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REPORT

Carnitine and Thyroid Disease

Why Hyperthyroid Patients Need Carnitine

By Julius G. Goepf, MD



Do you have unexplained weight loss, brittle bones (osteoporosis), difficulty sleeping, and muscle weakness?

If so, you may be suffering from hyperthyroidism, a serious medical condition characterized by an overactive thyroid gland. One of the most feared complications of undiagnosed and untreated hyperthyroidism is the dreaded thyroid storm—a medical emergency characterized by a racing heart beat and sky-high blood pressure.

Recently, a team of scientists discovered that the nutrient L-carnitine can play an important role in treating thyroid disease, including the potentially debilitating muscle weakness associated with hyperthyroidism. Furthermore, preliminary scientific findings suggest that L-carnitine may help protect against the lethal threat of thyroid storm.

Here, we'll explore the remarkable scientific journey that led to L-carnitine's recognition as a key nutrient for those with hyperthyroidism.

THE THYROID GLAND: REGULATING METABOLISM

Like all high-performance machines, the human body requires a sensitive fuel-management system. The thyroid gland serves us well in its role as a combination throttle and thermostat, varying the rate at which we burn our metabolic fuel in accordance with our needs. The thyroid, located in the front of the neck, manages this delicate control function mainly through the production of several iodine-containing thyroid hormones. When thyroid hormones reach their target tissues throughout the body, they stimulate those tissues to increase their metabolic rate. The thyroid itself is controlled, like most of the endocrine glands, by the "master gland" called the pituitary, itself under the control of the deep brain structure called the hypothalamus.

The combination of hypothalamus, pituitary, and thyroid normally functions flawlessly to maintain metabolism at the required levels, but like all complex control systems, it is subject to failure, especially with increasing age.¹ The most common form of thyroid disease is hypothyroidism, which occurs under any of a number of circumstances when there's insufficient thyroid hormone activity.² Symptoms of hypothyroidism include fatigue, muscle weakness, lethargy, weight gain, and a tendency to feel cold even in warm environments.³



Hyperthyroidism, or excessive thyroid activity, also occurs for a variety of reasons,⁴ the most common of which include the autoimmune conditions known as Grave's disease and Hashimoto's thyroiditis.⁵ Patients with hyperthyroid conditions, not surprisingly, experience symptoms that are largely opposite to those of hypothyroidism. These include nervousness, tremors, heart palpitations, weight loss, and sleep disturbances. Both hyper- and hypothyroid patients may also experience muscle weakness.⁶ Extreme hyperthyroidism, or thyrotoxicosis, can culminate in what's referred to as "thyroid storm."⁷ In this accurately named medical emergency, patients suffer from acute hypertension and elevated heart rates, putting them at high risk for stroke, heart attack, and other consequences of the increased metabolic state. Even with the best modern treatment, thyroid storm costs up to 50% of patients their lives.⁸

HYPERTHYROIDISM: THE LONG SEARCH FOR ANSWERS

Traditional treatment of hyperthyroid conditions has relied on so-called thyrotoxic drugs—medications that destroy or impair thyroid gland functioning to rein in the elevated metabolic rate. As their name implies, these drugs can have prominent side effects, and often leave patients in a hypothyroid state following treatment. A better form of therapy is clearly needed, but only

recently have the right clues been assembled to show the way to a surprisingly straightforward solution—one that's related to a common manifestation of thyroid disease.

One of the most prominent features of hyperthyroid states is a weakness of skeletal muscles that can be debilitating to the sufferer.^{7,9} Ironically, scientists have for more than four decades had many pieces of the puzzle regarding what causes this muscle weakness and how to treat it. Like so many other medical mysteries, however, this one had to await the alertness of a dedicated researcher and his team who could put all of the pieces in place.

To understand how Italian endocrinologist Dr. Salvatore Benvenga and colleagues arrived at their exciting insight, let's follow their tracks as they explored scientific findings dating back to the late 1950s to jump-start their own original research.

The first studies published in the modern literature on the effects of carnitine in hyperthyroidism came from post-war Germany in 1959, with the observation that carnitine had an impact on the hyper-functioning thyroid.¹⁰ Three years later the same researchers reported on the use of carnitine in the treatment of hyperthyroidism; they subsequently demonstrated that carnitine affected the accumulation of iodine in thyroid tissue itself.^{11,12} Although another German research group reported on the use of carnitine in treating hyperthyroidism in the late 1960s,¹³ little exploration of the nutrient as a potential therapy occurred for more than 30 years.

