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Cross-sectional investigation of serum creatine kinase concentration in Graves disease patients treated with oral antithyroid drugs

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Abstract

Elevated serum creatine kinase (CK) concentration was reported in some Graves disease patients during the treatment with oral antithyroid drugs (ATD). The pathogenesis of this abnormal biochemical value was considered to be related to the therapeutic drug. However, the relevant epidemiological investigation was absent.

Overall, 416 patients with Graves disease treated with oral ATDs were recruited from December 2017 to October 2019. Clinical characteristics such as the patient's medical history and therapeutic regimen were collected. Serum CK concentration and thyroid function were measured. Statistical analysis was adopted to clarify the relationship between serum CK level and these clinical parameters.

Elevation of serum CK concentration was emerged in 13.5% patients who were treated with oral ATDs. The proportion was significantly higher among men than among women (19.5% vs 10.8%). There was no correlation between increased serum CK concentration and age. More than 60% of serum CK elevations occurred within 6 months after taking oral ATDs. Free triiodothyronine and free thyroxine are negatively correlated with serum CK concentration. The correlation coefficients are respectively –0.222 ($P < .05$) and –0.234 ($P < .05$). There is positive correlation between thyroid stimulating hormone and serum CK concentration. The correlation coefficient is 0.405 ($P < .05$). There was no statistical correlation between drug dosage and increased serum CK level.

Increased serum CK level is a common adverse reaction of oral ATDs. It generally develops early after starting treatment. The cause of this adverse reaction is not clear. It is speculated that elevation of serum CK level is related to the fluctuation of thyroid function.

Abbreviations: ATD = antithyroid drug, CK = creatine kinase, FT_3 = free triiodothyronine, FT_4 = free thyroxine, GD = Graves disease, MMI = methimazole, PTU = propylthiouracil, TSH = thyroid stimulating hormone.

Keywords: Graves disease, oral antithyroid drug, serum creation kinase

1. Introduction

Graves disease (GD) is a common thyroid disorder. There are 3 therapeutic regimens for GD: oral antithyroid drugs (ATDs), radioiodine and thyroidectomy.[1–5] Oral ATDs are a predominant treatment for GD. During the treatment of oral ATDs, its side effects must be taken into account. Oral ATDs' common side effects include: rash, pruritus, liver damage, and leukopenia.[6,7] But there are some other rare adverse reactions, such as aplastic anemia,[8] increased serum creatine kinase (CK) that are easily ignored. We noticed that some GD patients with oral ATDs manifested myalgia and increased serum CK concentration. We have previously reported three such patients.[9] In order to further clarify the proportion of elevated CK and their clinical characteristics in GD patients treated with oral ATDs, we performed this cross-sectional investigation.

2. Methods

2.1. Subjects

A total of 416 patients with GD between December 2017 and October 2019 were enrolled in the study. The diagnosis of GD was based on the patient's symptoms, thyroid function, and thyrotropin receptor antibody level or high radioactive iodine uptake. These patients are all being treated with oral ATDs. Their thyroid function and serum CK concentration have been measured. Patients who had a history of autoimmune disease, taking statins, excessive exercise, alcoholism, myocarditis, and other factors that cause increased serum CK concentration were excluded. All clinical data was collected from the medical records. Ethical approval was waived because this investigation is a retrospective study. Oral ATDs are a conventional treatment for hyperthyroidism, and we have no additional interventions. All

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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patients receiving oral ATDs were informed of possible adverse drug reactions, and monitored for any adverse drug reactions.

2.2. Laboratory methods

Thyroid function was measured using electrochemiluminescence immunoassay kit. The reference range of serum free triiodothyronine (FT_3) is 2.38 to 4.34 pg/ml. The reference range of serum free thyroxine (FT_4) is 0.90 to 1.76 ng/dl. The reference range of thyroid stimulating hormone (TSH) is 0.550 to 4.780 mIU/L. Serum CK concentration was measured by colorimetry. The reference range is 25 to 175 IU/L.

