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# Different FT3/TSH correlation in acquired and congenital hypothyroid patients reveals a different hypothalamic set-point

Marco Russo | Damiano Gullo | Dario Tumino | Daniela Leonardi | Pasqualino Malandrino | Francesco Frasca

Endocrinology, Department of Clinical and Experimental Medicine, Garibaldi-Nesima Medical Center, University of Catania, Catania, Italy

**Correspondence**
Francesco Frasca, Endocrinology, Department of Clinical and Experimental Medicine, Garibaldi-Nesima Medical Center, University of Catania, Via Palermo 636, 95122 Catania, Italy.
Email: f.frasca@unict.it

## Abstract

**Objective:** To understand differences in thyroid hormone replacement therapy with levo-thyroxine (L-T4) between acquired and congenital hypothyroid (CH) patients.

**Design:** We compared biochemical thyroid parameters between euthyroid subjects (EU) and both CH adult patients and thyroidectomized patients (TP) under replacement therapy.

**Patients and Measurements:** A retrospective analysis was performed on a series of 98 consecutive adult CH patients (27 males and 71 females) with a median age of 24 years (range 18–58). Serum TSH, FT3, FT4, L-T4 dose and body weight were assessed. For comparison purposes, large series of 461 TP for thyroid cancer and 1852 EU followed at our Thyroid Clinic were used as control groups.

**Results:** The daily weight-based L-T4 dose was significantly higher in CH than TP group (1.9 vs. 1.7 mcg/kg, $p = .03$). FT3/FT4 ratio was significantly higher in the EU group, intermediate in CH and lower in TP groups (0.32, 0.28 and 0.24, respectively). Linear regression analysis displayed an inverse correlation between FT4 and TSH in all the groups. An inverse correlation between FT3 and TSH was observed in the TP group, but not in the EU and CH group suggesting that CH patients, under replacement therapy, display biochemical thyroid parameters similar to EU subjects.

**Conclusions:** Adult CH patients require a higher daily L-T4 dose than adult TP. However, the different correlation of TSH and FT3 values between CH and TP patients suggests an adaptive and different hypothalamic–pituitary–thyroid axis regulation that may depend on the early timing of the onset of hypothyroidism in CH.

KEYWORDS

congenital hypothyroidism, deiodinase, levo-thyroxine therapy, replacement therapy, T3/T4 ratio

## 1 | INTRODUCTION

Congenital hypothyroidism (CH) is the most frequent endocrine disease present at birth (1/2000 newborn).[1] CH is due to a defect in the developmental process of the thyroid gland during foetal life in 80%–85% of cases, resulting in either absence of any thyroid tissue (athyreosis) or a hypoplasic/ectopic gland. Less frequently (15%–20% of cases), genetic defects in thyroid hormones synthesis may result in a properly developed but nonfunctioning thyroid gland.[2]

Oral administration of levo-thyroxine (L-T4) is the therapy of choice in both congenital and acquired hypothyroidism and the L-T4 dose is based on the tissue requirement of thyroid hormone in hypothyroid patients.[3–5] Several studies reported that adult CH patients require a higher weight-based L-T4 dose than adult-acquired hypothyroid patients. Moreover, compared to adult hypothyroid subjects, many CH patients exhibit higher serum TSH levels despite normal serum FT4 and FT3 levels.[6–8] This apparent 'resistance' to L-T4 has been attributed to an altered hypothalamus–pituitary feedback set-point to T4 levels.[9,10]

The purpose of this study is to evaluate the L-T4 requirement dose and biochemical thyroid parameters in adult CH patients, in comparison with adult thyroidectomized subjects under L-T4 replacement therapy and euthyroid subjects (EU).

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

We retrospectively evaluated the medical records of a consecutive series of 98 adult CH patients (27 males and 71 females, median age 24 years, range 18–58 years) followed at the Thyroid Clinic of the Garibaldi Medical Center, University of Catania from 2000 to 2017. Clinical and biochemical parameters (body weight, age, serum TSH, FT3 and FT4 levels, FT3/FT4 ratio, L-T4 dose) of each patient were recorded. All patients were treated with the same brand of L-T4 preparation. Exclusion criteria were: medication interfering with L-T4 absorption, severe comorbidities and gastrointestinal disease (atrophic gastritis and coeliac disease). Biochemical data of CH adult patients were collected after the achievement of a stable condition of euthyroidism (data were extracted from the database when serum TSH levels ranged between 0.5 and 4.0 μU/ml). For each patient, blood collection for laboratory measurements was done in the morning before ingestion of L-T4 therapy.

