Clinical and Biochemical Features of Muscle Dysfunction in Subclinical Hypothyroidism

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ABSTRACT
Alterations in muscle structure and function have been reported in overt hypothyroidism, with decreased activity of enzymes involved in anaerobic and oxidative glucose metabolism. To test whether similar changes in muscle energy metabolism are present in subclinical hypothyroidism (sHT), we studied 12 patients with sHT who complained of mild neuromuscular symptoms. The control group included 10 sex- and age-matched healthy volunteers. Skeletal muscle lactate and pyruvate production were determined in the resting state and during dynamic arm exercise. During exercise, blood lactate was significantly higher in sHT patients than in controls from the third exercise step onward (P = 0.02 at 30%, P = 0.008 at 40%, and P = 0.002 at 50% of maximal voluntary contraction). Moreover, the mean increment in blood lactate during exercise was positively related (r² = 0.44; P = 0.02) to the duration of sHT, but not to serum levels of TSH, free T₃, or free T₄. No significant difference was found in blood pyruvate concentrations between the two groups at baseline or during exercise. Thus, the lactate/pyruvate ratio curve paralleled the lactate curve in patients as well as controls.

We conclude that muscle energy metabolism is impaired in sHT in rough proportion to the known duration of the disease. Early L-T₄ therapy may be useful not only to provide specific treatment for such metabolic changes, but also to avoid progression to frank hypothyroidism. (J Clin Endocrinol Metab 82: 3315–3318, 1997)

MUSCLE SYMPTOMS, including pain and cramps, proximal weakness, and slow reflexes, are common in hypothyroid patients (1). Impaired mitochondrial metabolism has been involved in the pathogenesis of abnormal skeletal muscle function (2–4).

Subclinical hypothyroidism (sHT) is defined solely by the elevation in circulating TSH levels in the face of normal free thyroid hormone levels (5). Several studies, however, suggest that sHT may be associated with significant psychiatric and neurological dysfunction. There is also growing evidence for the presence of metabolic and cardiovascular abnormalities similar to those typical of overt hypothyroidism (6–9).

The aim of the present study was to evaluate in patients with sHT the possible presence of alterations in muscle energy metabolism similar to those observed in overt hypothyroidism. To this purpose, circulating lactate and pyruvate levels measured in the resting state and during aerobic dynamic exercise were compared to those in healthy control subjects.

Subjects and Methods

Subjects

We studied 12 patients (10 women and 2 men; mean age, 44.5 yr; range, 24–63 yr) with sHT, as judged by elevated serum TSH levels (≥4.0 mIU/L) and normal free thyroid hormones (FT₃ and FT₄) within the normal range. The etiology of sHT was as follows: postsurgery (n = 2), Hashimoto’s disease (n = 8), and radioiodine therapy (n = 2). Nine patients complained of mild neuromuscular symptoms, such as fatigue, cramps, paresthesias, and muscle weakness. In all patients the onset of sHT was well established, as they had been followed for several months before serum TSH elevation was detected because of the known thyroid disease. The control group included 10 sex- and age-matched healthy volunteers (8 women and 2 men; mean age, 43.2 yr; range, 28–60 yr), recruited among staff and relatives of patients attending the Department of Internal Medicine.

Cardiovascular, respiratory, and neuromuscular diseases were excluded in both patients and controls by a complete clinical work-up. Routine laboratory chemistry was normal in all, and none were taking any drugs. Body mass index was 26.4 ± 3.1 kg/m² (mean ± sd) in the control group and 27.2 ± 2.7 in sHT patients. No study subject was involved in competitive sports. Before inclusion in the protocol, a blood sample for the determination of FT₃, FT₄, antithyroglobulin antibodies (AbTg), antithyroid peroxidase antibodies (AbTPO), and TSH was obtained at 0800 h after an overnight fast.