2.3. Statistical analysis

The clinical data was collected and analyzed using SPSS 18.0 software. Chi-square test was used to compare proportions of categorical variables. Analysis of significant differences between 2 independent samples using Mann-Whitney *U* test. *P*-value $<.05$ was considered statistical significant difference.

3. Result

A total of 416 patients diagnosed GD treated with ATDs were enrolled, and consisted of 128 males and 288 females. Increased serum CK concentration emerged in 56 cases of 416 patients, accounting for 13.5%. The proportion of elevated CK was 19.5% in males and 10.8% in females. Adopting Spearman correlation analysis, the correlation coefficient between increased serum CK and gender is 0.119 ($P=.016$). Compared with female patients, male patients with GD are more likely to have elevated serum CK after taking ATDs. There was no correlation between age and serum CK elevation. The patient's clinical characteristics are shown in Table 1.

The clinical characteristics of patients with normal CK and elevated CK were shown in Table 2. There was no statistical significant difference in the age of the 2 groups ($P=.610$). As shown in Figure 1, the proportion of CK elevation has nothing to do with age.

Compared with the normal CK group, the duration of GD and ATD treatment were shorter in the group of elevated CK ($P=.019$ and $P=.016$). More than half of elevated CK occurred within 6 months of diagnosis of GD and ATD treatment (Figs. 2 and 3). More than 60% of serum CK elevations occurred within 6 months after taking oral ATDs (Fig. 3).

Compared with patients with normal serum CK, patients with elevated CK had lower FT_3 and FT_4 and increased TSH. Pearson correlation analysis was used to analyze the relationship between patients' thyroid hormone levels and serum CK levels. FT_3 and FT_4 are negatively correlated with CK. The correlation coefficients are respectively –0.222 ($P=.000$) and –0.234 ($P=.000$). There is positive correlation between TSH and serum CK concentration. The correlation coefficient is 0.405 ($P=.000$).

Among 56 patients with elevated serum CK, there are 55 patients administrated with methimazole (MMI) and 1 patient treated with propylthiouracil (PTU). MMI dose range of normal CK group is 1.4 to 65.0 mg per day and elevated CK group is 2.5

Table 1

Demographic and clinical characteristics of patients.

	Total	Male	Female
No. of patients	416	128	288
Age (yr), median (range)	33 (8–75)	31 (18–71)	36 (8–75)
History of GD			
nonavailable	22	0	22
<3 mo	70	21	49
3∼<6 mo	69	20	49
6∼<12 mo	61	19	42
12∼<36 mo	86	36	50
≥36 mo	108	32	76
Duration of ATD			
nonavailable	16	0	16
<1 mo	47	14	33
1∼<3 mo	48	16	32
3∼<6 mo	77	23	54
6∼<12 mo	68	18	50
≥12 mo	160	57	103
Medication period (mo), median	10	12	9
Drug			
PTU	26	6	20
MMI	390	122	267
Daily dosage (mg)			
PTU, median (range)	150 (25–200)	175 (150–200)	50 (25–200)
MMI, median (range)	10 (1–65)	10 (3–50)	10 (1–65)
Thyroid function			
FT_3 (pg/ml), median (range)	3.43 (1.16–20.00)	3.62 (1.41–20.00)	3.37 (1.16–20.00)
FT_4 (ng/dl), median (range)	1.20 (0.20–12.00)	1.29 (0.48–5.55)	1.17 (0.20–12.00)
TSH (μIU/ml), median (range)	0.294 (0.000–71.752)	0.370 (0.003–31.982)	0.261 (0.000–71.752)
CK (IU/L), median (range)	92.05 (17.5–1029.8)	120.40 (40.30–413.90)	81.40 (17.50–1029.80)
No. of patients with elevated CK (%)	56 (13.5)	25 (19.5)	31 (10.8)

ATD = antithyroid drug, GD = Graves disease, MMI = methimazole, PTU = propylthiouracil.