Through the 1970s, Japanese researchers found that there was an increase in carnitine excretion in the urine of hyperthyroid patients.¹⁴ Carnitine is an essential nutrient for transporting fuel (mostly fatty acids) into the cellular "furnaces" known as mitochondria.^{15,16} As muscle cells burn fatty acids in a wasteful response to increased thyroid activity, carnitine turnover is dramatically increased,¹⁷ using up cellular stores of carnitine while potentially contributing to the increased urinary losses at the same time.¹⁸

Disturbingly, although increased thyroid activity increases the need for carnitine in cells and increases carnitine loss in urine, some evidence suggests that thyroid hormones could actually suppress natural production of carnitine,¹⁹ further reducing the availability of this vital nutrient just when it's needed the most. If muscle cells lose the carnitine supply that helps them import fatty acids—their best source of fuel—then muscle function could be weakened.²⁰

CARNITINE AND THYROID DISEASE: WHAT YOU NEED TO KNOW

- Hyperthyroidism is characterized by symptoms such as muscle weakness, nervousness, tremors, sleep difficulties, and weight loss. Affected individuals can also experience thyroid storm—a potentially deadly medical emergency that sends heart rate and blood pressure racing.
- Increased thyroid activity may increase cells' need for carnitine, while increasing carnitine loss in the urine. Individuals suffering from hyperthyroidism may therefore require supplemental L-carnitine.
- In clinical studies, L-carnitine supplementation helped prevent or reverse muscle weakness and other symptoms in individuals suffering from hyperthyroidism.
- In a case report, L-carnitine showed promise in helping prevent the possible lethal outcome of thyroid storm.
- L-carnitine may help protect muscle health and strength in a variety of conditions, including hyperthyroidism.



CAN CARNITINE BENEFIT HYPERTHYROID SUFFERERS?

At this point it would seem natural to wonder if supplementing with carnitine would make sense for patients with hyperthyroidism. That question was not taken up seriously until the new millennium, when it began to fascinate a new generation of researchers, led by Dr. Benvenga. In 2004, Dr. Benvenga noted his surprise that promising earlier studies had not been pursued further, since ideal methods of modulating thyroid hormone activity in hyperthyroid conditions had still not yet been developed.²¹ Intrigued by the earlier work and the lack of progress in the interim, Dr. Benvenga and colleagues searched out what was already known about the interactions of carnitine and thyroid hormone, and then designed their own series of investigations.

Studies of carnitine supplementation as treatment for hyperthyroidism were scanty, to say the least. One report in 1981 had

shown that adding carnitine to tissue cultures under hyperthyroid conditions helped cells process free fatty acids into useful energy.²² A further two short studies from the 1960s examined carnitine's interactions with thyroid hormones,^{23,24} but the previous research stopped there. Benvenga's team would have to start virtually from scratch.



The first step would be to gain a better understanding of how carnitine acts in tissue under hyperthyroid conditions. Following up on the studies done in the 1960s,²³ Benvenga and colleagues set up a three-way laboratory study.²⁵ Using cells from two human sources and one mouse cell line, the researchers demonstrated that carnitine influences the interaction between thyroid hormones and cell nuclei. Like most hormones, thyroid hormones work inside the cell nucleus to influence the rate at which vital enzymes and other proteins are produced in the cell. Carnitine supplementation, the researchers believed, might serve to break the cycle of inefficient fuel utilization, which ultimately leads to depletion and muscle weakness. It remained only to test that hypothesis in live patients.

That opportunity soon presented itself to this creative and resourceful group of clinician-researchers. They conducted a randomized, double-blind, placebo-controlled trial of oral carnitine

supplementation in a particularly elegant and efficient fashion.²³ Their subjects were 50 women who would be taking thyroid hormones to treat benign thyroid nodules (thyroid hormone suppresses the pituitary hormone called thyroid-stimulating hormone, or TSH, which causes the nodules to grow). In such patients, mild-to-moderate hyperthyroidism is frequently an undesired side effect, and the researchers chose to study this group of patients in order to capitalize on that effect, while potentially providing welcome relief from symptoms.²⁶

Beginning with their first doses of thyroid hormones, the women were divided into three groups as follows:

- placebo only for six months (Group 0)
- placebo for two months followed by carnitine 2 or 4 g/day for two months followed by a return to placebo (Groups A2 and A4)
- carnitine 2 or 4 g/day for four months followed by placebo (Groups B2 and B4).

