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Comparison of Muscle-derived Serum Carbonic Anhydrase III and Myoglobin in Dermatological Patients: Effects of Isotretinoin Treatment

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The serum levels of muscle-specific serum carbonic anhydrase III (S-CAIII) and myoglobin (S-Myo) were analyzed in various male dermatological patients of the same age. The mean levels of S-CAIII and S-Myo were essentially similar in patients with acne, psoriasis vulgaris, atopic eczema and tinea, suggesting that common dermatological diseases do not affect the serum levels of the muscle markers. Increased levels of S-CAIII, which is specific for skeletal muscle cells, were found in the acne patients who had been treated with isotretinoin. However, when S-CAIII and S-Myo were studied in 24 patients (16 males, 8 females) before and during isotretinoin treatment, no constant increases in these markers could be observed. When individual patients were followed for several months, transient increases or decreases could be observed. The changes in S-CAIII, or S-Myo, did not correlate with the dose of isotretinoin, nor with the duration of the treatment.

The results suggest that systemic isotretinoin does not specifically affect skeletal or myocardial muscles. The increases in these markers observed in the course of dermatological diseases and isotretinoin treatment are obviously due to other factors, such as exercise.

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Retinoids are extensively used for the treatment of various skin disorders. In particular, isotretinoin has been widely used for the treatment of severe acne. Treatment with isotretinoin produces serious and numerous side effects which have been well documented in clinical trials. One of the side effects is muscle pain, with mild to moderate increases of creatine phosphokinase activity (1–5).

Recently, the development of new assays for following changes in muscle metabolism has proved to be particularly useful. These assays utilize the accurate, simultaneous measurement of serum carbonic anhydrase III (S-CAIII) and myoglobin (S-Myo) levels (6). Isoenzyme III of CA has been shown to exist in appreciable amounts only in type I (slow-twitch, or red) skeletal muscle fibers (7, 8). Myoglobin is found in skeletal and cardiac muscles, but not in smooth muscle. The simultaneous measurement of S-Myo and S-CAIII can be used to evaluate the origin of muscle-derived proteins in serum and, thus, to differentiate between myocardial and skeletal muscle damage (6). Especially CAIII has been shown to be a more sensitive marker of muscle damage than creatine kinase in various neuromuscular diseases such as polymyositis (9). S-Myo and S-CAIII can also be used to study the intensity of physical exercise and both are decreased relatively rapidly (within 24 h) after exercise (10). In the present study, S-CAIII and S-Myo were measured in acne patients. The levels of S-CAIII and S-Myo were compared to those found in other common skin disorders and to those of patients receiving isotretinoin treatment.

PATIENTS AND METHODS

Morning serum samples were collected from young male dermatological patients (109 subjects) with various common skin diseases. In the second part of the study, serum samples were taken, before and during isotretinoin (Roaccutane®, Roche) treatment, from 16 male patients and 8 female patients. Clinical details of these patients are shown in Table I. The serum samples were kept at −20°C until assayed.

S-CAIII and S-Myo were assayed using a dual-labelled time-resolved fluoroimmunoassay (11). The control level of S-CAIII for males and females is 21 ± 8 μg/L, while those of S-Myo are 31 ± 11 μg/ml and 25 ± 10 μg/L for males and females respectively. Statistical analyses: Student's *t*-test and linear regression were used.

RESULTS

S-CAIII and S-Myo levels were measured in sera from 109 patients with acne, atopic eczema, psoriasis vulgaris, tinea, or some other common skin disorder (verruca vulgaris, condyloma, lichen ruber planus, various eczema, urticaria). All these patients were males and of about same age, in order to eliminate variations due to age and sex. The individual levels of S-CAIII and S-Myo were variable, as shown in Figs. 1 A and B. With respect to the various diagnostic groups, S-CAIII levels were superior to the mean + 2 SD of the control values in one patient having atopic exzema (50 μg/L), in one psoriasis vulgaris patient (38 μg/L), in two tinea patients (98 and 50

Table I. *Clinical details of acne follow-up patients treated with isotretinoin*

	n	Age mean (range)	Weight mean (range)	Isotretinoin mg/d/kg mean (range)	Isotretinoin[a] total dose (mg) mean (range)
Males	16	19.5 (16–29)	71.5 (60–90)	0.55 (0.32–0.67)	1450 (280–2800)
Females	8	21.5 (15–31)	59.9 (51–75)	0.68 (0.53–0.78)	1780 (1200–2960)

[a] Total dose corresponds to the cumulative isotretinoin dose (mg) that the patients had received until the serum carbonic anhydrase III and myoglobin were determined during treatment (see Fig. 3).