Among the entire group of patients, 45 were affected by thyroid agenesis, 10 by thyroid hypoplasia, 26 by thyroid ectopia, and 17 patients were with a nonfunctioning eutopic thyroid gland. The control group included 461 athyreotic patients after total thyroidectomy for thyroid cancer (TP group) in follow-up at our Thyroid Clinic and a consecutive series of 1852 (EU group), retrospectively study.[11] Control group patients and the CH group did not differ in age and weight from each other. TP group patients were followed at our Thyroid Clinic and were treated with L-T4 monotherapy to maintain TSH within the normal range (0.5 and 4.0 μU/ml). To ablate residual thyroid tissue, 33% of TP group patients were treated with 131-Iodine. All patients were disease-free from thyroid carcinoma as displayed by serum thyreoglobulin <0.5 ng/ml and a negative neck ultrasonography scan.

### 2.2 | Ethical approval

All procedures involving human participants were in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration as revised in 2013. Our retrospective study, with no patient identification, did not require the approval of the Ethical Committee. However, the study was carried out according to the recommendations of our IRB for the retrospective study.

### 2.3 | Laboratory assays

All hormone measurements were performed in our hospital laboratory. Serum TSH, FT4 and FT3 were measured by automated microparticle enzyme immunoassays (Abbott AxSYM-MEIA) with interassay coefficient of variation of less than 10% over the analytical ranges of 0.03–10.0 μU/L for TSH, 5.15–77.0 pmol/L for FT4 and 1.7–46.0 pmol/L for FT3. The within-run and between-run precisions for the TSH, FT4 and FT3 assays showed coefficients of variation <5%.

### 2.4 | Statistical analysis

All data are expressed as the median and interquartile range (IQR, 25th–75th quartiles). Correlation between variables was assessed using Spearman's coefficient; *T*-test was used for continuous variables normally distributed, and Mann–Whitney test was used for variables not normally distributed. To evaluate variables distribution, the Shapiro–Wilk test was preliminarily performed. $p < .05$ were considered statistically significant. Data were analysed with the Prism software package (GraphPad).

## 3 | RESULTS

### 3.1 | Comparison of T4 dose and thyroid hormone levels in CH and TP patients

Clinical and biochemical features patients are summarized in Table 1. Median serum TSH levels in CH group (1.5 μU/ml, IQR 0.9–2.1) were not different compared to TP group (1.2 μU/ml, IQR 0.6–2.4) and EU group (1.4 μU/ml, IQR 0.6–2.1). Serum FT4 levels were significantly higher in CH group (16.7 pmol/L, IQR 14.7–19.3) than EU group (13.5, IQR 11.6–15.4) ($p < .05$) but not significantly different than TP group (15.4 pmol/L, IQR 14.2–18.0). In contrast, serum FT3 levels

**TABLE 1** Clinical and biochemical characteristics of congenital hypothyroid (CH), thyroidectomized (TP) and euthyroid (EU) subjects.

| | CH | TP | EU |
|---|---|---|---|
| No. of subjects | 98 | 461 | 1852 |
| F/M | 2.63 | 4.42 | 4.14 |
| Age (years) | 24 (20–33) | 27 (23–35) | 25 (21–34) |
| Weight (kg) | 67 (56–75.8) | 69 (59.8–80) | 68 (51–81.5) |
| Daily weight-based L-T4 (μg/day/kg) | 1.9 (1.7–2.1) | 1.7 (1.5–2.0)* | |
| TSH (μU/ml) | 1.5 (0.9–2.1) | 1.2 (0.6–2.4) | 1.4 (0.6–2.1)** |
| FT4 (pmol/L) | 16.7 (14.7–19.3) | 15.4 (14.2–18.0) | 13.5 (11.6–15.4)*,** |
| FT3 (pmol/L) | 4.5 (4.2–4.9) | 3.8 (3.2–4.3)* | 4.5 (3.9–5.0)** |
| FT3/FT4 ratio | 0.28 (0.23–0.30) | 0.24 (0.20–0.27)* | 0.32 (0.28–0.38)*,** |

*Note*: Data are expressed as median (interquartile range 25%–75%).

