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Treatment of Congenital Hypothyroidism: Impact of Secular Changes in Levothyroxine Initial Dose on Early Growth

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Abstract
Introduction: Newborn screening of congenital hypothyroidism (CH) has enabled early treatment with levothyroxine (LT4), ensuring normal growth and development. The initial LT4 dose recommendation has increased over decades. We evaluated whether the increased LT4 dosing influenced thyroid-stimulating hormone (TSH) and thyroxine (fT4) concentrations, growth, or treatment-related symptoms. ***Methods:*** LT4 doses, TSH, fT4, anthropometrics, and treatment-related symptoms until age 2 years were evaluated in 172 Finnish CH patients born between 1980 and 2018. The patients were grouped according to birth decade: 1980s (n = 19, mean LT4 starting dose 6.8 µg/kg/day), 1990s (n = 50, 7.4 µg/kg/day), 2000s (n = 59, 9.7 µg/kg/day), and 2010s (n = 44, 10.8 µg/kg/day). ***Results:*** TSH concentrations were higher during the first 2 years of life in children born in the 1980s compared to children born later. TSH concentrations were often subnormal in children receiving higher LT4 doses (children born in the 2000s and 2010s). However, symptoms of overtreatment were uncommon. Linear or head growth showed no differences between the groups during the first 2 years of life. Although growth was within the normal spectrum, children in all groups were shorter than their target length at 2 years and their weight-for-length was above the mean through the first 2 years of life. ***Discussion:*** Current treatment practice with higher LT4 dose normalizes TSH rapidly without significant increase in side effects. However, irrespective of initial LT4 dose, children were shorter than expected at 2 years of age. Effects of different initial LT4 dose on cognitive development urges further investigation.

Introduction

Thyroid hormone is fundamental for normal growth and neurological development. Newborn screening protocols have enabled early diagnosis and treatment of congenital hypothyroidism (CH), thus preventing profound mental and growth retardation. During the last decades, the initial dose of levothyroxine (LT4) has evolved as more data of the optimal dosing has been gained. Undertreatment may lead to impaired growth and lower IQ, whereas overtreatment may also lower cognitive outcome and cause early fusion of cranial sutures and behavioral and attention problems [1–7]. Also, the significance of mild overtreatment (biochemical or subclinical hyperthyroidism with high or normal

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free thyroxine (fT4) and thyroid-stimulating hormone (TSH) below reference range without symptoms) is still controversial [8–10]. What makes this more challenging is the fact that the need of appropriate thyroid hormone dose coincides with the period of the most rapid growth and cognitive development in the entire human postnatal life.

During the first decades of CH screening, the LT4 starting dose was significantly lower than the current recommendation, and treatment began in many countries often as late as at 3–4 weeks of age. Current recommendations aim for initiation of treatment before 2 weeks of age with a dose of 10–15 μg/kg/day to rapidly normalize fT4 and TSH [11, 12].

Finland is unique among Western countries as CH is screened using umbilical cord blood [13]. This has made it possible to take confirming venous samples already at 3 days of age and start treatment exceptionally early, averaging at 3–6 days of age. The national practice for the initial LT4 dose in the 1980s was 6–8 μg/kg/day, which increased to 10–15 μg/kg/day during the 1990s. Here, we investigated whether the different initial doses of LT4 affected thyroid function tests or growth during the first 2 years of life in a retrospective cohort of 172 CH patients born in Finland between 1980 and 2018.

Materials and Methods

Study Population

Total of 172 CH patients born between 1980 and 2018 in Turku and Kuopio University Hospital districts were included. CH cases were identified from hospital patient registries using the following ICD codes ICD-8: 243; ICD-9: 243, 2430A, 2461A, 2534C; ICD-10: E03.1, E03.0. Only children with permanent primary CH were included in the study. Further inclusion criteria for permanent CH were initiation of LT4 treatment before 14 days of age, and confirmation of the diagnosis, if needed, at the age of 2–3 years by measurement of thyroid function tests after 2–3-week cessation of LT4 treatment. LT4 withdrawal test was performed for 78/172 (45%) patients. It was not done for 85/172 (50%) based on the judgement of the treating pediatrician (clear signs of permanent CH during treatment, e.g., extremely high TSH levels at birth, obvious rise in the need of LT4 with age or proven thyroid agenesis or ectopy). For 9 patients (5%), there was no mention whether the cessation was performed. Very preterm babies (born before gestation week 32, $N = 1$) and children with Down syndrome ($N = 2$) were excluded as these conditions affect the growth of the children irrespective of their thyroid function. This retrospective study was approved by the Ethics Committee of Northern Savo Hospital District (March 13th, 2018; No. 346/2018).

