Pain Medicine

Pain Medicine 2012; 13: 616–619
Wiley Periodicals, Inc.

Creatine Treatment to Relieve Muscle Pain Caused by Thyroxine Replacement Therapy

To the Editor:

The impact of thyroid deficiency and its reversal by T4 replacement therapy on glucose metabolism remained controversial [1–4]. Small doses of thyroxine (1 μg/kg) normalized most of the intermediary metabolic parameters of thyroidectomized rats [5], while 20-times-higher doses would be needed to depress the high rates of thyroid-stimulating hormone (TSH) release of pituitary *via* feedback inhibition [6]. Thyroxine levels can be brought up to normal with oral thyroxine pills from 25 to 200 μg/day. Under constant balanced conditions, low levels of thyroid hormones maintain normal intermediary metabolism; insufficient thyroxine administration results in hypothyroidism; and high thyroxine doses cause swinging to hyperthyreoidic symptoms. The regulatory functions of adenohypophysis and pituitary-dependent glands are to smooth out oscillations. In thyroidectomized patients, the negative feedback loop does not function, and the development of hypothyreoidic symptoms are prevented by thyroxine replacement therapy.

This letter presents a hypothyroid case where the muscular side effects following thyroxine replacement therapy manifested as muscle pain. Long-term protection against thyroxine replacement therapy-induced muscle pain has been provided by low doses (2 g/day) of creatine monohydrate administration.

In 1993, our male patient was 49 years old when his hyperthyreosis was diagnosed. In 2001, the patient had 7–8 kg loss in weight in 6 months and *hyperthyreosis recidiva* was diagnosed. A single dose of p.o. administered radioisotope ^{131}I (240 MBq) was applied in a capsular form. Three months later (December 2001), laboratory parameters showed high creatine kinase (894 U/L) and transaminase (GOT 65 IU/L, GPT 61 IU/L) activities. Elevated creatine kinase levels may reflect injury in myocardial infarction, muscle breakdown, muscular dystrophy, myositis, reduced adenosine triphosphate (ATP) level in muscle, and acute renal failure. Upon the radioactive destruction of thyroid function, the patient experienced excessive muscle pain and involuntary defecation of stool for several days. The urinary incontinence was even more distressing and lasted for several weeks. The repeated laboratory test (January 2002) showed high creatine kinase activity (478 U/L), while transaminase activities returned to normal. Hypothyroid symptoms were temporarily compensated by thyroid hormone substitution (50 μg L thyroxine/day) to the euthyreotic state (T4: 91.9 nmol/L; normal values: 58–154 nmol/L; TSH: 1.5 U/L; normal values: 0.3–3 U/L). In May 2002, the patient complained of cramps in legs and scapular arches accompanied by the inability to raise his hands and legs. Neurological examinations in the lower limbs and in the shoulder indicated strain and tenderness. Neurophysiology confirmed mild diffuse myelin damage in the motor fibers of the lower limbs, median neuropathy of the wrist (carpal tunnel syndrome) with paresthesias, numbness, and muscle weakness in the hand. Electromyography showed resting electrical potential in these muscles. In August 2002, scintigraphic visualization of the thyroid gland could not be performed due to the low radioisotope ^{131}I uptake. Ultrasound analysis showed an inhomogeneous thyroid gland with somewhat smaller lobes. Hormonal levels (TSH: 16.4 U/L, T4: 5.8 pmole/L, T3:1.4 nmole/L) indicated *hypothyreosis factitia*, which culminated at ~50 U/L TSH level. Under these hypothyreotic developments, neither degenerative spinal, nor cardiological, nor electrophysiological alterations could be detected. To compensate hypothyreosis, the thyroxine dose was raised from daily 50 to 75 and then to 100 μg L-thyroxine, which, however, aggravated the painful muscle symptoms without reaching the euthyroid state.

The extremely painful muscle cramps, 1–2 hours after taking 50 μg of T4, forced the patient to refuse the increase of thyroxine dose. After each thyroxine administration, muscle pain and extreme muscle weakness developed and lasted for several days. By day 4 and 5 after thyroxine administration, the stinging pain numbed his fingers and hands. As a pain reliever, daily one tablet of Rheosolon (100 mg phenylbutazone, 2 mg prednisolone; Rheosolon, Pannonpharma Kft, Pecs, Hungary) was administered. The anti-inflammatory prednisolone induced an aggressive behavior and hostile manner of the patient diagnosed as steroid "roid" rage. To avoid the corticosteroid side effects, its use was suspended.