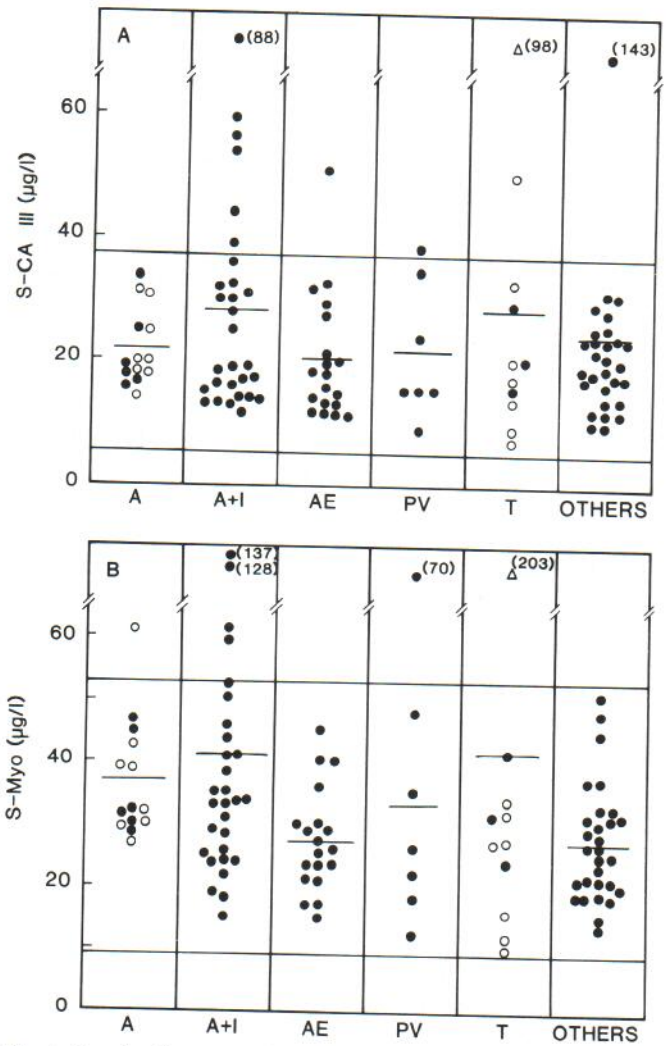

Fig. 1. Levels of serum carbonic anhydrase III (S-CAIII) (A) and myoglobin (S-Myo) (B) in various dermatological patients. The two solid horizontal lines indicate the mean ± 2 SD of S-CAIII and S-Myo in controls. The mean levels of S-CAIII and S-Myo in various diagnostic groups are shown by short lines. *A* = acne; *A + I* = acne plus isotretinoin; *AE* = atopic eczema; *PV* = psoriasis vulgaris; *T* = tinea. Open dots in acne patients indicate those who were treated with oral tetracycline. Open dots in tinea patients indicate those who were treated with griseofulvin. One tinea patient was treated with ketoconazole (△).

µg/L), who were treated with ketoconazole or griseofulvin respectively, and in one patient having eczema cruris (143 µg/L). S-Myo was superior to the mean + 2 SD in one psoriasis vulgaris patient (70 µg/L), in one acne patient (62 µg/L) and in one patient receiving ketoconazole treatment (203 µg/L). In acne patients who had been treated with isotretinoin, S-CAIII levels were superior to the mean + 2 SD in 6 out of 29 patients (20.7%), while S-Myo was high in 4 out of 29 patients (13.8%).