Exercise protocol

The exercise was performed at least 4 h after a normal mixed meal with the subjects sitting; the test arm rested on a cushioned table with the elbow extended upward to approximately heart level. At the start of each experiment, the patient performed three brief (<3-s) maximal efforts on a hand-grip dynamometer at 3-min intervals. The highest tension recorded was taken as the maximal voluntary contraction (MVC) (10). After a 15-min rest, the test began with a first bout at 10% of MVC, then continued through successive 10% increments, achieving 50% of MVC (unless exhaustion developed at lower levels of exercise). Exhaustion was defined as the subject being unable to keep up with exercise at the target force. Each bout consisted of 1-min intermittent (one per s) contractions on the hand-grip dynamometer followed by a 2-min rest.

The protocol was chosen on the assumption that exercise under these conditions is mainly aerobic at the beginning and then progressively anaerobic as the contraction level increases (11) due mainly to the recruitment sequence of slow and fast motor units (12).

Blood glucose, lactate, and pyruvate concentrations were measured in the resting state and at each interbout interval by collecting samples from a catheter inserted into an antecubital vein of the exercising arm. The average increment in lactate and pyruvate was calculated as the mean of all interstep increments (interbout value divided by the basal value).
The exercise protocol was approved by the local ethics committee, and all study subjects gave their written informed consent.

Methods

Serum FT₃, FT₄, and AbTPO levels were measured by specific RIA, AbTg levels were determined by specific immunoradiometric assay, and TSH was measured with the use of an ultrasensitive immunoradiometric method. The normal ranges are as follows: FT₃, 7.2-19.3 pmol/L; FT₄, 3.7-8.6 pmol/L; TSH, 0.3-4.0 mIU/L; AbTPO, less than 15 IU/L; and AbTg, less than 50 IU/L. Blood glucose was measured on an Automatic Analyzer Hitachi 717 (Boehringer Mannheim, Mannheim, Germany). Whole blood lactate and pyruvate levels were assayed spectrophotometrically on a ERIS Analyzer 6170 (Eppendorf Geratebau, Hamburg, Germany). The normal ranges are as follows: lactate, 0.6-1.7 mmol/L; and pyruvate, 60–170 μmol/L. Blood samples were collected into iced tubes containing 1 mol/L perchloric acid for immediate deproteinization; the supernatant obtained from centrifugation was stored at −20°C and assayed within 30 days.

Statistical analysis

Data are expressed as the mean ± sd. The data analysis was carried out using the Mann-Whitney U test for independent samples, the Wilcoxon test for paired data, ANOVA, and Spearman rank correlation test, as appropriate. Linear regression analysis was carried using standard techniques. Statistical significance was assigned for P < 0.05.

Results

Serum FT₃ and FT₄ levels were in the normal range in all patients and were not statistically different from those in the controls (4.8 ± 0.3 vs. 5.2 ± 0.3 pmol/L and 12.0 ± 1.0 vs. 12.2 ± 0.6 pmol/L, respectively), whereas TSH levels were significantly higher (5.87 ± 0.44 vs. 1.15 ± 0.42 mIU/L; P < 0.001). A significant AbTPO and/or AbTg titer was detected in eight patients.

Under basal conditions, blood glucose, lactate, and pyruvate levels were not significantly different between patients and controls (Table 1). Only one patient was unable to complete the exercise protocol, and he stopped at the fourth step (40% of MVC).

During exercise, blood lactate levels (Fig. 1A) were significantly higher in sHT patients than in controls from the third exercise step onward (2.6 ± 0.3 vs. 1.6 ± 0.2 mmol/L (P = 0.02) at 30%, 3.1 ± 0.3 vs. 1.9 ± 0.2 (P = 0.008) at 40%, and 3.4 ± 0.3 vs. 1.9 ± 0.2 (P = 0.002) at 50% of the MVC). Moreover, the mean lactate increment was significantly higher in patients than in controls (P = 0.02; Table 1) and was directly related (r² = 0.44; P = 0.02) to the duration of sHT (Fig. 2). In contrast, no correlation was found between mean lactate increments and serum TSH, FT₃, and FT₄ levels.

Although during exercise, blood lactate was tightly correlated with pyruvate (r² = 0.94; P = 0.002 and r² = 0.95; P = 0.001 in patients and controls, respectively), no significant difference was evident in pyruvate values between the two groups at any workload (Fig. 1B). As a consequence, the time course of the lactate/pyruvate ratio was essentially superimposable on that of lactate in both controls and patients (Fig. 1C). Thus, the mean lactate/pyruvate ratio increment was significantly higher in patients than in controls (P = 0.02; Table 1) and correlated (r² = 0.36; P < 0.05) with the duration of sHT, but not with serum TSH, FT₃, and FT₄ levels.