The patient was given temporarily L-carnitine (2 g/day) as a nutrition supplement to generate metabolic energy and to inhibit the accumulation of lactic acid in the muscle. Although the termination of prednisolone therapy ceased the steroid rage and improved the mental state, carnitine administration had no significant effect on muscle function and pain. The therapy was then switched from carnitine to creatine monohydrate. Creatine, a muscle-building supplement, is taken for loading in high doses (20–25 g/day) and in small doses (2.5–5 g/day) for maintenance. Creatine kinase catalyzes the conversion of creatine to creatine phosphate in the muscle. Phosphocreatine as an energy reservoir converts adenosine diphosphate to ATP. The daily creatine requirement is 2 g, half of it is produced by the organism, and the other half is ingested with meat.

Our patient was administered creatine monohydrate to overcome the muscle pain of high-intensity initial tremor

and muscle cramps that followed thyroxine intake. Creatine administration turned out to be a tolerable and efficient treatment after T4 induced muscle pain. The recent regime of hypothyroidism treatment involves p.o. administration of 50 μg of L-thyroxine (7:00 AM). To reduce and to eliminate other potential side effects, the patient took an initial 5 g of creatine monohydrate p.o. (8:30 AM) for 1 year, which was reduced to 2 g creatine monohydrate. The second dose (50 μg) of L-thyroxine is taken without creatine administration (4:00 PM). The patient is pain-free for 2.5 years, proving the efficiency of the treatment of muscular side effects caused by the thyroxine replacement therapy.

There is much debate about the dose of thyroxine replacement therapy and whether the suppression of the serum TSH concentration is a risk factor for osteoporosis [7]. It is also doubted whether the so-called replacement therapy of thyroxine could suppress the secretion of TSH. To achieve this goal, high thyroxine doses could lead to serious cardiac complications, such as atrial fibrillation, cardiomyopathy, and focal myocarditis [8], and even to life-threatening ventricular fibrillation [9].

The effects of thyroxine replacement therapy in patients with hypothyroidism [10] are in conformity with animal experiments, which provided evidence that after thyroxine administration, glycogenolysis predominates over glycogen synthesis [11]. However, the long-term replacement therapy could have exhausted the muscle glycogen stores of our patient. The ATP shortage in the hypoxic muscle was at least temporarily alleviated by creatine administration. Creatine addition seems to be justified under intermittent hypoxic-normoxic exposures characterized by the decrease of the muscular contents of creatine phosphate, citrate, alpha-ketoglutarate, and glutamate [12]. Creatine supplementation can be especially useful in the hypothyroidic muscle when the mitochondrial functions are hampered. That thyroid ablation induces a decrease in muscle mitochondrial oxygen consumption and can be reversed by thyroxine was proved in hypothyroid rats [13]. The depletion of citrate and the retarded mitochondrial function in muscle under hypoxic conditions are shown in Figure 1.

Moreover, thyroxine treatment stimulates the breakdown of glycogen and glycogenic amino acids into glucose. Under hypoxic conditions, lactate production (net gain 2 ATP) causes pain in muscle. Lactate carried to the liver by the blood is converted back to glucose through gluconeogenesis in a quite expensive (6 ATP) manner (Figure 2).

Creatine is converted to creatine phosphate and stored (>90%) in the skeletal muscle. In the healthy muscle, supplementary ATP production comes from the conversion of phosphocreatine to creatine catalyzed by the creatine kinase, and at maximal exercise, the main source of ATP in oxidative (type I) muscle fibers is oxidative phosphorylation [14]. In hypothyroid state when anaerobic glycolysis plays a significant role, the inadequate ATP production in the mitochondria of muscle cells is supplemented by a higher creatine kinase activity as manifested in our patient. Inadequate ATP production in mitochondria was indicated by the supplementary substrate level phosphorylation observed in our patient by the elevated creatine kinase activity. That creatine may improve muscle strength was demonstrated in muscular dystrophies [15]. Other studies also indicate that creatine supplementation is beneficial for skeletal muscle function in the McArdle glycogen storage disease [16] and provides a safe, effective, and inexpensive treatment in inflammatory myopathies [17]. The side effects of low doses of creatine either could not be traced or were negligible [18,19]. The long-term use of moderate doses of creatine (14 g/day for 3 years) was described to be safe [20]. Creatine was reported to have a protective effect on the heart, muscle, and neurological diseases by reducing significantly the cholesterol level [21,22]. One report described individuals suffering from kidney problems after using creatine [23], giving a warning that further studies are necessary to demonstrate the protective and adverse effects of creatine.

