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Published in:

European Journal of Endocrinology

Publication status and date:

Published: 01/09/2021

DOI (link to publisher):

[10.1530/EJE-21-0677](https://doi.org/10.1530/EJE-21-0677)

Citation for the published version (APA):

Peeters, R. P., & Brito, J. P. (2021). Response to the letter of Hoermann and colleagues. *European Journal of Endocrinology*, 185(3), L7-L8. <https://doi.org/10.1530/EJE-21-0677>

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1 **Response to the letter of Hoermann and colleagues**

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12 Total word count: 454

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21 We read the letter by Hoermann and colleagues with great interest and are thankful for the
22 opportunity to discuss some of their remarks (1).

23 The authors raise the issue that part of the controversy regarding the treatment of
24 subclinical hypothyroidism (SCH) is related to how we define SCH and whether it is a true
25 disease or merely a laboratory constellation.

26 Although we wrote a debate on whether SCH should be treated or not, we generally agree
27 that the biochemical diagnosis of SCH covers a wide spectrum of patients. We, therefore,
28 agree that SCH can be a true disease in one patient, but a laboratory constellation in
29 another. Based on the progression rate to overt hypothyroidism, the extent of TSH elevation
30 is a good discriminator between the two (2, 3). Consequently, we have a consensus on the
31 treatment of SCH in the vast majority of cases. For example, in case of a very mildly elevated
32 TSH, and FT4 above the median and negative TPO-antibodies (case A), we both agreed not to
33 start with levothyroxine (LT4) therapy, whereas in the case of a clearly elevated TSH, positive
34 TPO-antibodies and a low-normal FT4 (case B) we both agreed to start with LT4 therapy (4).

35 However, as always in medicine, there is a grey zone, such as when SCH is diagnosed based
36 on a TSH between 7 and 10mIU/L and nonspecific symptoms. Unfortunately, adequately
37 powered clinical trials with patients in this grey zone are lacking. For these patients, we fully
38 agree with Hoermann and colleagues that the measurement of only a TSH cannot reliably
39 discriminate between true disease or laboratory variation. This uncertainty about SCH
40 diagnosis and its association with patient symptomatology has confused patients and
41 clinicians in how to best address it. Hoermann and colleagues proposed a strategy that relies
42 more on clinical manifestations (e.g., symptoms of hypothyroidism) and less on TSH values.

43 The fact the hypothyroidism symptoms are nonspecific (5) suggests that this approach will
44 not be able to provide a clear-cut answer either. Alternatively, we see this grey zone as an
45 opportunity to bring the uncertainty about SCH diagnosis and treatment in the conversation
46 with the patient to find the best strategy that responds to the situation. Sometimes this
47 clinician's response demands focusing on addressing symptoms (e.g., investigate other
48 etiologies of fatigue) as opposed to lowering TSH values. Other times, the clinician's
49 response is a therapeutic trial with the LT4 to normalize TSH and patient re-assessment for
50 symptom change or resolution. Future research will provide more clarity about the diagnosis
51 of SCH and the effectiveness of treatment. In the meantime, we should welcome the

52 uncertainty of SCH diagnosis and treatment as an opportunity to work together with our
53 patients and uncover what is best for them.

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56 **Declaration of interest:**

57 Dr Peeters has received lecture fees from IBSA and Merck. Dr Brito reports no conflicts of
58 interest.

59

60 **Funding**

61 This research did not receive any specific grant from any funding agency in the public,
62 commercial or not-for-profit sector.

63

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