By examining the results of supplementation on Group A, the researchers could study the ability of carnitine to treat the effects of hyperthyroidism, since patients wouldn't get the supplement until after two months of symptom-inducing treatment. By studying the impact of supplementation on Group B they could determine how well carnitine worked to prevent symptoms of the excess hormone levels, since the patients would be getting the supplement right from the start of treatment with thyroid hormones.

DRAMATIC RESULTS WITH SUPPLEMENTATION

The results were nothing short of dramatic. As expected, symptoms and blood chemistry results worsened in Group 0, who received thyroid hormone but only placebo in addition. These women displayed the symptoms of mild hyperthyroidism, including muscle weakness, shortness of breath, heart palpitations, nervousness, insomnia, and tremors. They also had increased knee reflexes and heart rates, and substantial loss of body weight. Women in Group A experienced similar worsening of symptoms during the two months that they initially took placebo, but those symptoms disappeared after two months on the carnitine supplementation, only to return during their final two months of placebo. Meanwhile, women in Group B, who took carnitine from the start of their thyroid hormone treatment, had no worsening of their symptoms until they stopped receiving carnitine at the end of the first four months. They then rapidly developed symptoms similar to the other subjects who were not receiving carnitine. There were improvements in certain laboratory parameters as well during the times that the subjects supplemented with carnitine. Of particular interest was the fact that bone mineral density increased in both supplemented groups, with the greatest increase in Group B, who received carnitine supplementation for a full four months.²⁶

Dr. Benvenga and colleagues summarized their findings from these studies in the following fashion: "Since hyperthyroidism impoverishes the tissue deposits of carnitine, there is a rationale for using L-carnitine at least in certain clinical settings... and since carnitine has no toxicity, teratogenicity [birth defects], contraindications, and interactions with drugs, carnitine can be of clinical use."^{21,26} As the researchers point out, many patients on thyroid hormone therapy discontinue their treatment as the result of side effects, so carnitine supplementation may not only offer relief from symptoms, but could help patients adhere to their medication regimens.²¹

But what about patients with more severe forms of thyroid disease? Benvenga's original patients had mild symptoms as a result of their carefully controlled doses of thyroid hormones. Patients with true thyrotoxicosis can have much more troubling, and even life-threatening symptoms. Such people may suffer from autoimmune conditions such as Hashimoto's thyroiditis and Graves'

disease, or other causes of elevated thyroid activity such as post-partum thyroiditis, sub-acute thyroiditis, drug-induced thyroiditis, or a condition known as autonomous nodular goiter. Can carnitine offer some hope in these situations as well?

The answer appears to be a resounding “yes,” based on very recent data. Dr. Benvenga and colleagues didn’t stop evaluating people with thyroid disease after their last large study. They proceeded to treat individual patients with all of the above-noted causes of hyperthyroidism with doses of carnitine ranging from 2 to 4 g/day, in order to reduce the doses and side effects of traditional anti-thyroid drugs.²¹

CARNITINE—CALMING THE STORM

Thyroid storm provides the most powerfully dramatic demonstration of carnitine’s ability to control the symptoms of excess thyroid hormone. During a thyroid storm, patients experience a massive release of thyroid hormones that can overwhelm the body’s metabolic resources. Thyroid storm is lethal in up to 50% of patients,⁸ and typically requires very high doses of traditional anti-thyroid drugs, many of which have their own serious side effects. Thyroid storm is almost always triggered by some other illness or event, such as an infection or a traumatic injury, in patients with underlying hyperthyroidism.^{8,27} Although thyroid storm is rare, some hyperthyroid patients may experience recurring episodes of this terrifying condition.

Dr. Benvenga’s group was the first to report the success of supplemental carnitine in treating recurrent thyroid storms,²⁸ when they used it to treat a young man with Graves’ disease. After suffering a severe thyroid storm, the patient was prescribed a low dose of an anti-thyroid drug along with 2 g/day of L-carnitine. (The patient was unable to take larger doses of the anti-thyroid drug due to his low white blood cell and platelet counts.)