Growth Measurements

All growth parameters (length, weight, and head circumference) were measured by a trained nurse during regular hospital or health care center visits and collected from the patient's growth charts. Length was measured prone using a baby board to the nearest millimeter, weight using an electronic scale to the nearest 10 g, and head circumference using non-elastic measuring tape measuring the greatest occipitofrontal circumference to the nearest millimeter. Length SDS (as deviation in SD score from the age and sex-specific mean), weight-for-length percentage (as deviation in percentage from the sex and length specific median weight), and head circumference SDS were calculated using national growth references for Finnish children [14, 15]. The age points used were birth, 3 months (range 1.5–4.49 months), 6 months (4.5–7.49 months), 9 months (7.5–10.49 months), 12 months (10.5–13.49 months), 18 months (15–20.9 months), and 24 months (21–26.9 months). For preterm infants (born between gestation weeks 35^{+3}–36^{+6}, $n = 5$), age-corrected measurements were used. Expected target length SDS at 2 years of age was obtained from the charts.

Laboratory Analyses

In Finland, national umbilical cord blood TSH screening was introduced to all newborns in 1980. Umbilical cord blood TSH-value >25–60 mU/L (depending on the birth year and hospital, see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000528567) was used as cut-off. If above, confirmatory analyses were taken from venous blood on average at 3–6 days of age. Abnormal TSH and fT4 (cut-offs in online suppl. Tables 3 and 4) in confirmatory samples led to CH diagnosis and prompt LT4 treatment. Patients born in the 1980s did not have fT4 measured but instead total thyroxine (T4). TSH and fT4 values were collected from birth to 2 years of age and grouped into birth, age at confirmatory laboratory samples (0-month age point, always before 2 weeks of age), 1 month (range 2–5.9 weeks), 2 months (6–9.9 weeks), 3 months (10–13.9 weeks), 6 months (4.5–7.49 months), 9 months (7.5–10.49 months), 12 months (10.5–13.49 months), 15 months (13.5–16.49 months), 18 months (16.5–19.49 months), 21 months (19.5–22.49 months), and 24 months (22.5–25.49 months). TSH and fT4 methods and reference intervals varied over the study period (see online suppl. Tables 1–4). If TSH or fT4 level was above or below the detectable levels, the highest/lowest detection limits of the assay were used.

LT4 Doses

All patient records were manually reviewed to find the LT4 doses throughout the first 2 years of life. We then calculated the dose at all age points (same as in laboratory analyses, see above) as μg/kg/day.

Symptoms and Signs of Overtreatment or Undertreatment

Symptoms related to overtreatment, i.e., hyperthyroidism (troubled sleep, diarrhea, tremor, notable hidrosis, restlessness, decrease in relative weight, decelerated head circumference growth, palpitation, defiantness) or undertreatment, i.e., hypothyroidism (tiredness, constipation, hypotonia, dry skin, growth deceleration) were systematically collected from the patient records. The symptoms were evaluated irrespective of the TSH value. The TSH values of the children were grouped into <0.5 mU/L, 0.5–2 mU/L, 2–4.5 mU/L, and >4.5 mU/L at all visits with a possible treatment-related symptom and occurrence of hyperthyroid/hypothyroid symptoms were compared.

Table 1. Birth characteristics (mean ± SD) of 172 children with CH born in 1980–89 ("1980s"), 1990–1999 ("1990s"), 2000–2009 ("2000s"), and 2010–2018 ("2010s")

	All	1980s	1990s	2000s	2010s
n (male/female)	172 (67/105)	19 (6/13)	50 (22/28)	59 (20/39)	44 (19/25)
Difference in days from full term (40 weeks)	1.8±10.4	−1.6±8.9	−0.7±11.0	4.4±10.4	3.0±9.4
Length, cm	50.5±1.9	51.0±2.6	50.2±2.0	50.6±1.8	50.5±1.6
Weight, kg	3.6±0.5	3.7±0.6	3.6±0.6	3.7±0.5	3.6±0.4
Head circumference, cm	35.5±1.5	35.7±1.5	35.7±1.5	35.7±1.7	35.5±1.4
Umbilical cord TSH mU/L	298.4±192.4	267.9±127.5	334.7±219.9	268.9±160.9	309.7±214.5
Umbilical cord fT4 pmol/L	8.8±3.1	NA	8.4±2.6	8.4±3.0	10.0±3.7
Confirmatory TSH	292.4±224.7	299.3±191.9	364.1±266.0	258.4±200.0	257.2±207.7
Confirmatory fT4	10.3±6.8	NA	9.1±6.2	9.9±6.6	11.6±7.4
Age at start of treatment, days*	4.1±2.0	5.9±1.5	4.4±2.0	3.7±1.9	3.5±1.6
Starting dose, µg/kg/day**	9.0±2.2	6.8±1.0	7.4±1.4	9.7±1.8	10.8±1.7

TSH, thyroid-stimulating hormone; fT4, free thyroxine. * $p < 0.05$, except between groups 1980s and 1990s and between groups 2000s and 2010s. ** $p < 0.05$, except between groups 1980s and 1990s.