The ratio of S-CAIII/S-Myo was lowest in the acne group, but there were no statistically significant differences between the various patient groups. When the acne patients who had received isotretinoin, and who exhibited elevated levels of S-CAIII, were analyzed more carefully, no correlation with other parameters was found. In particular, the dose of isotretinoin (mg/kg/d) was almost identical in this group (0.51 ± 0.11 mg/kg/d), when compared to those presenting normal levels of S-CAIII (0.46± 0.14 mg/kg/d).

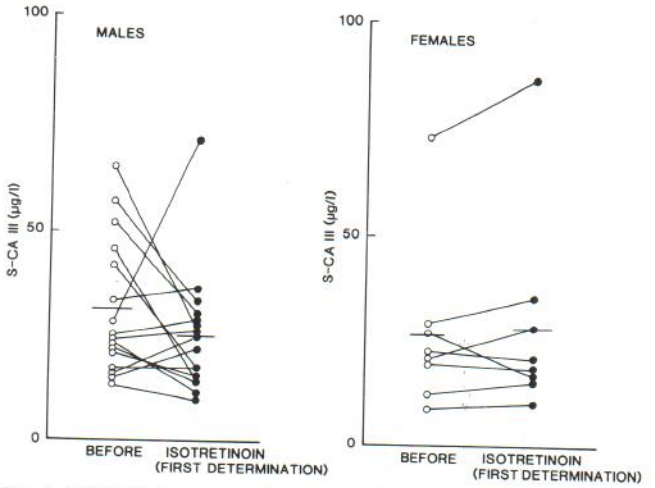

Fig. 2. S-CAIII in acne patients treated with isotretinoin. Samples were taken before and during the treatment in males and females (first determination). Mean levels are shown by the short horizontal lines.

Follow-up of acne patients receiving isotretinoin

Since it seemed that systemic isotretinoin might increase the levels of S-CAIII, and S-Myo in some patients, S-CAIII and S-Myo levels were measured in 24 patients before and during treatment (see also Table I) (Fig. 2). In some patients, assays were carried out several times during isotretinoin treatment (Fig. 3). As shown in Fig. 2, isotretinoin did not have any constant effect on S-CAIII in males or females. S-Myo did not change markedly during isotretinoin treatment (not shown). When individual patients were followed for 3–4 months, changes in S-CAIII were, in general, relatively small (Fig. 3). In only one patient was S-CAIII elevated over the mean + 2 SD of the controls (patient 4). S-Myo changes were more pronounced (Fig. 3), but, here again, no constant increase or

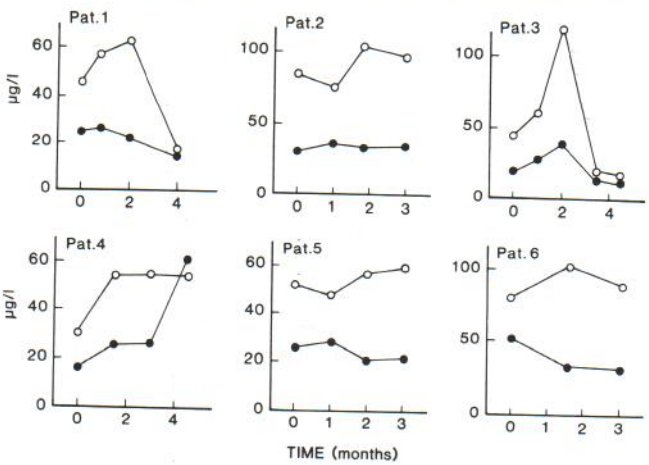

Fig. 3. S-CAIII and S-Myo in 6 representative patients who were followed for variable periods. *Patient 1:* a 16-year-old male, 0.63 mg isotretinoin/kg/d; *Patient 2:* a 15-year-old female, 0.78 mg isotretinoin/kg/d; *Patient 3:* a 19-year-old female, 0.63 mg isotretinoin/kg/d; *Patient 4:* a 20-year-old male, 0.32 mg isotretinoin/kg/d; *Patient 5:* a 17-year-old male, 0.47 mg isotretinoin/kg/d; and *Patient 6:* a 20-year-old male, 0.61 mg isotretinoin/kg/d. Symbols: ● – ● S-CAIII, ○ – ○ S-Myo.