While the patient did suffer from two subsequent episodes of thyroid storm, he again managed to survive these potentially fatal events. Remarkably, even though his measured blood levels of thyroid hormones were comparable to those of his severe first storm, his actual symptoms were considerably milder during the attacks he suffered while taking supplemental carnitine. Dr. Benvenga points out that because carnitine works in target tissues such as muscle, and not in the thyroid itself, it is not at all surprising that this patient suffered subsequent storms while taking carnitine (which would have no effects on the thyroid gland’s production of thyroid hormone).

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CARNITINE—THE LATEST FINDINGS

As noted, virtually all of the modern work on carnitine in hyperthyroidism has come from the Italian research group led by Dr. Benvenga. Though their work is dramatic and compelling, scientists often have legitimate concerns about findings that haven't been replicated or supported by additional researchers. In just the past two years, several new studies have come from completely different laboratories, each examining separate issues that together provide strong assurance of carnitine's value for individuals who suffer from thyroid disease.



Specifically interested in the muscle weakness that accompanies both hyper- and hypothyroid conditions, Dr. Christopher Sinclair and colleagues at Brown Medical School in Rhode Island performed their own set of studies, which were published in 2005.⁶ The researchers obtained skeletal muscle samples from both hyper- and hypothyroid patients, as well as from a group of normal controls. Samples from patients with thyroid disease were also repeated after a course of appropriate traditional treatment. When they measured muscle carnitine content in the samples, the researchers found a significant reduction in hyperthyroid patients, with a return to normal levels as the condition improved under treatment. They found smaller, less significant decreases in muscle carnitine content in the hypothyroid group as well, which also improved with treatment. Dr. Sinclair and his colleagues, like their Italian counterparts, recognized that

the decreased availability of carnitine in muscles means that "there will be less energy (in the form of long-chain fatty acids) transported into the mitochondria" and further point out that "this might lead to diminished fatty acid oxidation in skeletal muscle and, consequently, lead to weakness."

A completely separate line of evidence about the importance of carnitine in protecting muscle integrity comes from the world of cancer treatment. In a 2005 study of a new chemotherapy drug called aplidine, French scientists included carnitine supplements to assure the safety of the new drug.²⁹ Aplidine is a chemical derived from marine creatures called tunicates, or sea-squirts. It has potent anticancer effects but its dose is limited by myotoxicity, or muscle damage and weakness. When 3 of their 14 patients experienced toxicity from aplidine that limited their ability to increase the dose, the researchers simply provided oral carnitine. Carnitine was able to reverse the muscle toxicity, and patients who continued on the supplement were able to increase their chemotherapy doses by 40%. The researchers intend to conduct further studies of carnitine as a muscle protectant in future research.

USING CARNITINE

There is no doubt that carnitine, a humble molecule used in the basic economics of cellular energy, holds the key to preventing and even reversing muscle damage and weakness from a variety of causes, including hyperthyroidism. Clinical trials investigating L-carnitine in thyroid conditions have utilized doses ranging from 2,000 to 4,000 mg daily. While these studies have focused on L-carnitine, advanced carnitine formulations such as acetyl-L-carnitine, acetyl-L-carnitine arginate, and propionyl-L-carnitine may also offer promise for individuals who suffer from thyroid conditions. More research is needed to determine which carnitine formulations are most beneficial for modulating the adverse effects of hyperthyroidism.

Carnitine is safe and has no known side effects, and is in widespread use for a number of indications, including the muscle fatigue that can result from strenuous exercise. The story of carnitine's rise from obscurity is truly one of modern medical science's most dramatic and compelling tales of success.



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COMPARING CARNITINE FORMULATIONS

To date, clinical trials have shown that doses of 2,000-4,000 mg/day of L-carnitine are helpful in individuals who suffer from

hyperthyroidism. Future studies may uncover similar benefits of other carnitine formulations such as acetyl-L-carnitine, acetyl-L-carnitine arginate, and propionyl-L-carnitine, along with the doses needed to match the efficacy provided by 2,000-4,000 mg L-carnitine.

Until scientists reveal the most effective dosages of each carnitine formulation, the following chart may provide preliminary guidance for individuals seeking relief from the effects of hyperthyroidism:

L-carnitine:2,000-4,000 mg/day

Acetyl-L-carnitine: 800-2,000 mg/day

Acetyl-L-carnitine arginate: 600-1,000 mg/day

Propionyl-L-carnitine: 600-2,000 mg/day

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