*$p < .05$ versus CH; **$p < .05$ versus TP.

were similar between CH and EU (4.5 pmol/L, IQR 4.2–4.9 and 4.5 pmol/L, IQR 3.9–5.0, respectively) groups but higher than TP (3.8 pmol/L, IQR 3.2–4.3) group ($p < .05$). FT3/FT4 ratio was higher in EU group (0.32, IQR 0.28–0.38) than CH patients (0.28, IQR 0.23–0.30, $p < .05$) and TP group (0.24, IQR 0.20–0.27, $p < .05$). Daily weight-based L-T4 therapy was significantly higher in CH group than TP group (1.9 μg/day/kg, IQR 1.7–2.1 vs. 1.7 μg/day/kg, IQR 1.5–2.0 $p = .03$), despite the (not significantly) higher TSH level.

### 3.2 | Comparison of TSH response to thyroid hormones in CH and TP patients

To explore the sensitivity of CH to the effects of thyroid hormones, we evaluated the negative feedback of thyroid hormones on the hypothalamic–pituitary axis. Linear regression analysis revealed that in the CH patient group, TSH serum values were inversely related to serum FT4 values ($r^2 = 0.4037$ $p < .01$), but not with the FT3 serum values ($r^2 = 0.0209$ $p = .15$) (Figure 1), with a trend similar to that observed in the EU group. This pattern was different to that reported in TP groups, where serum TSH was inversely correlated to both with serum FT4 ($r^2 = 0.09$ $p < .01$) and serum FT3 ($r^2 = 0.06$ $p < .01$) as previously reported from Gullo et al.[11]

## 4 | DISCUSSION

The daily L-T4 dose in hypothyroid patients is approximately 1.4–1.8 mg/kg/day.[12,13] Although the major determinants of L-T4 dose are related to body mass,[14,15] other factors may be also involved, including age, body size and the absence of residual thyroid function.[16,17] Moreover, several factors may influence TSH, FT4 and FT3 concentrations, including food, drugs, enteral absorption, sex, sampling time, age and cigarette smoking.[18–20] In addition to all these factors, the genetic background may be also relevant.[21]

Several reports indicate that the T4 daily dose is higher in CH than in TP patients.[6–8] Although this observation is well established, the mechanisms underlying the increased T4 requirement in CH patients are still under debate. Newborns and children with CH display median serum TSH levels above the reference range despite serum normal FT4 levels, while TSH levels within the reference range may be associated with higher FT4 concentrations.[6–8] These observations were obtained in both children and adolescents and suggest that increased L-T4 requirement occurs at an early age.[9,22]

In this paper, we confirm that adult CH patients require a higher T4 daily dose and have higher levels of serum FT4 despite higher TSH, at variance with patients who became hypothyroid later on. These data suggest that, in CH patients, a higher amount of FT4 is required to obtain a normal level of TSH. This observation is in accordance with the hypothesis of a certain hypothalamic resistance to thyroid hormones.[10] In line with this view, it is interesting to note that, in CH patients, thyroid hormone set-point, including FT4, FT3 and TSH levels, are different than those of TP patients who became hypothyroid later in life. This difference cannot be attributed to the presence of residual functioning thyroid tissue as the TP patients included in the study were negative for thyroglobulin and neck ultrasonography scan. It is reasonable to suppose that CH patients may require a higher L-T4 replacement dose because the thyroid hormone deficiency in embryonic life, during the maturation of hypothalamic–pituitary–thyroid axis, may have determined a different set point. This hypothesis is supported by two in vivo observations: (1) rats, who were transiently exposed to an excess of L-T4 during the neonatal period, display central hypothyroidism with decreased TSH levels and a blunted response to TRH during adulthood[23]; (2) adult CH patients require larger doses of L-T4 to inhibit TSH response to TRH stimulation than adult TP patients.[24]