Table 2

Clinical characteristics of patients with normal CK and elevated CK.

	Normal CK	Elevated CK	*P* value
No. of patients (M/F)	360 (103/257)	56 (25/31)	
Age (yr), median (range)	33 (8–75)	31 (9–71)	.610
History of GD (%)			
nonavailable	20 (5.56%)	2 (3.6%)	
<3 mo	62 (17.2%)	8 (14.3%)	
3~<6 mo	49 (13.6%)	20 (35.7%)	
6~<12 mo	57 (15.8%)	4 (7.1%)	
12~<36 mo	77 (21.4%)	9 (16.1%)	
≥36 mos	95 (26.4%)	13 (23.2%)	
Medical history (mo), median	13.0	6.0	.019
Duration of ATD (%)			
nonavailable	14 (3.9%)	2 (3.6%)	
<1 mo	46 (12.8%)	1 (1.8%)	
1~<3 mo	38 (10.6%)	10 (17.9%)	
3~<6 mo	54 (15.0%)	23 (41.1%)	
6~<12 mo	65 (18.1%)	3 (5.4%)	
≥12 mo	143 (39.7%)	17 (30.4%)	
Medication period (months), median	10.5	5	.016
Drug			
PTU	25	1	
MMI	335	55	
Daily dosage (mg)			
PTU, median (range)	150.0 (25.0–200.0)	100.0	
MMI, median (range)	10.0 (1.4–65.0)	10.0 (2.5–20.0)	.256
Thyroid function			
FT_3 (pg/ml)	4.81±3.73	3.09±0.96	.000
FT_4 (ng/dl)	1.55±1.14	0.99±0.34	.003
TSH (μIU/ml)	1.95±4.98	5.31±13.65	.000
CK (IU/L)	87.85±34.99	289.71±167.05	.000
Male	106.51±32.01	247.07±72.79	
Female	80.37±33.35	324.09±210.21	

to 20.0 mg per day. No difference in MMI dose between the 2 groups ($P = .256$). There is no statistical relationship between MMI dosage and serum CK level ($P = .781$) or whether serum CK concentration exceeds the reference range ($P = .270$).

There are 45 patients whose serum CK concentration did not exceed twice the upper limit of reference range among 56 patients with elevated CK concentration. It accounted for 80.4% of the total patients.

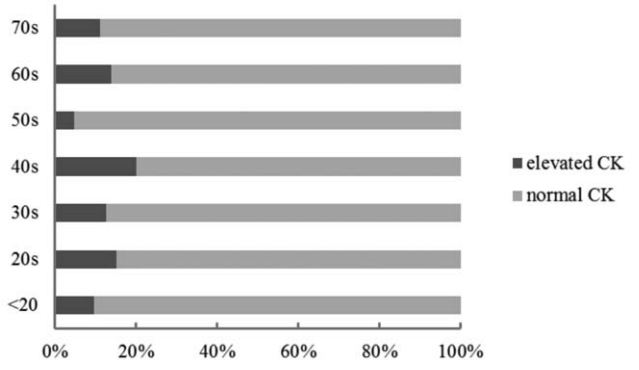

Figure 1. Proportion of elevated CK in different age groups. As shown in the figure, the proportion of CK increase is independent of age. CK = creatine kinase.