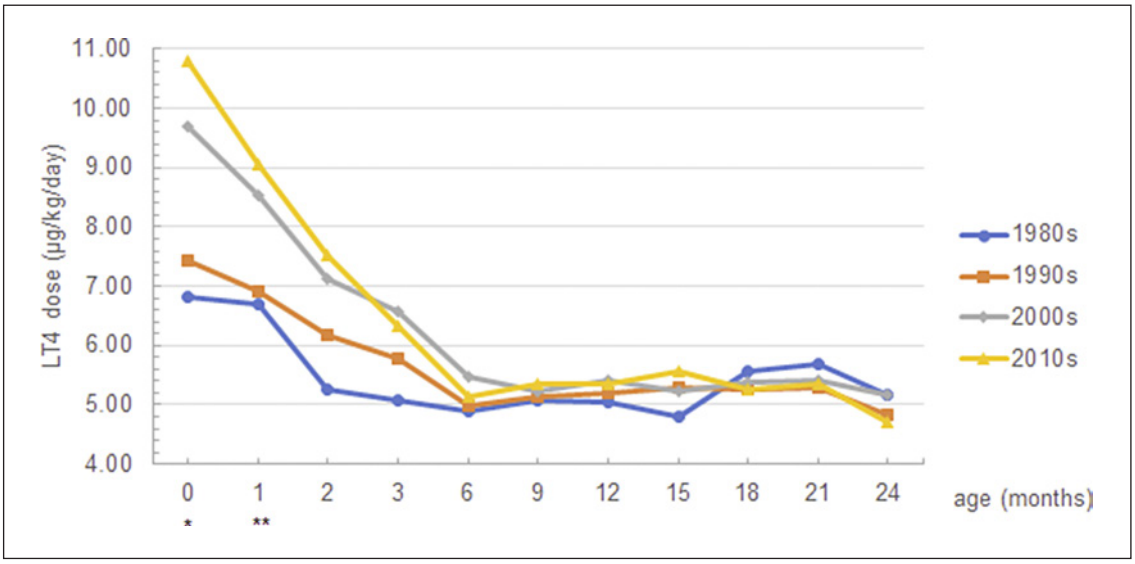

Fig. 1. The mean doses (µg/kg/day) of levothyroxine (LT4) used for treatment of congenital hypothyroidism in patients born in 1980s, 1990s, 2000s, and 2010s from initiation of treatment to 2 years of age. *$p < 0.05$ between groups except between 1980s and 1990s. **$p < 0.05$ between groups except between 1980s and 1990s and between 2000s and 2010s.

Statistical Methods

Statistical analysis was performed using IBM SPSS Statistics program version 26.0 (IBM Corp, Armonk, NY, USA). For birth and treatment initiation data, Kruskal-Wallis or ANOVA was used depending on the distribution of the data. Natural logarithmic transformation was applied to nonparametric TSH concentrations. After the start of the treatment, mixed-effects regression was performed using a generalized linear model for the dose, TSH and fT4 levels, and growth parameters. Repeated measures within subjects were assumed to have first-order autoregressive covariance structure. For the target length, ANOVA was used for the comparison of different groups. For the comparison between the actual length SDS and the target, a paired-samples *t* test was used. Distribution of the treatment-related symptoms was tested with Fisher's Exact and Pearson χ^2 tests. The mean (± standard deviation in online suppl. material) is shown except for TSH, for which median (with the interquartile range in online suppl. material) is presented. A *p* value <0.05 was considered statistically significant. *p* values from the analyses considering multiple pairwise comparisons were adjusted for multiplicity by sequential Bonferroni correction method.