No significant changes in blood glucose levels were observed during exercise in either patients or controls.

Discussion

Several alterations in muscle function have been reported in overt hypothyroidism (1). Furthermore, biochemical abnormalities such as glycogen accumulation and decreased activity of enzymes involved in energy production, have been described in hypothyroid red (type I) fibers (13–15). This is not surprising, as skeletal muscle is a target organ for thyroid hormones (2). The rapid decline in energy reserves of exercising hypothyroid muscle has been attributed to reduced mitochondrial activity in two studies with phosphorus nuclear magnetic resonance (2, 3), whereas another study using the same technique proposed a defect in glycogen breakdown as the mechanism (16). Thus, the precise contribution of glycogenolysis, glycolysis, and mitochondrial metabolism to abnormal skeletal muscle function in hypothyroidism remains to be elucidated.

We tested the possibility that defective mitochondrial oxidative metabolism may be present in sHT. As excessive lactate production during submaximal exercise is one of the main markers of in vivo functional mitochondrial impairment (17, 18), we studied venous lactate kinetics during incremental exercise in a group of patients with sHT of known origin and duration.

As previously reported in overt hypothyroidism (19), this study shows no differences in blood lactate and pyruvate levels between patients and controls at rest. However, the absolute lactate value as well as the mean lactate increment were significantly higher in sHT patients than in controls during exercise. This result is consistent with the possibility that during step-up exercise, muscle glycolysis exceeds pyruvate oxidation, resulting in rates of lactate production and release in excess of simultaneous lactate uptake; lactate, therefore, accumulates in the venous effluent. The higher lactate/pyruvate ratio of the sHT patients and the normal pyruvate absolute concentrations suggest that more severe intracellular acidosis may be responsible for pushing the excess pyruvate through the lactic dehydrogenase reaction.

Abnormal accumulation of lactate has been reported in hypothyroid dog muscles during exercise (20), but similar results in patients with overt hypothyroidism have not, to
our knowledge, been reported. Nuclear magnetic resonance studies in working hypothyroid human and rat muscles (3, 4) have documented a decreased intracellular pH during muscle exercise. As intracellular pH changes are related to lactate production (21), these results have been interpreted to reflect reduced mitochondrial oxidative capacity. The presence of T₃ receptors on the mitochondrial membrane of skeletal muscle (22) suggests a direct impact of thyroid hormones on oxidative metabolism and may provide a biochemical basis for the muscle dysfunction observed in frank hypothyroidism. In our study, however, there was no correlation between mean lactate and lactate/pyruvate ratio increments during exercise and serum TSH or thyroid hormone levels. Furthermore, the definition of sHT implies that circulating thyroid hormone levels are still in the normal range. Therefore, it may seem puzzling to find metabolic abnormalities similar to those typical of frank hypothyroidism. However, our study shows that the duration of sHT may play an important role in the development of defective muscle energy metabolism. Thus, exposure (i.e. time × concentration product) of skeletal muscle to thyroid hormones may be an important parameter in the coupling of glycolysis and oxidation. Minute decrements in hormone synthesis may over time lead to both biochemical signs and clinical symptoms qualitatively similar to those of overt hypothyroidism. If this hypothesis is correct, it should be possible to show that early l-T₄ treatment of sHT patients corrects muscle energy metabolism at the same time as it improves symptoms. With regard to this, multiple metabolic defects, including dyslipoproteinemia (8, 9), altered cardiac performance (6, 23), and neurobehavioral changes (7), had been previously reported in sHT, and l-T₄ treatment appeared effective in correcting at least some of these conditions.

In conclusion, our data show that patients with sHT and
muscle symptoms present evidence of mitochondrial oxidative dysfunction, possibly heralding the severe abnormalities of muscle metabolism of frank hypothyroidism. Early l-T4 therapy may be useful not only to provide specific treatment for such metabolic changes, but also to avoid progression to frank hypothyroidism.

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**References**