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OPEN PEER REVIEW

Lazy Adrenals in Severe Hypothyroidism - Myth or Mirage?

Swaraj Waddankeri, Meenakshi Swaraj Waddankeri

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

More about open peer review: brieflands.com/knowledgebase/opr

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1 Original submission

0 comments

No public comments in this round.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewer 1:
1. Regarding the use of morning cortisol levels, why was a cutoff point of 3.3 mg/dL not selected for diagnosing adrenal deficiency?

2. In the absence of a cosyntropin stimulation test, the diagnosis of adrenal insufficiency remains questionable.

3.What is the clinical significance of cortisol levels ranging from 4-9 mg/dL compared to those exceeding 9 mg/dL up to 18 mg/dL?

4. What were the follow-up results for the patients? Were those with cortisol levels below 4 mg/dL treated with cortisol?

5. Can the tables be consolidated into fewer, more comprehensive tables?

Reply:

1. *While 3.3 µg/dL is suggested in literature such as PLoS One for high specificity, our study used a pragmatic cut-off of 4 µg/dL based on clinical consensus and common endocrinological guidelines to avoid missing early adrenal insufficiency. We have added this rationale to the Methods section. Reference: Martin-Grace J, Dineen R, Sherlock M, Thompson CJ. Adrenal insufficiency: Physiology, clinical presentation and diagnostic challenges. Clin Chim Acta. 2020 Jun; 505:78-91. Harbeck B, Lehnert H. [Diagnosis and Management of Adrenal Insufficiency]. Dtsch Med Wochenschr. 2018 Aug;143(17):1242-1249.*

2. *Due to logistical constraints, cosyntropin testing was not performed.*

3. *We have added a new paragraph in the Discussion to elaborate on the possible clinical implications of intermediate cortisol values (4–9 µg/dL), indicating a possible adrenal reserve compromise that requires monitoring.*

4. *Only 3 subjects suspected of Adrenal insufficiency were treated with injection hydrocortisone for 3 months.*

5. *As advised, we have consolidated Tables 1 and 3, and removed redundant tables.*

Associate Editor 1:
1. Introduction, Lines 36-39: Please refer to articles published regarding low cortisol in severe hypothyroidism in the literature, define study gap that encouraged you to perform this clinical study.

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2. Lines 51-55: Add number of patients visited in 3 years; include No. of patients with hypothyroidism and No of those with severe hypothyroidism.

Reply: We have included only patients with severe hypothyroidism. 71 treatment-naïve adults with TSH >100 mIU/mL and 40 age- and sex-matched euthyroid controls.

3. Line 62: Please explain which clinical symptoms and signs you evaluated for AI.

Reply: Symptoms such as fatigue, hypotension, and salt craving were considered

4. Line 74: Add name of kit, company and country for measurement of cortisol and its CV.

Reply: Cortisol measured using AIA360® Tosoh Bioscience kit (Japan); CV <2%. AI defined as cortisol <4 µg/dL.

5. Line 73: Explain why you used cut off of 4 µg/dL for the low serum cortisol?

Reply: This has been added as per earlier reviewer response. Martin-Grace J, Dineen R, Sherlock M, Thompson CJ. Adrenal insufficiency: Physiology, clinical presentation and diagnostic challenges. Clin Chim Acta. 2020 Jun; 505:78-91.

6. Line 75: Please create a title of "Definitions" and describe sever hypothyroidism, definition of AI etc....

Reply: Definitions

Severe Hypothyroidism:
Defined as a state with a thyroid-stimulating hormone (TSH) level >100 mIU/mL in a treatment-naïve individual, often associated with marked symptoms and biochemical evidence of thyroid hormone deficiency (low T3 and T4 levels).

Adrenal Insufficiency (AI):
Defined in this study as a morning (8:00 AM) serum cortisol level <4 µg/dL, based on accepted endocrine guidelines and clinical practice standards.

Euthyroid Controls:
Age- and sex-matched individuals without known thyroid disease or systemic illness and with normal TSH, T3, and T4 levels.

7. Lines 75-82: Did you check the normality of variables. Which test you used for correlation coefficients and why this test was chosen?

Reply: Yes, we checked the normality of the continuous variables using the Shapiro-Wilk test. Based on the results, we used Pearson's correlation for normally distributed variables and Spearman's rank correlation for non-normally distributed data.