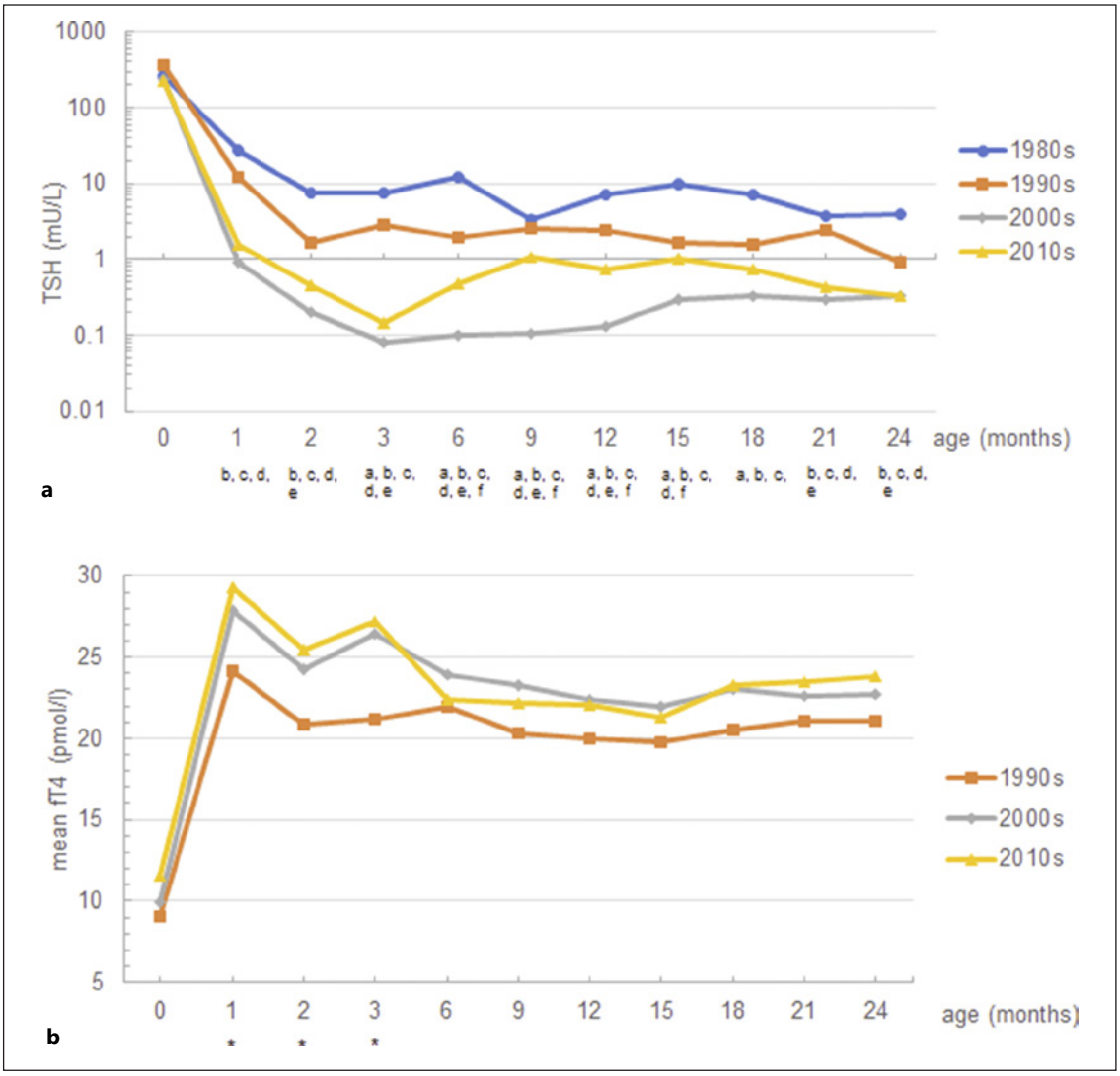

Fig. 2. a Median thyroid-stimulating hormone (TSH; mU/L) of congenital hypothyroidism patients born in 1980s, 1990s, 2000s, and 2010s from initiation of treatment to 2 years of age. TSH is modified on a logarithmic scale and is shown as median in the different groups at given ages. Letters indicate statistical difference $p < 0.05$ between [a]groups 1980s and 1990s, [b]groups 1980s and 2000s, [c]groups 1980s and 2010s, [d]groups 1990s and 2000s, [e]groups 1990s and 2010s, [f]groups 2000s and 2010s. **b** The mean free thyroxine (pmol/L) (fT4) of congenital hypothyroidism patients born in 1990s, 2000s, and 2010s from initiation of treatment to 2 years of age. *$p < 0.05$ except between groups 2000s and 2010s.

Results

Demographics of the Study Population and Initial LT4 Doses

A total of 172 patients with CH were included: 19 born between 1980 and 1989 ("1980s"), 50 between 1990 and 1999 ("1990s"), 59 between 2000 and 2009 ("2000s"), and 44 between 2010 and 2018 ("2010s"). The female to male ratio was 1.6:1. The clinical and hormonal data at birth are shown in Table 1.

