Graves' disease: Why less antithyroid drug may be more

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> Graves' disease management often involves prolonged antithyroid drug (ATD) therapy, but the optimal duration remains elusive. Patients frequently endure persistent symptoms and face an unpredictable treatment course, often leading to long-term or definitive interventions. A recent multicenter randomized trial explored whether adjunctive L-carnitine and selenium could shorten this therapeutic journey and improve outcomes.1

KEY TAKEAWAYS

- The Pivot: Adjunctive L-carnitine and selenium significantly reduced the duration of antithyroid drug therapy and accelerated TRAb negativity in Graves' disease.
- The Data: The intervention group achieved TRAb negativity significantly earlier (HR = 2.35; 95% CI, 1.14-4.81; p = 0.016) and had a significantly higher rate of spontaneous remission (OR = 11.22; 95% CI, 3.35-46.11; p < 0.001).
- The Action: Clinicians might consider L-carnitine and selenium as an adjunct to methimazole for newly diagnosed Graves' disease, particularly in patients seeking to minimize ATD exposure.

Managing Graves' disease (GD) presents a persistent challenge for endocrinologists and general practitioners alike. The standard approach with antithyroid drugs (ATDs) like methimazole (MMI) aims to restore euthyroidism, but the journey is often protracted, with many patients experiencing a prolonged course of treatment and an uncertain prognosis. The duration of ATD therapy is not standardized, leading to variability in clinical practice and patient experience. Patients frequently report lingering symptoms that do not always correlate with their thyroid hormone levels, contributing to a diminished quality of life. This clinical reality highlights the need for strategies that can shorten disease duration, reduce drug exposure, and improve the likelihood of remission.1

A multicenter prospective randomized trial, published in Nutrients, investigated the impact of adding a combined L-carnitine (LCT) and selenium (Se) supplement to standard MMI therapy. The trial enrolled 60 consecutive patients with newly diagnosed overt GD. Participants were randomized into two groups: a Control Group receiving MMI alone, and an Intervention Group receiving MMI plus the combined LCT/Se supplement. The study followed patients for up to 24 months, or until spontaneous remission or the need for definitive therapy. Researchers assessed TSH, fT3, fT4, and TSH-receptor antibodies (TRAb) levels every two months. Patients also completed a symptom questionnaire at each visit, addressing the frequency and severity of typical thyrotoxic symptoms.1

The Biochemical Markers and Remission Rates

The primary objective of the trial was to determine if LCT and Se supplementation could influence the biochemical profile and quality of life in patients with overt GD. The investigators tracked several key thyroid markers. They found no significant differences between the two groups in the trend or time-to-normalization of TSH, fT3, and fT4 levels. This indicates that the supplement did not accelerate the initial biochemical control of thyroid hormones, which is primarily driven by MMI. But the Intervention Group reached TRAb negativity significantly earlier, with a hazard ratio of 2.35 (95% CI, 1.14-4.81; p = 0.016). This suggests a synergistic interaction with MMI therapy, accelerating the resolution of the autoimmune component of Graves' disease.1

Beyond TRAb negativity, the trial demonstrated a clear benefit in terms of MMI requirements. Patients in the Intervention Group consistently required lower average MMI dosages (p = 0.013) and accumulated a lower cumulative dose over the study period (p = 0.020). This reduction in ATD exposure is a clinically meaningful outcome, potentially mitigating the risk of MMI-related adverse effects and improving patient adherence. The most striking finding, but, was the significantly higher rate of spontaneous remission in the Intervention Group, with an odds ratio of 11.22 (95% CI, 3.35-46.11; p < 0.001). This suggests that the combined supplementation may fundamentally alter the disease course, leading to a more durable resolution.1

The mechanism behind these effects likely involves the distinct roles of L-carnitine and selenium. L-carnitine is known for its nuclear antagonistic properties on thyroid hormone action, potentially reducing the peripheral effects of excess thyroid hormones. Selenium, on the other hand, plays an important immunomodulatory role, particularly in thyroid autoimmunity. It is a component of selenoproteins, which are involved in antioxidant defense and thyroid hormone metabolism. The combination appears to address both the hormonal and immunological aspects of GD, offering a more comprehensive approach than MMI alone. This dual action may explain why the supplement did not hasten initial hormone normalization but significantly impacted TRAb levels and remission rates, which are more closely tied to the underlying autoimmune process.1

Symptom Burden and Quality of Life

While the biochemical markers and remission rates showed clear advantages, the impact on overall symptom burden was less pronounced. The study found no significant difference in the overall symptom burden between the two groups. But the supplement did exert an independent effect in reducing the severity of specific thyrotoxic symptoms. Patients receiving LCT and Se reported reduced severity of tremor, irritability, mood lability, heat intolerance, and exertional dyspnea. These are common and debilitating symptoms of hyperthyroidism that significantly impair a patient's quality of life. Even if the overall symptom score did not differ, the alleviation of these specific symptoms could translate into a tangible improvement in daily functioning for patients. This effect on symptoms highlights the complexity of patient-reported outcomes, where a global score may mask improvements in individual, highly bothersome symptoms.1

