SHORT REPORT

ABSTRACT: Weakness is common in both hyper- and hypothyroidism, and skeletal muscle L-carnitine may play a role in this regard, as suggested by studies indicating abnormal levels of carnitine in serum and urine of patients with thyroid dysfunction. Skeletal muscle samples were obtained for carnitine analysis from control subjects, and from hyperthyroid and hypothyroid patients before and after treatment. There was a significant reduction in carnitine, especially the esterified portion, in hyperthyroid individuals, with a return to normal as euthyroid status was regained. In hypothyroid patients, there was a trend for carnitine to be lower than normal and for improvement once euthyroid status was attained. Our data indicate that muscle carnitine levels are affected by both hypo- and hyperthyroidism. A decrease in muscle carnitine in both conditions may contribute to thyroid myopathy.

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MUSCLE CARNITINE IN HYPO- AND HYPERTHYROIDISM

CHRISTOPHER SINCLAIR, MD,[1] JAMES M. GILCHRIST, MD,[1] JAMES V. HENNESSEY, MD,[2] and MANJU KANDULA, MD[1]

[1]Department of Neurology, Rhode Island Hospital, Brown Medical School, 593 Eddy Street, Providence, Rhode Island 02903, USA
[2]Department of Medicine, Rhode Island Hospital, Brown Medical School, Providence, Rhode Island, USA

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It is unclear what causes the weakness in hypothyroidism and hyperthyroidism, and it is possible that a perturbation in skeletal muscle L-carnitine may play a role. Carnitine is a carrier molecule that transports fatty acids into mitochondria for subsequent oxidation.[5] It is necessary to the production of energy in those organs that depend on fatty acid metabolism for their performance (e.g., skeletal muscle). If carnitine were depleted in thyroid dysfunction, this might lead to diminished fatty acid oxidation in skeletal muscle and, consequently, to weakness. Previous studies have demonstrated abnormal levels of carnitine in the serum and urine of subjects with thyroid dysfunction.[4]

The present study seeks to determine whether an alteration in carnitine levels occurs in the skeletal muscle of persons with thyroid hyper- or hypofunction.

Abbreviations: CPT-1, carnitine palmitoyltransferase-1; TSH, thyroid stimulating hormone

Key words: carnitine; hyperthyroidism; hypothyroidism; myopathy

Correspondence to: J. M. Gilchrist; e-mail: James_Gilchrist@Brown.edu

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MATERIALS AND METHODS

Following approval by our Investigational Review Board, skeletal muscle samples were obtained with the consent of all participants from 10 normal control subjects, 6 hyperthyroid patients, and 6 hypothyroid patients, none of whom had symptomatic or clinical weakness. Samples were obtained from the vastus lateralis by punch biopsy using a Bergström cutting trocar.[2] A second biopsy was taken from the hyper- and hypothyroid subjects after they had been treated and were chemically euthyroid. All subjects received monetary reimbursement. Tissue samples were frozen in liquid nitrogen at −70°C and sent for quantification of total, free, and esterified carnitine at Metabolic Analysis Labs, Inc. (Madison, Wisconsin). All samples were tested simultaneously. The quantitative radio-isotope assay used for L-carnitine analysis has been described previously.[6] Statistical analysis of results was performed using a standard two-tailed Student's *t*-test.

RESULTS

Controls. Age averaged 33.3 years and ranged from 28 to 48 years. Five of the 10 subjects were male. Total, free, and esterified muscle carnitine levels are shown in Table 1. There was a significant inverse

Table 1. Skeletal muscle carnitine levels.[†]

Subjects	Total	Free	Esterified (% of total)	Total	Free	Esterified (% of total)
Controls	8.97 ± 1.73	7.78 ± 1.69	1.19 ± 0.75 (13.3)			
	Pretreatment			Posttreatment		
Hyperthyroid	6.10 ± 2.27*	5.80 ± 1.93	0.30 ± 0.92** (4.9)	7.25 ± 1.32	6.13 ± 0.98	1.12 ± 1.22 (15.4)
Hypothyroid	7.78 ± 1.80	6.53 ± 1.90	1.25 ± 0.24 (16.1)	8.74 ± 1.88	7.80 ± 1.88	0.94 ± 0.54 (10.8)

NCP, noncollagen protein.
[†]Mean carnitine (nmol/mg NCP) ± SD.
**P < 0.01.*
***P < 0.02.*

correlation between total carnitine levels and subject's age ($r = -0.81$, $P < 0.00012$).

