Central hypothyroidism: are patients undertreated?

Joke Marlier, Guy T’Sjoen, Jean Kaufman and Bruno Lapauw

Department of Endocrinology, Ghent University Hospital, Ghent, Belgium
Department of Internal Medicine & Pediatrics, Ghent University, Ghent, Belgium

Correspondence should be addressed to J Marlier Email joke.marlier@uzgent.be

Abstract

Introduction: Thyroid hormone replacement in central hypothyroidism (CHT) is more difficult than in primary hypothyroidism (PHT), putting patients at risk for inappropriate substitution. In this study, we compared the dosage of thyroid hormone replacement in patients with CHT with that of patients with PHT. In addition, we explored and compared quality of life (QoL) between both groups, based on two questionnaires, the SF-36 health score and the thyroid-specific ThyPRO score.

Methods: This is a monocentric, cross-sectional study, performed at the Ghent University Hospital (Belgium). We included 82 patients in total, 41 patients with CHT and 41 patients with PHT. At the time of inclusion, all patients had to have a stable dose of levothyroxine over the past 6 months and patients with PHT needed to be euthyroid (defined as having a thyroid-stimulating hormone level within the reference range, 0.2–4.5 mU/L). All data were retrieved from medical files, and questionnaires on QoL were self-administered.

Results: The CHT and PHT groups were comparable regarding age and BMI. There was no significant difference between both groups regarding total daily dose of levothyroxine (100 (93.75–125.00) vs 107.14 (75.00–133.93) μg in CHT and PHT, respectively; P = 0.87) or daily dose of levothyroxine per kg body weight (1.34 (1.16–1.55) vs 1.55 (1.16–1.82) μg/kg, respectively; P = 0.13). Serum levels of fT4 (P = 0.20) and fT3 (P = 0.10) also did not differ between the two groups and both were in the normal (mid)range for the two groups. Regarding QoL, patients with CHT scored worse in terms of depressive and emotional symptoms, impaired daily and social life.

Conclusion: We could demonstrate a difference in QoL between patients with CHT and PHT. Although patients with CHT had a somewhat lower levothyroxine substitution dose than patients with PHT, this difference was also not significant and probably does not explain the difference in QoL.

Introduction

Hypothyroidism indicates the pathological condition of thyroid hormone (TH) deficiency and when untreated, it can lead to severe health effects. Hypothyroidism can be categorised as primary (PHT) or central hypothyroidism (CHT). CHT is a rare condition, accounting for about 1 in 1000 hypothyroid patients, and is typically observed in patients with hypothalamic (tertiary hypothyroidism) or pituitary (secondary hypothyroidism) pathology (1, 2). It can be isolated, which is extremely rare, or combined with other pituitary hormone deficiencies (3) and the majority

1Department of Endocrinology, Ghent University Hospital, Ghent, Belgium
2Department of Internal Medicine & Pediatrics, Ghent University, Ghent, Belgium

Key Words
- hypothyroidism
- pituitary
- hypopituitarism
- hormonal substitution
- thyroid

https://doi.org/10.1530/ETJ-21-0128

Published by Bioscientifica Ltd.

© 2022 The authors

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.
Exclusion criteria included malabsorptive disease, status post coronary artery bypass grafting, patients with chronic kidney disease (CKD 4 and further), concomitant use of amiodarone and high dose glucocorticoids, thyroid malignancy and craniopharyngioma (in case of CHT) – for a complete list, see Supplementary Table 1 (see section on supplementary materials given at the end of this article). Patients with PHT should be euthyroid (TSH levels between 0.2 and 4.5 mU/L). Only patients using the l-thyroxine® brand of LT4 (Takeda) were included. Patients using Euthyrox® (Merck), the only alternative LT4 brand available in Belgium and only used by a small minority of patients, were excluded because of a minor difference in bioavailability between both formulations (4). All the patients had the ability to complete paper-and-pencil questionnaires in Dutch.

**Materials and methods**

We performed a monocentric cross-sectional study at the Department of Endocrinology of the Ghent University Hospital, Belgium. Medical records were consecutively screened to identify patients with CHT during a period of 12 months, for each subject, a patient with PHT was also recruited. If there were no exclusion criteria, patients were asked to participate in the study during the routine outpatient visits. The study was approved by the Ethics Committee of the Ghent University Hospital (2019/0304). A written informed consent was obtained from participants to participate in the study and there were no conflicts of interest.