The mean age at the start of treatment was 5.9 ± 1.5 d, 4.4 ± 2.0 d, 3.7 ± 1.9 d, and 3.5 ± 1.6 d in 1980s, 1990s, 2000s, and 2010s, respectively. The mean starting dose of LT4 increased significantly from 6.8 μg/kg/d in the 1980s to 10.8 μg/kg/d in the 2010s (shown in Fig. 1 and online suppl. Table 5; $p < 0.05$ in pairwise comparisons except between 1980s and 1990s). Significant differences were seen in LT4 dose at 1 month of age (except between groups 1980s and 1990s and groups 2000s and 2010s). From 6 months of age onwards, the LT4 doses were almost identical in all decades.

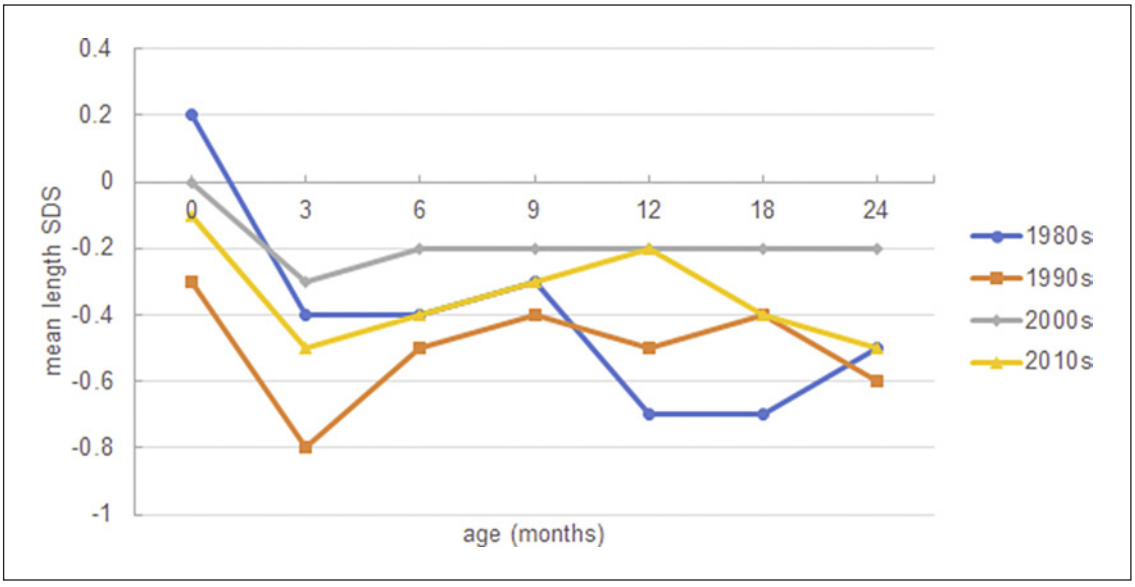

Fig. 3. The mean length SDS of congenital hypothyroidism patients born in 1980s, 1990s, 2000s, and 2010s from birth to 2 years of age.