The trial's findings align with a growing understanding of the importance of micronutrients in autoimmune thyroid disease. Selenium supplementation, for instance, has been explored in other thyroid conditions, including Hashimoto's thyroiditis, where it has shown some benefit in reducing thyroid antibody levels. The role of L-carnitine in mitigating thyrotoxic symptoms has also been investigated, particularly in patients with subclinical hyperthyroidism or those awaiting definitive therapy. This study provides further evidence for the utility of these supplements in a specific clinical context. For a deeper dive into how biochemical responses at specific time points can predict long-term outcomes in

endocrine diseases, clinicians might review our previous coverage on why 12-month biochemical response is the critical pivot in endocrine disease.1

Caveats and Clinical Considerations

The trial, while showing a significantly higher rate of spontaneous remission in the Intervention Group, has several limitations that warrant consideration. The sample size was relatively small, enrolling only 60 patients. This limits the generalizability of the findings and the ability to detect smaller, but still clinically relevant, differences in outcomes or to perform robust subgroup analyses. A larger, multicenter trial would be necessary to confirm these results and explore potential variations in response across different patient demographics or disease severities. The study duration of up to 24 months is reasonable for assessing remission, but longer-term follow-up would provide valuable data on the durability of remission and the incidence of relapse after cessation of therapy.1

The open-label design is another obvious caveat. While objective biochemical markers like TRAb levels are less susceptible to placebo effects, patient-reported symptoms can be influenced by the knowledge of receiving an active supplement. The investigators attempted to mitigate this by using a standardized symptom questionnaire, but a double-blind design would have strengthened the evidence regarding symptom improvement. The specific formulation and dosage of L-carnitine and selenium used in this study are also important. The trial used a combined supplement, making it difficult to ascertain the individual contribution of each component. Future research could explore whether one nutrient is more important than the other, or if the synergistic effect truly requires both.1

The study population consisted of patients with newly diagnosed overt GD. Whether these benefits extend to patients with long-standing disease, those who have relapsed after previous ATD therapy, or those with subclinical hyperthyroidism remains unclear. The trial also did not explicitly detail the incidence of adverse events associated with the supplementation, beyond the general statement that MMI requirements were lower. While L-carnitine and selenium are generally considered safe, a comprehensive safety profile in this specific patient population would be beneficial. Clinicians considering this adjunctive therapy should also consult a comprehensive reference like the Oxford Handbook of Endocrinology and Diabetes for broader guidance on thyroid disease management.1

The findings do raise an important question about the role of nutritional support in autoimmune conditions. While not a replacement for conventional pharmacotherapy, targeted supplementation may offer a way to modulate the immune response and improve therapeutic outcomes. This approach could be particularly appealing to patients who are wary of long-term drug exposure or those who experience persistent symptoms despite biochemical euthyroidism. The reduction in cumulative MMI dose is a significant advantage, potentially reducing the risk of rare but serious adverse effects such as agranulocytosis or hepatotoxicity.1

The trial did not explore the cost-effectiveness of adding these supplements, which is a practical consideration for healthcare systems and patients. The availability and cost of high-quality L-carnitine and selenium supplements can vary, and this would need to be factored into clinical decision-making. Still, the potential for earlier TRAb negativity and higher remission rates could lead to overall cost savings by reducing the duration of MMI therapy and the need for more invasive definitive treatments like radioiodine ablation or surgery. The study provides a compelling argument for further investigation into the role of adjunctive therapies in Graves' disease, moving beyond a sole focus on pharmacological agents.1

CLINICAL IMPLICATIONS

This trial offers a compelling argument for reassessing the standard of care in newly diagnosed Graves' disease. The notion that a simple, well-tolerated supplement could significantly shorten the duration of antithyroid drug therapy and increase remission rates is not trivial. Clinicians should consider these data, particularly for patients who express concerns about long-term methimazole exposure or who are struggling with persistent, specific thyrotoxic symptoms.

The reduction in cumulative MMI dose is a tangible benefit, potentially lowering the risk of adverse drug reactions. While the overall symptom burden did not change, the targeted improvement in tremor, irritability, and heat intolerance addresses common patient complaints that often persist even with normal thyroid hormone levels. This suggests a more holistic approach to patient well-being, beyond just biochemical normalization.

But the small sample size and open-label design mean these results, while showing a significantly higher rate of spontaneous remission in the Intervention Group, require replication in larger, double-blinded trials. It is not yet time to rewrite guidelines, but it is certainly time to initiate a conversation with patients about these adjunctive options. The field has long sought ways to improve remission rates and reduce treatment burden; this study points towards a viable, non-pharmacological avenue.

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REFERENCES

1. 1. Rossi M, Meomartino L, Zavattaro M. Adding L-Carnitine and Selenium to Methimazole in Graves' Disease: A Prospective Randomized Trial on Thyroid Markers and Quality of Life. Nutrients. 2025;17(1):17. doi:10.3390/nu17010017

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