis (year)	59 ± 2.4	56 ± 4.8	NS
AST (U/l)	49 ± 8.9	44 ± 7.5	NS
ALT (U/l)	40 ± 7.9	30 ± 4.8	NS
LDH (U/l)	599 ± 86	450 ± 40	NS
CPK (U/l)	1095 ± 338	395 ± 80	<0.05
Total cholesterol (mg/dl)	266 ± 30.9	261 ± 20.9	NS
HDL cholesterol (mg/dl)	66 ± 6.4	69 ± 5.3	NS
Triglyceride (mg/dl)	215 ± 50.8	138 ± 17.5	NS

Values are mean ± SE. Statistical significance was determined by Wilcoxon matched pairs signed rank test.

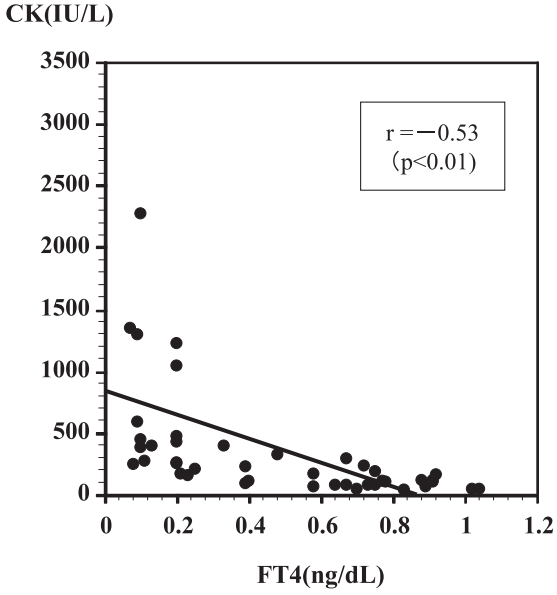

Fig. 1. Relationship between FT_4 levels and CK in non-statin group. The line represents the least-squares regression.

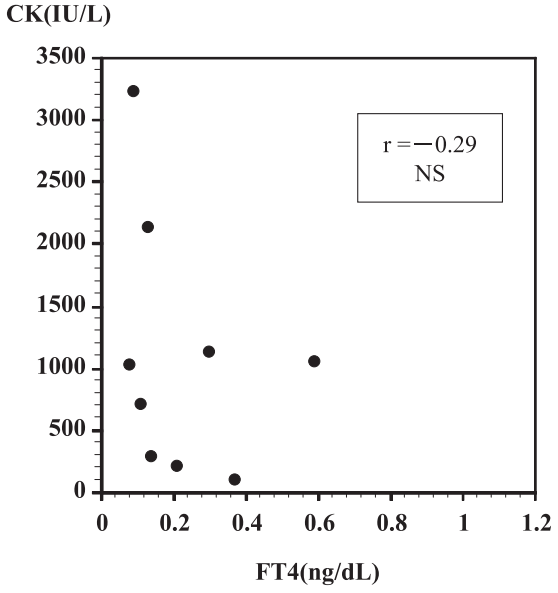

Fig. 2. Relationship between in FT_4 levels and CK in statin group.

problems, and asymptomatic mild to moderate CK elevations are common in the patients with hypothyroidism. On the other hand, clinically important increases in CK can be seen in the presence of a precipitate factor. There have been several case reports of rhabdomyolysis in hypothyroidism [15–18]. Most of the cases were precipitated with exercise [15, 16]. Marked elevation of CK and rhabdomyolysis have been reported in patients with unnoticed hypothyroidism using antihyperlipidemic agents, including fibrates [19, 20] and statins [3–6]. As for statins, a revised edition of drug information in Japan recommends very careful use of such drugs in patients with hypothyroidism. But this important point is not emphasized in general clinicians.

In our study, 11.7% of patients with primary hypothyroidism accidentally received statins without diagnosis of hypothyroidism. They were treated as primary hypercholesterolemia which was difficult to control. To exclude other diseases which cause secondary hyperlipidemia such as diabetes mellitus, nephrosis, and hypothyroidism, is of great importance. In our hospital, statins were given to 925 patients with hypercholesterolemia in July 2005. We analyzed medical records of 102 patients among them. Fasting plasma glucose levels, renal function and urinalysis were checked in most patients before using statins. But screening tests of thyroid functions were performed in only 23 (22.5%) of these 102 patients. If clinicians do not suspect hypothyroidism, they can easily miss hypothyroidism by routine physical examination. We must pay special attention to complaints of patients with hypercholesterolemia, such as easy fatigability, coldness, constipation, and muscle cramps, especially in elderly women. We also need to check for goiter and past history of thyroid disorder. In such cases screening for hypothyroidism need to be carried out. It might be insufficient to exclude hypothyroidism when we start statins.

According to clinical studies in Japan, the incidence of elevated CK levels in patients treated by statins were not high. There were clinical studies which excluded patients with hypothyroidism. Elevated CK levels were noted in 6 (1.6%) out of 368 patients treated by pravastatin [21]. As for atorvastatin, CK elevation was noted in 2.19% in postmarketing analysis [22]. In patients with hypothyroidism treated by statins, the incidence of CK elevation is unknown.

In patients accidentally receiving statins with hypothyroidism, CK levels were three times higher, while FT_4 levels were about 50%. Severity of hypothyroidism might be partially associated with elevation of CK. But statins are likely to elevate CK levels in patients with hypothyroidism for the following reasons. First, there was an inverse correlation between CK and FT_4 in hypothyroidism patients not receiving statins. CK was not correlated with FT_4 in those receiving statins. Second, even after matching FT_4 levels, CK levels are significantly higher in patients accidentally receiving statins. Five (56%) patients revealed high CK levels over 1000 U/L. On the other hand, in 18 FT_4-matched patients not receiving statin, only 2 (11%) patients revealed high CK levels over 1000 U/L. The mechanism behind CK elevations in hypothyroidism receiving statins is unclear. But these agents might be a risk factor for severe myopathy and rhabdomyolysis in patients with hypothyroidism.

In conclusion, we described high CK elevations in patients with unnoticed hypothyroidism accidentally receiving statins. We need to assess the possibility of hypothyroidism not only before treatment with statins but also during treatment, especially when CK levels markedly increase. As for CK, prior use of statins can enhance serum CK levels in patients with hypothyroidism. We must start and continue these agents while paying special attention to the existence of hypothyroidism in order to avoid unwanted side effect.

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