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LETTER

Redefining Thyroid Hormone Sensitivity in Diabetic Kidney Disease: A Paradigm Shift in Pathophysiological Understanding [Letter]

Yanni Gao[1], Zhenliang Fan[2]

[1]The First School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310053, People's Republic of China; [2]The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, Zhejiang, 310006, People's Republic of China

Correspondence: Zhenliang Fan, Email fanmlov@sina.cn

Dear editor

The study by Ma et al[1] illuminates a critical gap in our understanding of diabetic kidney disease (DKD) pathogenesis: the role of thyroid hormone (TH) sensitivity in euthyroid patients with type 2 diabetes mellitus (T2DM). While traditional paradigms focus on glycemic control and hemodynamic factors, the authors demonstrate that subtle dysregulation of TH signaling—reflected by indices such as PTFQI, TFQI, and FT3/FT4—may serve as a novel biomarker for renal injury. The study's most provocative insight lies in its redefinition of euthyroidism. Elevated PTFQI and TFQI, alongside reduced FT3/FT4 ratios, reveal a latent state of tissue-specific TH resistance that conventional TSH/FT4 thresholds fail to capture. In 2024, a cross - sectional data from 20,084 cases[2] has shown that high PTFQI is strongly associated with metabolic abnormality traits such as insulin resistance and chronic inflammation, offering a systems biology explanation for the development of DKD. Such findings necessitate a paradigm shift: euthyroidism in T2DM should be reclassified as a spectrum of functional TH sensitivity rather than a static hormonal range, with profound implications for risk stratification.

Clinical Paradoxes: Bidirectional Relationships in Renal Outcomes

Intriguingly, the study hints at bidirectional effects of TH sensitivity on renal health. While impaired central sensitivity (high PTFQI/TFQI) linearly correlates with albuminuria and reduced eGFR, peripheral indices (low FT3/FT4) exhibit a J-shaped association, initially protective in early DKD but deleterious in advanced stages. This duality suggests context-dependent roles for THs: compensatory upregulation of renal deiodinases may mitigate early injury, whereas chronic TH resistance may accelerate fibrosis via mitochondrial dysfunction and podocyte apoptosis.[3] Such findings resolve longstanding clinical ambiguities, explaining why some euthyroid patients exhibit rapid DKD progression despite standard glycemic control.

Mechanistic Complexity: Crosstalk with Non-Classical Pathways

The authors' observations transcend traditional TH-kidney interactions. Impaired TH sensitivity likely intersects with insulin resistance, RAAS hyperactivity, and inflammasome activation, creating a self-perpetuating cycle of renal injury.[4] For instance, TH resistance may amplify renal lipotoxicity by impairing fatty acid oxidation, while hyperinsulinemia downregulates hepatic thyroid-binding globulin, further distorting TH bioavailability. This interconnectedness positions TH sensitivity as both a biomarker and mediator of systemic metabolic chaos, urging clinicians to view DKD not as an isolated nephropathy but as a manifestation of multisystem hormonal disarray.

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Therapeutic Implications: Targeting Thyroid Sensitivity in Precision Nephrology

The study's findings demand a reevaluation of therapeutic strategies. While TH replacement in euthyroid patients carries risks, modulating downstream effectors—such as deiodinase activators or thyroid receptor co-regulators—could restore tissue-specific TH action without systemic hormonal disruption. Additionally, integrating TH sensitivity indices into existing DKD risk models may identify subpopulations benefiting from early, tailored interventions. Future trials should prioritize interventions that concurrently address TH resistance and renal pathways, such as SGLT2 inhibitors, which paradoxically improve both glycemic control and mitochondrial function.[5]

Ma et al's work compels the scientific community to abandon rigid definitions of thyroid health in diabetes. By reframing TH sensitivity as a dynamic, tissue-specific phenomenon, we unlock opportunities for early detection and mechanistic intervention in DKD.

Disclosure

The authors declare no conflicts of interest in this communication.

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