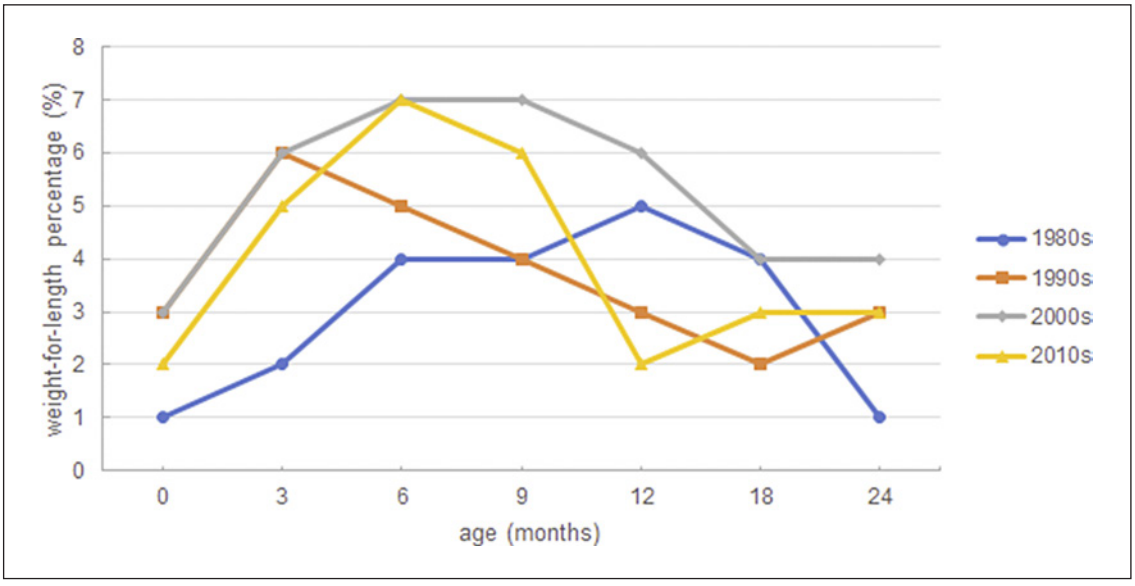

Fig. 4. The mean weight-for-length percentage* (%) of congenital hypothyroidism patients born in 1980s, 1990s, 2000s, and 2010s from birth to 2 years of age. *Weight-for-length percentage = deviation in percentage from the median weight of Finnish children of the same length and sex.

Secular Trends in Thyroid Function Tests and Occurrence of Treatment-Related Symptoms

There were no differences between the groups' thyroid function tests at the time of diagnosis (shown in Fig. 2a, b). Thereafter, TSH differed significantly between most of the pairwise comparisons at all age points (shown in Fig. 2a and online suppl. Table 6). In line with the lower TSH values in 2000s and 2010s and higher initial LT4 starting dose, their fT4 concentrations were also significantly higher than in 1990s for the first 3 months (shown in Fig. 2b and online suppl. Table 7). Thereafter, there were no statistical differences in the mean fT4 levels

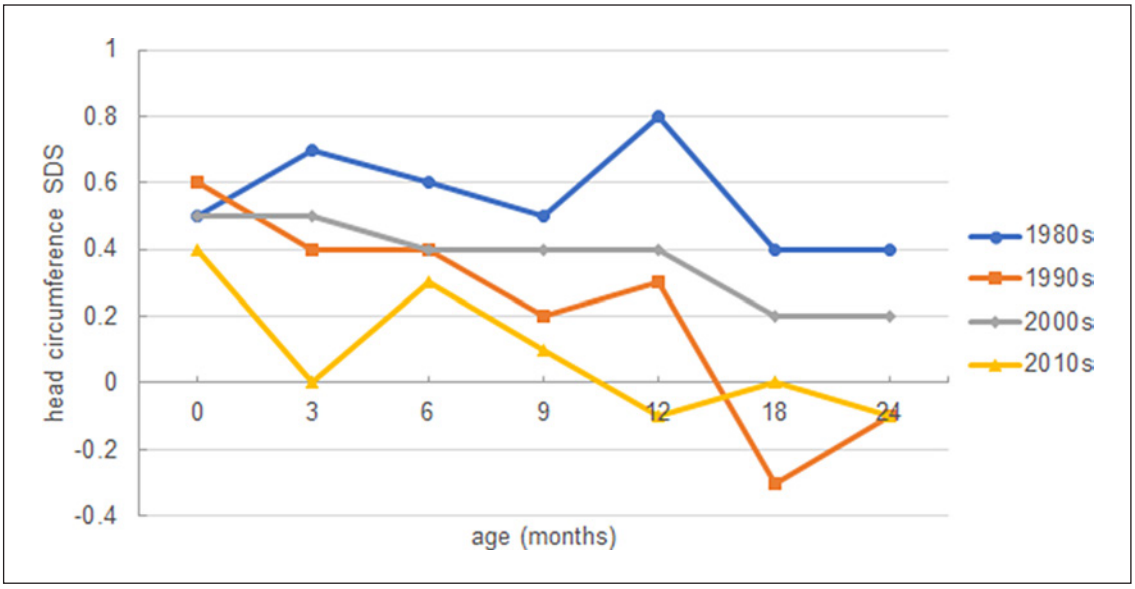

Fig. 5. The mean head circumference SDS of congenital hypothyroidism patients born in 1980s, 1990s, 2000s, and 2010s from birth to 2 years of age.

between 1990s, 2000s, and 2010s. In 1980s, total T4 was above the lower limit of the reference range in all patients from 2 months of age onward (online suppl. Table 8).

Median TSH in the 1980s remained relatively high throughout the 2-year study period (shown in Fig. 2a and online suppl. Table 6). TSH reached normal range in 1990s at 2 months of age (median TSH 1.7 mU/L [IQR 0.8–13.5 mU/L]) and in 2000s and 2010s already at 1 month of age (median TSH 0.9 mU/L [IQR 0.4–3.7 mU/L] and 1.6 mU/L [0.5–5.8 mU/L], respectively). However, the median TSH remained rather low in 2000s and 2010s; median TSH was actually below 0.5 mU/L in 2000s from 2 months onwards.