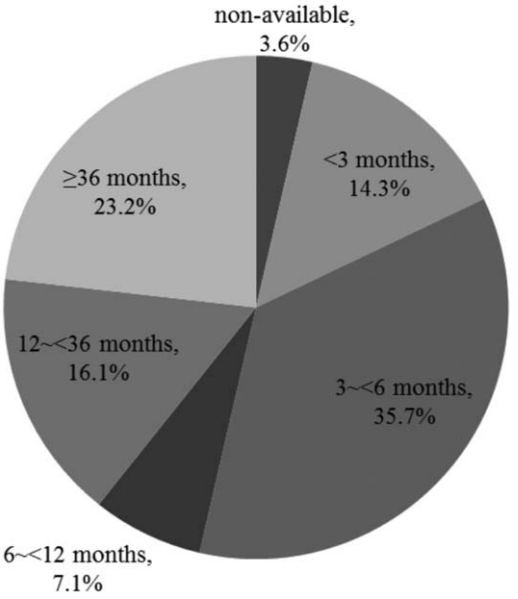

Figure 2. Medical history of elevated CK patients. 14.3% of patients with elevated serum CK had a medical history of hyperthyroidism for less than 3 months. 35.7% of patients are between 3 and 6 months. 7.1% of patients are between 6 and 12 months. 16.1% of patients are between 12 and 36 months. 23.2% of patients had a medical history of more than 36 months. In addition, 3.6% of patients did not provide disease duration. CK = creatine kinase.

4. Discussion

Oral ATDs are an effective treatment for GD. But it is a common problem that some side effects emerged in the process of oral ATDs treatment. They include pruritus, skin rashes, agranulocytosis, hepatic injury, aplastic anemia, and so on.[6–8] In addition,

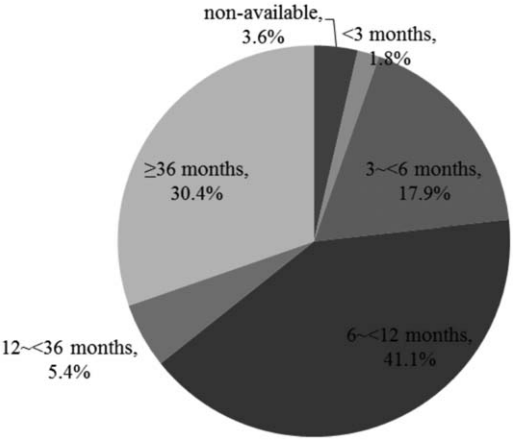

Figure 3. Medication period of elevated CK patients. 1.8% of patients with elevated serum CK took antithyroid drugs for less than 3 months. 17.9% of patients are between 3 and 6 months. 41.1% of patients are between 6 and 12 months. 5.4% of patients are between 12 and 36 months. 30.4% of patients had a medication period of more than 36 months. In addition, 3.6% of patients did not provide duration of medication. CK = creatine kinase.

we noticed that some patients with GD treated with oral ATDs manifested symptom of myalgia. CK is a muscle-specific kinase. Elevation of serum CK concentration is a useful indicator of muscle damage. So we performed a measurement of serum CK concentration in these patients with myalgia, and found that some patients had an increase in serum CK concentration. We also noticed that as early as 2016, the World Health Organization (WHO) had issued a warning related to risk of rhabdomyolysis caused by MMI. At the same time, we noticed that some patients without myalgia also had elevated serum CK concentration. To know more about the change of serum CK levels in patients treated with oral ATDs, we designed this study.

Finally, we found 56 cases with elevated serum CK concentration in 416 GD patients treated with oral ATDs. The proportion of patients with elevated CK level accounted for 13.5% of the total. The ratio is much higher than other adverse effects such as agranulocytosis and hepatic injury.[4,7] This data showed that this phenomenon was universal in patients treated with oral ATDs. In the long course of treatment, we may ignore this common side effect. After retrieving relevant literature, we found some documents related to serum CK elevation caused by oral ATDs, but they were almost limited to case reports[10–14] and epidemiological investigation was absent.

We found that serum CK concentration after taking ATDs has no correlation with the patient's age, but it is significantly related to gender. Male patients are more prone to this adverse reaction. In previous case reports, the majority were also young and middle-aged male patients. Interestingly, although the proportion of elevated serum CK level in female patients is lower than that in males. But if it emerged, serum CK increase will be more serious and it is far exceeding than that of male patients.

Elevation of serum CK concentration is also related to the duration of receiving oral ATDs treatment. In most patients, serum CK elevation occurred within 6 months from the beginning of treatment. Therefore, it is need to pay more attention to the adverse effects of increased serum CK concentration in the early stage of oral ATD treatment.