8. Lines 98 and 99: Delete non-significant p values?

Reply: Okay, deleted

9. Line 106: Omit this sentence.

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10. Table 3 should be combined with table 1. Use two columns in table 1 for findings of case and control groups and compare all variables.

Reply: Combined to Table 1

11. Have a separate table for characteristics that you only have them in case group.

Reply: Okay

12. Line 100: Mean±SD of 100±00 is not acceptable. This is because all of your patients had TSH> 100 mIU/mL. However you cannot use SD for these values.

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13. Table 4: omit Pearson correlation values and add those to the text; DC T3 group and T4 group titles; you should compare T3 and T4 results in 3 categories of serum cortisol using non-parametric statistical tests. This is very important and should be added.

Reply: Have made the changes accordingly

14. Delete table 4 and fig 2 (scatter plots) and include results in the text.

Reply: Done.

15. Line 118: Discussion should be started with overall findings of this study and their importance.

Reply: Yes it was done same, Minor corrections were made.

16. Line 181: Please add recommendations regarding approach to patients with severe hypothyroidism regarding when to start combination of LT4 and corticosteroid therapies and methods of follow up.

Reply: This is because thyroid hormone therapy can accelerate cortisol metabolism and precipitate adrenal crisis in patients with unrecognized adrenal insufficiency. Therefore, ***it is recommended to empirically initiate corticosteroid therapy (e.g., hydrocortisone 50–100 mg IV every 8 hours) prior to or concurrently with levothyroxine (LT4) in critically ill or high-risk patients****, pending confirmatory tests such as morning serum cortisol or ACTH stimulation testing[^1,^2].*

Levothyroxine is typically started intravenously in myxedema coma, but in stable patients, an oral loading dose of 200–400 µg may be followed by 1.6 µg/kg/day as a maintenance dose. ***Corticosteroids may be tapered and stopped once adrenal insufficiency is biochemically ruled out*** *(e.g., normal basal cortisol >15 µg/dL or normal response to ACTH stimulation).*

Follow-up should involve regular clinical monitoring and laboratory evaluation of TSH and free T4 levels every 4–6 weeks until euthyroidism is achieved.

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17. Lines 187-191: Two major limitations of this study are lack of definite diagnosis of AI with synacthen test and lack of informations regarding treatment and follow up; these items should be emphasized and discussed more appropriately.

Reply: It has been discussed n discussion section. the absence of a definitive diagnosis of adrenal insufficiency (AI) using the ACTH (Synacthen) stimulation test is a key limitation of this study. However, in many real-world and resource-constrained clinical settings, including ours, access to dynamic endocrine testing remains limited. In such contexts, basal morning serum cortisol levels continue to be a widely accepted screening tool for adrenal dysfunction, especially when used with clinically defined thresholds (<4 µg/dL for high likelihood of AI and >15 µg/dL to exclude AI).

Additionally, the lack of detailed documentation regarding treatment protocols and long-term follow-up is noted. The retrospective and observational nature of our study restricted our ability to uniformly capture data on levothyroxine initiation timing, corticosteroid use, and subsequent symptom evolution. Nevertheless, the objective of our study was not to assess therapeutic outcomes but rather to explore the hormonal correlations at presentation.

Ethical Statements:

Clinical Trial Registration Code:

Ethical Approval: This code is approved under the ethical approval code of EC/NEW/INST/2022/KA/0194

Informed Consent: The study was approved by the institutional ethics committee on February 13, 2021. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The procedures in the study follow the guidelines laid down in the Declaration of Helsinki.

Data Availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

List of Uploaded Files:

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2 Revision 1

1 comment · 4 May 2025

Editor-in-Chief

MINOR REVISION 4 May 2025

Comments:
In response to each question from the reviewers, the authors should specify the lines of the revised manuscript in which their response to the question has been included.
Please add all references in the reply text to the list of references and show their numbers in the manuscript.
For important negative replies, such as the lack of a cosyntropin stimulation test, the authors should give their explanation as a “limitation” at the end of the “Discussion”.
Please return your revised manuscript at your earliest convenience.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

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3 Revision 2

1 comment · 11 May 2025

Editor-in-Chief

ACCEPT 11 May 2025

The revised version is acceptable for publication in the IJEM.