The proportion of visits with reported possible symptoms of overtreatment or undertreatment was significantly higher when TSH was <0.5 mU/L (symptoms in 7.2% of the visits), compared to when TSH was 0.5–2.0 mU/L (3.7%), 2.0–4.5 mU/L (4.5%) or >4.5 mU/L (3.3%). However, the distribution of overtreatment and undertreatment symptoms was not significantly different between the groups.

Anthropometric Analyses of CH Children with Different LT4 Initial Doses

There were no significant differences in length or weight between the groups at any age. All groups were slightly shorter than the national reference from 3 months of age onwards (shown in Fig. 3 and online suppl. Table 9). They were also slightly heavier from birth onwards than average Finnish children (shown in Fig. 4 and online suppl. Table 10). These did, however, fall within the range regarded as normal growth. At 2 years children in all treatment groups were, though, significantly shorter than expected (mean target length +0.08 SDS in 1980s, 0.0 SDS in 1990s, +0.1 SDS in 2000s, and +0.2 SDS in 2010s; data available in 63% of the patients, midparental heights 172.4 cm in 1980s, 170.5 cm in 1990s, 172.1 cm in 2000s, 172.6 cm in 2010s with no significant differences between the decades).

All groups had a mean head circumference larger than an average Finnish child at birth. After this head circumference, SDS decreased in all groups (shown in Fig. 5 and online suppl. Table 11), least in group 1980s which had the highest TSH values through early childhood and lowest initial LT4 dose. There were no statistically significant differences between the groups and the average measures were within the range regarded as normal head growth.

Discussion

In this retrospective study of 172 CH patients, we found that the lower LT4 dose regimen in the 1980s resulted in significantly higher serum TSH concentrations throughout the first 2 years of life when compared to the higher dose regimen in the 2000s and 2010s. The CH

children in all groups were shorter and heavier than an average Finnish child, but the recommended higher dose regimen did not cause significant differences in growth parameters between the groups. In addition, in the higher dose groups of 2000s and 2010s, TSH values were often below the lower reference range (0.5 mU/L), but treatment-related side effects were uncommon.

Here, we showed that the starting dose of LT4 has evolved over the last four decades from 6.8 μg/kg/day in the 1980s to the currently recommended 10.8 μg/kg/day in the 2010s [12]. The differences in LT4 doses during the first month of life were reflected in slower normalization of TSH in children with lower starting dose. In line with decreased TSH levels, there was a trend for higher fT4 levels, though only significant during the first 3 months.

We found that despite different LT4 starting doses as well as TSH and fT4 levels, growth parameters remained similar in all groups. However, in general, regardless of LT4 dose, the length of the CH patients was below the national average, and significantly below their target length at 2 years of age. This impaired early growth has been previously described, but it is considered a temporary feature resolving after 1 year of age [16–18]. Impaired early growth most likely reflects the delayed bone development observed in CH patients at birth [19]. The higher dose of LT4 was not associated with growth closer to the genetic growth potential for the first 2 years of life, but it remains to be seen whether full growth potential is reached later on in all groups or only in those with a higher initial LT4 dose. It has been shown earlier that CH children attain their target height at the end or puberty or may even exceed it. Whether the initial LT4 dose influences the growth remains controversial [20–22]. Leger and Czernichow (1989) suggested that growth becomes thyroid hormone dependent immediately after birth [23]. It is possible that since all our groups received treatment promptly after birth and had similar initial thyroid hormone values, even the lower dose used in the 1980s might have been sufficient to ensure similar growth as higher doses used later. Our results are, indeed, in line with several studies showing that the higher dose does not significantly improve growth compared to lower dose [8, 9, 24]. Further follow-up is needed to investigate growth in later childhood and adolescence to see whether the slight impairment of linear growth is temporary or permanent.

We found that all four groups of children with different LT4 initial doses had a slightly higher weight-for-length percentage than an average Finnish child throughout the 2-year study period, although still within normal range. Thus, this finding is not due to possible undertreatment because even children treated with higher doses and with suppressed serum TSH levels were heavier than the reference population. This phenomenon has been shown in earlier studies [18, 21, 24]. However, opposing findings with average weight gain have also been published [17, 25]. A definite cause of increased weight remains unclear.