**Study population**

To be included, both CHT and PHT patients had to be on a stable LT4 replacement dose for at least 6 months.

Exclusion criteria included malabsorptive disease, status post coronary artery bypass grafting, patients with chronic kidney disease (CKD 4 and further), concomitant use of amiodarone and high dose glucocorticoids, thyroid malignancy and craniopharyngioma (in case of CHT) – for a complete list, see Supplementary Table 1 (see section on supplementary materials given at the end of this article). Patients with PHT should be euthyroid (TSH levels between 0.2 and 4.5 mU/L). Only patients using the l-thyroxine® brand of LT4 (Takeda) were included. Patients using Euthyrox® (Merck), the only alternative LT4 brand available in Belgium and only used by a small minority of patients, were excluded because of a minor difference in bioavailability between both formulations (4). All the patients had the ability to complete paper-and-pencil questionnaires in Dutch.

**Personal and biochemical data**

We recorded disease-related variables such as aetiology, current LT4 dose and other medications, the performed treatment in case of pituitary or hypothalamic pathology (medical, surgery, radiotherapy), other hormonal deficiencies and respective treatments and other co-morbidities. Data were retrieved from patients’ digital medical files. Anthropometric data were obtained during consultation, and BMI was calculated as weight/height² (kg/m²). Biochemical data such as serum TSH, fT4, fT3, total cholesterol and LDL cholesterol levels were collected retrospectively or based on blood samples drawn after consultation for the routine clinical purpose (either in the university hospital or in an external lab). All biochemical analyses were performed by established standard assays in accredited clinical chemistry labs. Generally, patients administer LT4 in a single dose, fasting and 30 min before breakfast. There were no instructions on how and when to perform the blood sampling (in relation to LT4 intake), and this information was not collected.

**Questionnaires**

QoL and patient-reported outcomes (PRO) were measured by the QoL assessment SF-36 and the disease-specific ThyPRO questionnaires.

The SF-36 health survey is a generic instrument and applicable to patient populations independently of the underlying disease or health status. It is the most widely used health-related QoL instrument, measuring eight subdomains (physical functioning, body pain, emotional well-being, etc.) and a single item that provides...
an indication of perceived change in health (5). Disease-specific instruments, like the ThyPRO questionnaire, are designed for a specific patient group. They are mostly more accurate to evaluate clinical change over time (6). The disease-specific ThyPRO questionnaire is developed by Watt et al. to estimate the impact of any benign thyroid disease on health-related QoL. It consists of 84 items, summarized in 13 scales as well as a single item measuring overall impact of thyroid diseases on QoL. The average score of items in a scale is divided by 4 and multiplied by 100 to yield thirteen 0–100 scales. Positively worded items were scored reversely when constructing scales. These scales were then scored as a summary score. A higher score indicates a worse health status (7, 8). For the SF-36 questionnaire, there are 36 items which are summarized in eight 0–100 scales, calculated as instructed by the RAND-36 item health survey (8). Unlike the ThyPRO questionnaire, a higher score indicates a more favourable status (9). Patients filled out the questionnaires during consultations or returned them afterwards.

Data Analysis

Data were analysed using IBM SPSS (version 28.0, Chicago, IL, USA). Data were verified for normal distribution using the Shapiro–Wilk test. Normally distributed values are shown as mean ± s.d., whereas non-normally distributed values are described as median (percentile 25–percentile 75). Differences between groups were analysed by unpaired Student’s t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. To assess whether frequency distributions differed between the two groups, Fisher’s exact test was used. As sex distribution was significantly different between both groups, all hypotheses were re-tested using analyses of covariance. Sex did not have a significant impact on the reported results. P-values < 0.05 were considered statistically significant.

Results

The study population consisted of 82 patients, 41 patients with CHT and 41 patients with PHT. Characteristics of the study population are shown in Table 1. There were more men in the CHT group and more women in the PHT group (P = 0.002).

Aetiology of CHT was most often pituitary (micro- or macro) adenomas (n = 26), for which 15 patients underwent transsphenoidal resection. Only one patient had an isolated TSH deficiency, all other patients had two or more affected hormonal axes. Thirty-two patients were on hydrocortisone therapy, 24 patients were on testosterone replacement therapy, 10 patients were on growth hormone and 3 patients were on oestrogen substitution therapy. The aetiology of PHT was most often surgical (total thyroidectomy, n = 16) and autoimmune thyroid disease (n = 14), shown in Table 2 (see Supplementary files).