Despite 13.5% patients occurred increased serum CK concentration, we have observed that more than 80% patients' serum CK concentration did not exceed twice upper limit of normal reference range among 56 patients with elevated serum CK concentration. Among the data we collected, the highest CK was 1030 IU/L, which was 5.9 times the upper limit of normal reference range. Therefore, although elevated CK is not rare in patients treated with oral ATDs, most patients have mild increased serum CK levels without serious clinical symptoms. In patients with significantly increased serum CK level, there is no correlation between serum CK concentration and the course of disease, the duration of treatment or drug dosage. Anyway, although muscle damage due to oral ATDs is relatively common, most cases are not serious. This may explain why this side effect was often ignored in the past.

Previous research has found that oral ATDs related myopathy was mostly involved MMI and carbimazole,[15,16] PTU has also been reported. Carbimazole is rarely used in China. Most of our patients are treated with MMI, and only a few patients are treated with PTU. Therefore, it is not clear which drug is more closely related to increased serum CK concentration. There was no significant difference in the MMI dosage between the normal CK group and the elevated CK group, and there was no statistical correlation between MMI dosage and increased serum CK concentration. Because it is a cross-sectional study, we have no way to analyze if the drug dosage modification is related to serum CK concentration fluctuation.

GD is associated with many muscular diseases. For example, thyrotoxic myopathy, hypokalemic paralysis, and myasthenia gravis.[17–19] Despite some cases were reported rhabdomyolysis associated with thyrotoxicosis.[11,12] Our investigation revealed that decreased thyroid hormone is associated with elevated serum CK concentration. FT_3 and FT_4 are negatively correlated with serum CK concentration and TSH is positively correlated with serum CK concentration. Kim[20] reported a 13-year-old girl who has increased serum CK level during MMI treatment. He speculated that the possible mechanism of CK elevation is the rapid decline of thyroid hormone levels. Based on these results, it is reasonable to speculate that the increases of serum CK concentration during the process of oral ATDs treatment is related to the rapid reduction of thyroid hormone levels and has nothing to do with drug per se. It is estimated that rapid reduction of thyroid hormone levels led to a relative lack of triiodothyronine in skeletal muscle and induced myositis. However, Japanese scholar Ito[10] had reported a case and this patient's therapeutic process suggested that the muscle damage tends to be related to the drug per se. This patient manifested increased serum CK concentration during MMI treatment. After MMI switched to potassium iodide, the serum CK level decreased. Serum CK level increased again after potassium iodide was exchanged to PTU. When PTU was discontinued, serum CK levels returned to normal.

Due to the limited information collected in this investigation, it is not clear whether there are other relevant factors affecting the elevation of CK in patients, such as combined medication, excessive exercise, blood potassium level, vitamin D levels, etc. The mechanism of serum CK elevation in GD patients during antithyroid treatment is unclear. Vitamin D deficiency was viewed as an etiological factor of myopathy.[21] Previously, we reported a case with elevated serum CK concentration whose vitamin D levels were measured.[9] This patient was not enrolled in this investigation. Her minimum vitamin D level was 28.64 nmol/L and the highest serum CK level was 6251.5 IU/L. Vitamin D supplement was added during the course of treatment and her vitamin D level was up to 54.75 nmol/L. However, in the process of treatment, this patient's serum CK concentration did not decrease accompanied by the increase of vitamin D level, but it was related to the treatment of coenzyme Q10. Therefore, more research is needed to clarify the relationship between vitamin D deficiency and ATD-related myopathy. Khalil[22] reported a case of MMI induced myositis. Biopsy proved eosinophil infiltration of damaged muscles. Therefore, increased serum CK concentration in some patients may be related to autoimmune diseases.

We have also noticed that most cases of ATDs related to CK elevation were Asian patients in previous reports. So this side effect may tend to genetic susceptibility.[16] We should pay more attention to this adverse effect on Chinese GD patients.

Author contributions

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