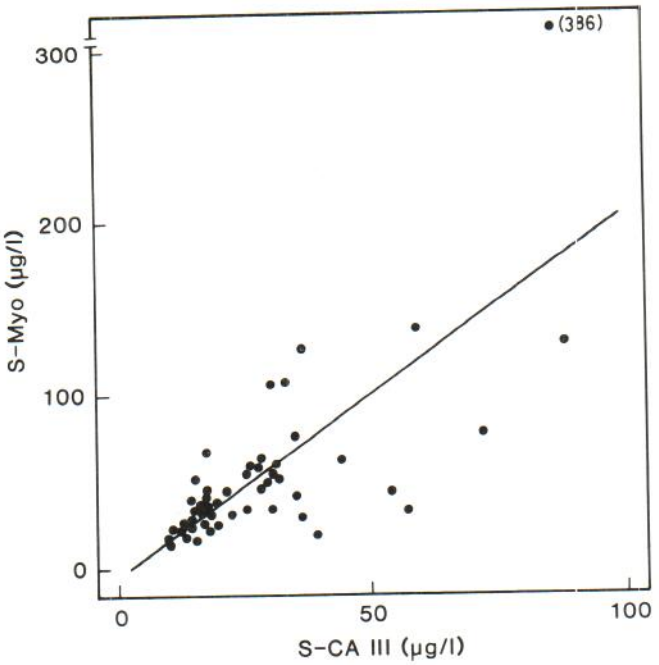

Fig. 4. Correlation between S-Myo and S-CAIII in patients who had received isotretinoin ($r = 0.703$, $p < 0.001$).

decrease could be observed during isotretinoin treatment (Fig. 3). In some patients, S-Myo was constantly high during treatment (see patients 2, 5 and 6), while in others, transient increases could be observed (patients 1 and 3).

Correlation between S-Myo and S-CAIII

There was a significant correlation between S-Myo and S-CAIII in acne patients both with (Fig. 4) ($r = 0.703$, $p < 0.001$), and without isotretinoin treatment ($r = 0.715$, $p < 0.001$). Thus, the isotretinoin treatment did not change the relative ratio of S-Myo and S-CAIII. S-Myo and S-CAIII levels did not correlate with the daily dose of isotretinoin used (mg/kg/day), nor with the total amounts of isotretinoin given to the patients.

DISCUSSION

In the first part of the study, increased levels of S-CAIII, a highly specific marker for skeletal muscle cells, were found in randomly collected serum samples from various dermatological patients, especially in those who had received systemic isotretinoin. Over 20% of these patients presented abnormally high S-CAIII values (superior to the mean + 2 SD of control levels). This suggested that systemic isotretinoin might increase serum levels of S-CAIII. High levels of S-CAIII were also found in some other dermaotlogical patients not receiving any isotretinoin treatment. These included, for example, cases of psoriasis vulgaris, atopic eczema, eczema cruris, as well as two tinea patients who had been treated with systemic griseofulvin, or ketoconazole. In the second part of the study, S-CAIII and S-Myo were followed in 24 patients receiving isotretinoin treatment. Surprisingly, levels of S-CAIII in males were even lower during isotretinoin treatment than those found in the same patients before treatment (statistically not significant).

Previously, transient increases in creatine kinase (CK) had been observed during isotretinoin treatment (1–5). In some patients, isoenzyme fractionation has suggested that elevated CK levels were derived from skeletal muscles (4). However, accumulated data indicate that a direct effect of isotretinoin on muscles is not evident in most patients presenting elevated levels of CK, whereas the status and intensity of exercise are more important causal factors (12). Our results are in agreement with these previous studies, even though we have used different muscle markers. Since S-CAIII is the most specific marker of skeletal muscle cells, the failure to find constant increases in this marker during isotretinoin treatment indicates that isotretinoin does not generally affect skeletal muscles. This suggests that routine measurements of carbonic anhydrase III and myoglobin are not necessary during isotretinoin treatment.

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