We found no significant difference in total daily dose of LT4 (P = 0.87) or in LT4 dose per kg of body weight (P = 0.13) between both groups. The mean total daily dose of LT4 (µg per day) was 100 (93.75–125.00) and 107.14 (75.00–133.93) in CHT and PHT, respectively. The mean dose LT4 per kg body weight was 1.34 (1.16–1.55) for

Table 1  Characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CHT (n = 41)</th>
<th>PHT (n = 41)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex distribution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (n, %)</td>
<td>27 (65.9%)</td>
<td>13 (31.7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Women (n, %)</td>
<td>14 (34.1%)</td>
<td>28 (68.3%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range (min–max)</td>
<td>22–79</td>
<td>30–78</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>54.00 (44.00–66.50)</td>
<td>60.00 (41.00–67.50)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>18.10–38.40</td>
<td>19–41</td>
<td></td>
</tr>
<tr>
<td>Range (min–max)</td>
<td>26.50 (23.95–29.83)</td>
<td>25.00 (22.50–29.75)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>100.0 (93.75–125.00)</td>
<td>107.14 (75.00–133.93)</td>
<td></td>
</tr>
<tr>
<td>Levotirothyrone dose (µg)</td>
<td>50–200</td>
<td>37.50–200</td>
<td></td>
</tr>
<tr>
<td>Range (min–max)</td>
<td>100.0 (93.75–125.00)</td>
<td>107.14 (75.00–133.93)</td>
<td></td>
</tr>
<tr>
<td>Levotirothyrone dose per kg body weight (µg/kg)</td>
<td>0.71–2.44</td>
<td>0.48–2.64</td>
<td></td>
</tr>
<tr>
<td>Range (min–max)</td>
<td>1.34 (1.16–1.55)</td>
<td>1.55 (1.16–1.82)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.30 (0.54–2.29)</td>
<td>1.60 (1.40–1.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSH (mU/L) (0.27–4.2)</td>
<td>0.001–1.39</td>
<td>0.20–4.30</td>
<td></td>
</tr>
<tr>
<td>Range (min–max)</td>
<td>0.01 (0.005–0.150)</td>
<td>1.30 (0.54–2.29)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.40 (1.20–1.80)</td>
<td>6.00 (1.40–1.80)</td>
<td></td>
</tr>
<tr>
<td>FT4 (ng/dL) (0.9–1.7)</td>
<td>0.97–2.30</td>
<td>0.89–2.20</td>
<td></td>
</tr>
<tr>
<td>Range (min–max)</td>
<td>1.40 (1.20–1.80)</td>
<td>1.60 (1.40–1.80)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.30 (2.70–3.80)</td>
<td>2.90 (2.70–3.10)</td>
<td>0.10</td>
</tr>
<tr>
<td>FT3 (pg/mL) (2.5–4.4)</td>
<td>2.00–5.50</td>
<td>2.10–3.30</td>
<td></td>
</tr>
<tr>
<td>Range (min–max)</td>
<td>3.00 (2.70–3.80)</td>
<td>2.90 (2.70–3.10)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>191.00 (161.00–228.00)</td>
<td>185 (166–201.00)</td>
<td>0.28</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>115–281</td>
<td>104–242</td>
<td></td>
</tr>
<tr>
<td>Range (min–max)</td>
<td>191.00 (161.00–228.00)</td>
<td>185 (166–201.00)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>109.00 (92.00–141.00)</td>
<td>98 (83.4–115.00)</td>
<td>0.08</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>49–192</td>
<td>35–156</td>
<td></td>
</tr>
<tr>
<td>Range (min–max)</td>
<td>0.00 (0.00–25.00)</td>
<td>0.00 (0.00–25.00)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.00 (0.00–25.00)</td>
<td>0.00 (0.00–25.00)</td>
<td></td>
</tr>
<tr>
<td>Total ThyPro score*</td>
<td>0.00 (0.00–25.00)</td>
<td>0.00 (0.00–25.00)</td>
<td></td>
</tr>
<tr>
<td>Range (min–max)</td>
<td>0.00 (0.00–25.00)</td>
<td>0.00 (0.00–25.00)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.00 (0.00–25.00)</td>
<td>0.00 (0.00–25.00)</td>
<td></td>
</tr>
<tr>
<td>Jostel's index</td>
<td>0.03–2.27</td>
<td>0.11–3.91</td>
<td></td>
</tr>
<tr>
<td>Range (min–max)</td>
<td>0.99 (0.51–1.56)</td>
<td>2.63 (2.40–2.95)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Total ThyPro score is a summary score: please see Table 2 for the different domain scores of ThyPro.