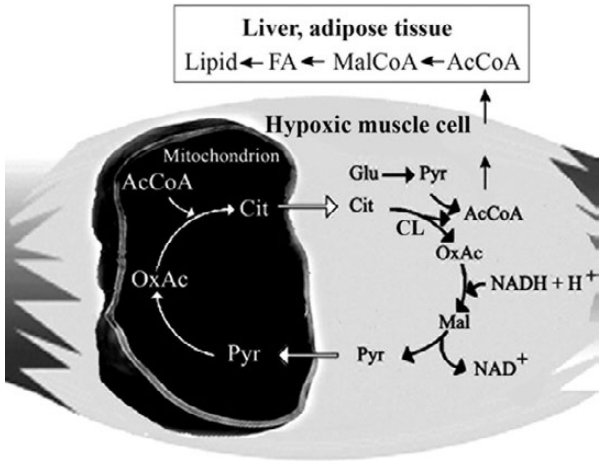

Figure 1 Lipogenic pathway under hypothyroid state in hypoxic muscle cell. In the mitochondria of a hypoxic muscle cell, the citrate cycle, the terminal oxidation, and oxidative phosphorylation are retarded. In the absence of normal aerobic conditions, the overproduction of acetyl-CoA induces fatty acid and lipid synthesis in the liver and adipose tissue. Glu = glucose; AcCoA = acetyl-CoA; Cit = citrate; CL = citrate lyase; Pyr = pyruvate; OxAc = oxaloacetate; Mal = malate; MalCoA = malonylCoA; FA = fatty acid.

The observation that high-dose creatine treatment worsened the main clinical symptoms of exercise intolerance in McArdle disease prompted investigations to clarify the effective creatine dose without adverse effects, which limited it between 60 and 150 mg/kg daily [24]. The same

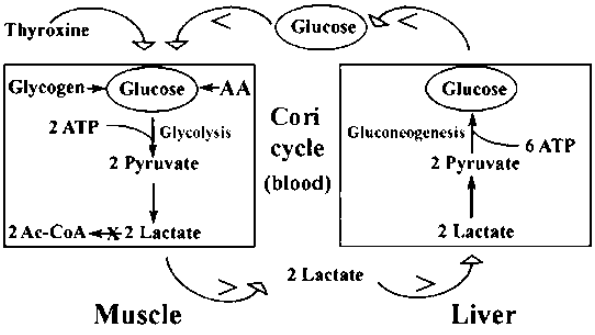

Figure 2 The effect of thyroxine on the metabolism of skeletal muscle in hypothyroidism. Upon T4 replacement, the glycogen levels of the muscle are depleted and many proteins are hydrolyzed to amino acids (AA). Glycolysis breaks down glucose into lactic acid under anaerobic conditions, resulting in muscle fatigue. The conversion of lactic acid to glucose is performed in the liver as muscles lack enzymes for gluconeogenesis. The lactic acid is transported by the blood to the liver and the recycling of neogenetic glucose takes place via the Cori cycle. Acetyl-CoA (AcCo) formation is scarce in the hypoxic muscle. The conversion of acetyl-CoA to citrate and mitochondrial pathways including citrate cycle, β-oxidation of fatty acids, terminal oxidation, and oxidative phosphorylation are also depleted under hypoxic conditions. The > sign indicates increased transport in the lower, while the < sign indicates diminished transport in the upper loop of the Cori cycle.

authors confirmed that high-dose creatine increased muscle pain in this glycogen storage disease type V [25]. These findings are in conformity with the observations of others that creatine improved muscle strength in exercising healthy individuals and in patients with neuromuscular disease and heart failure, but did not improve pulmonary rehabilitation [26]. There was a mild, but significant, improvement in muscle strength and daily activities also in muscular dystrophies [27]. Creatine was well-tolerated in myotonic dystrophy without clinically relevant side effects, but did not result in significant improvement of muscle strength or daily life activities [28].

Finally, to safely use creatine without any doubt, it should be taken only in low doses. People with low creatine levels (e.g., vegetarians) seem to benefit more by taking creatine supplements than those who have higher levels of creatine. The saturation level can be reached within a few days by taking an initial higher (5 g/per day) loading dose to relieve muscle pain, followed by a lower (2 g/day) maintenance dose as we have recommended to our patient.

The effects of thyroxine replacement therapy on patients with hypothyroidism [10] are in conformity with animal experiments, which provided evidence that in thyroxine administration, glycogenolysis predominates over glycogen synthesis [11], leading to the exhaustion of the stored energy. The inadequate amount of chemical energy of ATP in muscular mitochondria was indicated by the supplementary substrate level phosphorylation manifested by the elevated creatine kinase activity of our patient. ATP shortage in the hypoxic muscle can be at least temporarily alleviated by creatine administration, which was stored (>90%) in the skeletal muscle. Based on this case study, creatine seems to be a useful energy supplement in hypothyroidism when the mitochondrial functions in the hypoxic muscle are retarded.

Acknowledgment

This work was supported by Hungarian Scientific Research Fund (OTKA grant) T42762 grant.

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