Hyperthyroid Patients. The six hyperthyroid patients had an average age of 38.5 years (range, 28 to 48); one patient was male. Pretreatment thyroid stimulating hormone (TSH) levels were suppressed in all. Pretreatment free thyroxine ranged from 3.5 to 16.5 ng/dl, and was less than 1.3 ng/dl (normal, <1.5 ng/dl) in all after treatment. There was a significant ($P < 0.01$) reduction in total carnitine in the skeletal muscle of hyperthyroid individuals (Table 1). Once the subjects became euthyroid, carnitine levels were no different than controls. Much of the reduction in total carnitine levels during the hyperthyroid state could be attributed to dramatically lower levels of esterified (acyl) carnitine ($P < 0.02$; Table 1), which returned to normal once the patients were euthyroid. There was no correlation between serum free thyroxine levels and total carnitine levels.

Hypothyroid Patients. The six hypothyroid patients had an average age of 39 years (range, 26 to 63); two patients were male. Pretreatment TSH levels ranged from 49.3 to 149.4 μIU/ml, and varied from 0.06 to 4.1 μIU/ml after treatment. In hypothyroid patients, lower carnitine levels were observed but did not reach statistical significance ($P < 0.14$) when compared to controls (Table 1). This difference resolved by the time the patients became euthyroid. No significant change was noted in levels of esterified carnitine compared to control subjects, or between pre- and posttreatment values. There was, however, a significant inverse correlation between pretreatment serum TSH and muscle carnitine levels ($r = -0.60$, $P < 0.01$).

DISCUSSION

Carnitine is critical to energy production in skeletal muscle.[5] It provides for the transport of long-chain fatty acids into the mitochondria, where they are oxidized to produce adenosine triphosphate. Disturbance in the level of carnitine in the muscle of persons with thyroid hyper- and hypofunction may provide insight to the cause of weakness occurring in this clinical context. If there is less carnitine available, as our results indicate, then there will be less energy (in the form of long-chain fatty acids) transported into the mitochondria. What remains unclear is the mechanism by which carnitine becomes depleted in these states.

One possible cause for carnitine depletion in hyperthyroidism may be increased esterification and excretion. The transcription of carnitine palmitoyltransferase-1 (CPT-1), which is responsible for the esterification (or acylation) of carnitine, is dramatically upregulated in the liver of hyperthyroid animals, and this upregulation is governed by thyroid hormone.[3] The increase in CPT-1 activity may lead to an increased synthesis of acylcarnitine from carnitine and long-chain acyl-CoA. Acylcarnitine is preferentially excreted, whereas free (nonesterified) carnitine is preferentially reabsorbed, by the tubular system of the kidney. An earlier study showed markedly elevated levels of carnitine in the urine of hyperthyroid individuals[4] but did not determine the proportion of esterified to total carnitine. It would seem from our study, and the results of Maebashi et al.,[4] that carnitine is leaving the muscle and appearing in the urine. What is not clear is why a larger percentage of esterified than total carnitine is leaving the muscle. Perhaps the increase of esterified carnitine is overloading the β-oxidation pathway, leading to increased urinary excretion. The increased transcription of CPT-1 in hyperthyroidism may ultimately lead to increased excretion of acylcarnitine, resulting in a chronic depletion in the pool of total carnitine.

Hypothyroidism may deplete carnitine levels for entirely separate reasons. The final step in the synthesis of carnitine involves the conversion of butyro-

betaine to carnitine in the liver and kidney.[5] This conversion is catalyzed by the enzyme gamma-butyrobetaine hydroxylase.[7] The activity of this enzyme in the liver of rats is decreased in the hypothyroid state.[1] The decrease in carnitine in hypothyroid individuals observed in the present study may be due in large part to a similar reduction, as we found no evidence for a decrease or increase in the esterified portion of carnitine. The reduction in carnitine levels occurring in hypothyroid patients in our study did not reach statistical significance, but it is possible the trend would have reached significance with a larger number of subjects. The present study is provocative in that it suggests a relationship between thyroid function and the level of carnitine in human skeletal muscle, which may play a role in the development of thyroid myopathy.

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