Bold indicates statistical significance, P < 0.05.
patients with CHT and 1.55 μg/kg per day (1.16–1.82) for patients with PHT. In addition, median serum levels of fT4 and fT3 did not differ between both groups (P = 0.20, P = 0.10, respectively) and were in the midnormal range for both groups. The mean TSH level (mU/L) in the CHT group was 0.01 (0.005–0.15), nevertheless, 5 patients had a TSH level ≥ 0.5 mU/L, of which 2 patients with a TSH level ≥ 1.0 mU/L. The fT4 levels for these 5 patients ranged from 1.08 to 1.6 ng/dL, and the patient with the lowest fT4 level received the lowest dose LT4 per kg body weight of these patients, namely, 0.71 μg/kg body weight per day, and had a BMI of 31.4 kg/m². The other 4 patients received a replacement dose of LT4 ranging from 1.01 to 1.65 μg/kg per day. In neither patient group, BMI was found to correlate with either thyroid function test (all P > 0.1).

Regarding total and LDL cholesterol levels, there were no statistically significant differences between the two groups (P = 0.28 and P = 0.08, respectively). In neither group, total cholesterol and LDL cholesterol were correlated to fT4 or TSH.

The total ThyPro score was statistically significant between the CHT and PHT group (P = 0.006), more specifically patients with CHT had higher scores for the ThyPro subdomains depressive symptoms, impaired social and daily life (all P < 0.05), shown in Table 2. SF-36 scores did not differ between the two groups, except for role limitations due to emotional problems (P = 0.014) in which patients with CHT again scored worse, see Supplementary Table 3. Overall, ThyPro scores were low and SF-36 scores high, indicating overall acceptable well-being in our patients. Subgroup analyses, for example, on aetiology or concomitant hormonal replacement therapy were not possible because of low sample size.

We also calculated the Jostels’ TSH index, which provides an estimate of the severity of pituitary dysfunction in hypopituitary patients (10). A low TSH index can support the diagnosis of CHT in uncertain conditions. This index was statistically significant between both groups.

### Discussion

In this cross-sectional, single-centre, real-life study, with (for a rare disease) a considerable number of patients with CHT who all were treated in a tertiary referral centre, we could not find a difference in TH replacement dose as compared to patients with PHT. However, we did observe a difference between both groups in terms of QoL, more specifically did patients with CHT score somewhat worse for depressive symptoms, impaired daily and social life.

Although control participants were not matched, the two groups were comparable regarding age and BMI, so it was not necessary to correct for these possible confounding factors. We observed a statistically significant imbalance in distribution between both groups with more men in the group of patients with CHT and more women in the group of patients with PHT. Therefore, all hypotheses were re-tested using analyses of covariance and sex did not have a significant impact on the reported results.

In our study, although absolute and body weight-adjusted mean daily doses of LT4 were slightly lower in patients with CHT, these differences were not significant. It thus not seems to be the case that patients with CHT are undertreated in our centre, although we acknowledge the rather low sample size of both groups and the fact some patients with PHT had autoimmune hypothyroidism in which we cannot rule out some residual endogenous
TH secretion. However, a major impact from the latter seems rather implausible as substitution doses of both groups were in the expected range. The American Thyroid Association guidelines recommend an average dose of LT4 of 1.6 μg/kg body weight per day, which was subsequently enforced by the Endocrine Society (ES) (11, 12). The most recent ETA guideline on hormonal replacement in adult hypopituitary patients, however, proposes a mean dose of 1.2–1.6 μg/kg body weight per day (1). Given our findings, aiming for a universal substitution dose of 1.6 μg/kg body weight per day might hold a risk of overtreatment, especially in elderly patients. But no matter which guidance is followed, one should be aware that due to the important interindividual variation in TH sensitivity, even a substitution dose within this proposed range might still not be appropriate for an individual patient. As monitoring of substitution therapy using serum TSH levels is not possible in patients with CHT, under -and overtreatment is more difficult to evaluate and is a risk one should be aware of.