It has been shown that thyroid hormone excess accelerates development of the skull and might lead to craniosynostosis, while thyroid hormone deficiency causes delayed craniofacial development resulting in a larger head circumference [26]. CH children in our study had a mean head circumference greater than average at birth with a downward growth trend. A similar result has been reported already in 1985 [27]. In our study, the children born in the 1980s, thus receiving lower LT4 supplementation dose, tended have a slightly larger mean head circumference than children with higher dose, although this did not reach statistical difference. Similarly, earlier studies have shown that patients who are treated with a lower dose of LT4 have greater head circumferences than the reference populations whereas the head circumference seems to be normal when treated with higher doses [17, 25, 28]. Other studies, on the other hand, have shown relatively large head circumferences, not depending on the initial dose or the severity of the disease in early childhood [10, 24]. In some studies, the etiology and severity of the disease have affected head circumference [18, 29]. All our groups had similar baseline thyroid function laboratory results. Thus, differences in the severity of the disease between our groups are unlikely.

In Finland, the screening sample is taken from the umbilical cord blood as opposed to a heel prick. Therefore, the treatment was started very early, on average at 5.9 days in the 1980s and in 2010s as early as 3.5 days. Earlier studies have shown that TSH rapidly normalizes during the first month of life if the currently recommended dose of 10–15 μg/kg/day is used [8, 25, 30]. We showed that TSH remained high in patients born in the 1980s through the first 2 years of age. This phenomenon has been found before in an earlier study where a group treated with 25 μg/day (comparable to our treatment regimen in the 1980s) had a significantly poorer reduction in median TSH [24]. In children born in the 2000s and 2010s, TSH rapidly normalized but it frequently dropped to subnormal levels.

Parents reported significantly more symptoms of any kind during visits with subnormal TSH. Still, the distribution of symptoms was similar in the groups with low, normal, and high TSH values. Higher doses have been associated with subnormal TSH levels in earlier studies as

well, but they have seldom caused any symptoms [8–10]. Previous studies have shown that tri-iodothyronine (T3)/free-T3 seems to remain in the normal range even though TSH may be subnormal and fT4 supraphysiological [8, 10]. In our study, the mean fT4 was significantly higher for the first 3 months children born in the 2000s and 2010s than in the 1990s, but still within the physiological range for the first year. After this, there were occasional supraphysiological mean fT4 levels in children born in 2000s and 2010s, more so in the 2010s. Median TSH values, on the contrary, were lowest in children born in the 2000s. This is probably due to a clinical protocol used in the 2000s that instructed the families to raise the LT4 dose according to a chart when a specific weight at well-baby clinic visit was reached (see online suppl. Table 12). Currently, the LT4 is adjusted mainly according to the thyroid function test results during the pediatrician visits.

Our results show that low TSH was not necessarily combined to excessively high fT4 values and did not automatically translate to clinical overtreatment. Symptoms of overtreatment or undertreatment are often vague and doctors might be more prone to enquire them when TSH is off the reference range, which might bias the data.

In the 1980s, total T4 was used as fT4 was introduced later on, which is a limitation of this study. Furthermore, the number of patients in the 1980s was smaller than in the other decades. However, our total sample size was large, and treatment was started early in all groups. In addition, the diagnosis and treatment protocols were congruent in all our hospitals, making the data and comparison credible.

We conclude that different LT4 starting doses, ranging from 6.8 to 10.8 μg/kg/day, do not have a major impact on growth of children with CH. However, all groups, regardless of their LT4 dose, showed a slight catch-down growth in linear and head circumference with their weight slightly above average during the first 2 years of life. The lower initial dose of LT4 was associated with significantly higher TSH values throughout the first 2 years of life, while the higher initial doses led to lower, often subnormal TSH values. Yet, this was not usually associated with clinical symptoms of overtreatment or undertreatment but, instead, was mainly a biochemical finding. Whether these differing LT4 doses influence the neurodevelopment of the children as shown in earlier studies and whether the growth and weight gain of CH children normalize in later childhood demand further investigation.

Statement of Ethics

This retrospective study was approved by the Ethics Committee of Northern Savo Hospital District (March 13th, 2018; No. 346/2018). Written consent is not required for this study in accordance with national guidelines.

Conflict of Interest Statement

The authors declare no conflict of interest.

Funding Sources

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Author Contributions

Laura Niuro, Emmi Danner, Jukka Kero, Liisa Viikari, Hanna Huopio, Jarmo Jääskeläinen, and Harri Niinikoski contributed to conception and design of the study and to the interpretation of data; Emmi Danner and Laura Niuro to the acquisition of data; Laura Niuro to the analysis of data and drafted the article; and all other authors have revised it critically for important intellectual content. All authors have approved the final version.

Data Availability Statement

On ethical and legal grounds the patient data are not publicly available. Further inquiries can be directed to the corresponding author.

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