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EFFECTS OF TREATMENT WITH L-THYROXINE ON CHRONIC URTICARIA IN SUBJECTS WITH AUTOIMMUNE THYROIDITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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1. BACKGROUND & PATHOPHYSIOLOGY

Chronic Urticaria (CU) is characterized by continuous or recurrent wheals and/or angioedema lasting for ≥6 weeks. Approximately 10–28% of CU patients present coexisting Autoimmune Thyroiditis (AT), exhibiting a significantly higher disease burden and treatment resistance.

RATIONALE FOR LT4 THERAPY:

- Autoantibody Activation: Anti-TPO autoantibodies (IgE/IgG) directly cross-link FcεRI receptors on mast cells and basophils, triggering degranulation.
- TSH Signalling: Elevated TSH acts as a pro-inflammatory mediator, increasing serum TNF-α, IL-1β, and IL-6.
- Levothyroxine Target: Exogenous LT4 suppresses TSH secretion and thyroid antibody titers, aiming to induce clinical remission of urticarial skin lesions.

2. SISTEMATIC REVIEW METHODOLOGY

Search Protocol: Comprehensive search across PubMed, Scopus, and Web of Science up to October 2025 (PROSPERO Registration: CRD420251133491).

Study Selection Criteria: 102 total records screened → 19 full-text articles assessed → 9 qualitative and 5 quantitative meta-analysis studies included.

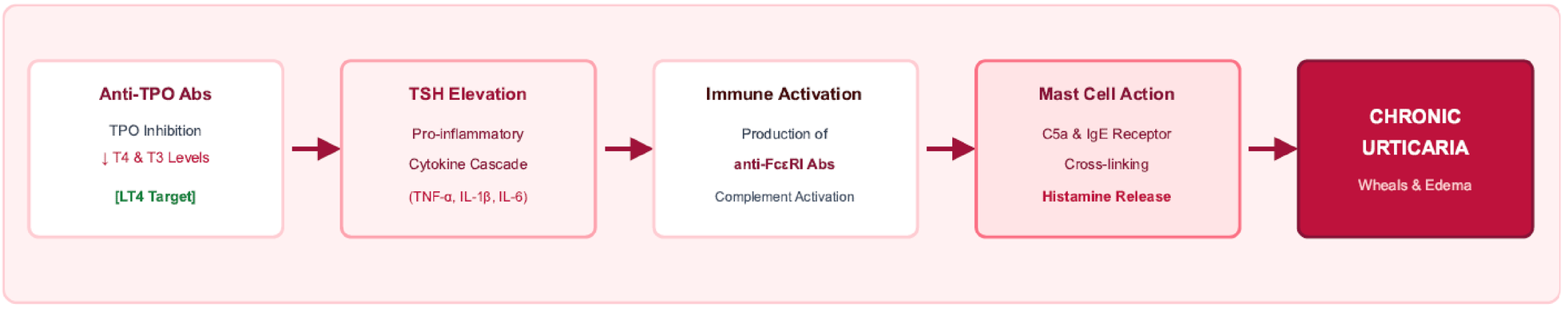
Statistical Framework: Executed using RevMan 5.4.1 employing Standardized Mean Difference (sMD) and Odds Ratios (OR) with a Random-Effects model.

3.QUANTITATIVE ANALYSIS

Primary Meta-Analysis Takeaway: While uncontrolled before-after analysis demonstrates a statistically significant reduction in urticaria symptoms following LT4 administration, LT4 fails to demonstrate superiority when directly compared against placebo or standard care alone.

Comparison / Subgroup Analysis	No. Studies (n)	Effect Size (95% CI)	p-value	Heterogeneity (I^2)
Before vs. After LT4 Treatment	5 studies (n=129)	sMD -2.31 [-2.98, -1.64]	**< 0.00001**	75% (p=0.001)
• Euthyroid Patients (Suppression/Substitution)	1 study (n=8)	sMD -2.48 [-3.88, -1.09]	0.0005	N/A
• Hypothyroid Patients (Replacement)	1 study (n=44)	sMD -1.64 [-2.13, -1.16]	< 0.00001	0%
• Suppressive Target (TSH < 0.3-0.5 mIU/L)	3 studies (n=55)	sMD -2.89 [-4.24, -1.53]	< 0.0001	81%
• Substitutive Target (Normative TSH)	2 studies (n=74)	sMD -1.84 [-2.23, -1.45]	< 0.00001	0%
LT4 vs. Placebo / Standard Care (Activity Score)	3 studies (n=207)	sMD -0.21 [-0.67, 0.25]	**0.37 (NS)**	57%

4. PROPOSED PATHOGENETIC NETWORK: AT and CU LINK



5. DISCUSSION

- **Euthyroid vs. Hypothyroid:** Subgroup difference was not statistically significant (p = 0.27), suggesting LT4 benefits are not strictly dependent on overt thyroid state.
- **Suppression vs. Substitution:** TSH suppression showed a trend toward greater score improvement (sMD -2.89 vs -1.84), but subgroup comparison failed to reach significance (p = 0.14).
- **Risks of Suppressive Therapy:** Iatrogenic subclinical hyperthyroidism carries documented risks of osteoporosis, atrial fibrillation, and ischemic events, offsetting uncertain skin benefits.
- **Key Limitations:** high risk of bias (moderate-to-poor quality studies), heterogeneous tools (lack of standardised scales), publication gap (no eligible studies between 2018 and 2025)

6. CONCLUSIONS

1. **Insufficient Evidence for Routine Use:** LT4 cannot currently be recommended as a routine targeted therapy for Chronic Urticaria in patients with Autoimmune Thyroiditis unless indicated for underlying hypothyroidism.
2. **Lack of Superiority:** Apparent clinical improvements in uncontrolled series are likely driven by the natural history of CU, concurrent antihistamine therapy, or placebo effect.
3. **Future Research:** Methodologically robust, well-powered RCTs using standardized UAS7 scores and post-treatment antibody titrations are strictly needed to clarify molecular links