As an alternative to TSH levels, some experts and guidelines suggest using serum fT4 (and fT3) levels to monitor treatment in patients with CHT. The goal would be to keep serum fT4 levels in middle-upper normal range while fT3 levels should be in the normal range. In our study, although serum levels of fT4 were non-significantly lower in patients with CHT compared to patients with PHT, levels of fT4 in both groups were in the normal range. Serum levels of fT3 were comparable between both groups and also in the normal range. However, both the ES and the ETA guideline advise that blood should be taken before the administration of LT4 since fT4 levels increase transiently by up to 20% after LT4 administration (1, 12, 13). It is a limitation of this study that we did not give instructions to our patients (that blood should be taken before the administration of LT4), which make our results more difficult to generalize. Nevertheless, based on our findings and the available literature in both patients with CHT as PHT, we think that targeting fT4 levels in the upper normal range in a sample obtained before the scheduled intake of LT4 poses a risk for overtreatment. One should keep in mind that overtreatment also carries its risks (e.g. premature osteoporosis and adverse cardiovascular effects). From a physiological point of view, there are also difficulties with the recommendation to aim for an fT4 in the normal-upper range, because of the wide reference range of fT4 in the normal population and the large variety of factors influencing fT4 levels in normal circumstances (e.g. age, oestrogen exposure, comorbidities, drugs, and clinical context).

CHT and its impact on QoL is relatively rarely investigated. In our study, we included two different questionnaires, the health-related SF-36 survey and the ThyPRO questionnaire, to explore the impact of CHT and PHT on patients’ QoL. Not completely unexpected, we found a statistically significant difference between both groups regarding QoL, more specifically for depressive symptoms and impaired social and daily life. Intuitively, we indeed presumed that patients with CHT would have had a decreased QoL because of the underlying pathology, concomitantly affecting other pituitary axes and comorbidities. On the other hand, we should note that patients with PHT seen in our clinic might also have other comorbidities (although most severe comorbidities were excluded – see Methods) as generally patients with uncomplicated PHT are managed by their general practitioner. Anyways, we should keep in mind that a chronic disease as CHT can reduce QoL and that we should pay more attention to this in clinical management. Nevertheless, we should try to strive for optimal LT4 substitution therapy given its important potential effects on cardiometabolic risk and overall well-being.

Conclusion

In summary, the aim of this study was to investigate the dose of TH replacement therapy in patients with CHT and to compare this dose with the TH replacement therapy in patients with PHT. In the group of patients with CHT, median LT4 dose was within the suggested range and although numerically somewhat lower, not significantly different from that in patients with PHT. We do have to admit that some differences may have been missed due to low statistical power inherent in relatively small sample sizes. So, we cannot confirm the hypothesis that patients with CHT would be undertreated. However, in our opinion and given the relatively broad range of substitution doses in both groups, a more individual appraisal of every patient, with attention to age, comorbidities and frailty is more appropriate than a one-size-fits-all approach in prescribing TH replacement therapy.

Regarding QoL, we found that patients with CHT scored somewhat worse for some subdomains of the ThyPro and SF36 score. This also shows that it is important that larger studies further investigate the QoL and PRO, since the subjective assessment of the impact of disease and its treatment should be an integral part of the management.

Currently, we still lack clear-cut parameters that can guide us in the management of patients with CHT.
Monitoring of some biochemical indexes of TH action at tissue level (e.g. serum levels of sex hormone binding globulin, angiotensin-converting enzyme, low-density lipoprotein cholesterol, etc.) has been suggested for titration of thyroxin treatment in these patients, but there is still insufficient evidence to use them to guide the management of CHT (14, 15).

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/ETJ-21-0128.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This study did not receive any specific grant from any funding agency in the public, commercial or non-for-profit sector.

Statement of ethics
The study was approved by the Ethics Committee of the institution (2019/0304). Written informed consent was obtained from participants to participate in the study.

Data sharing and data accessibility
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgements
We thank the patients for their contribution to the study. We would also like to thank the colleagues at the Endocrinology department to help including the patients.

References
9 Ware J. The SF-36, measuring health-related quality of life on eight dimensions: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Medical Care 1992 30 473–483.
13 Ain KB, Pucino F, Shiver TM & Banks SM. Thyroid hormone levels affected by time of blood sampling in thyroxine- treated patients. Thyroid 1993 3 81–85. (https://doi.org/10.1089/thy.1993.3.81)

Received in final form 4 October 2022
Accepted 7 October 2022
Accepted Manuscript published online 7 October 2022