Several evidence indicate that maternal thyroid balance during pregnancy is important for the setup of hypothalamus–pituitary–thyroid axis[25–27]: excessive functioning of thyroid hormone during pregnancy may alter axis feedback,[26,27] resulting in central

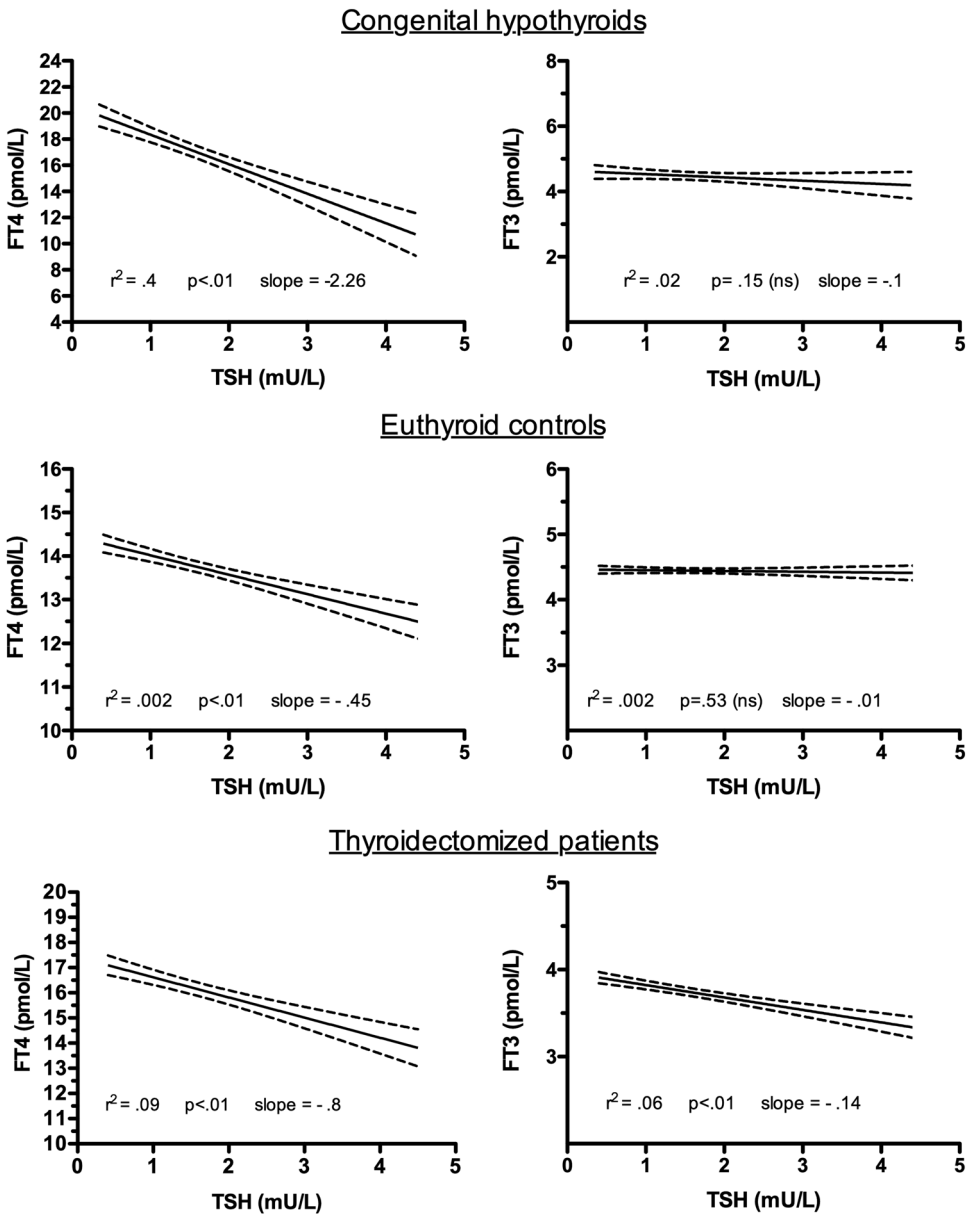


**FIGURE 1** Correlation between TSH and FT3–FT4 in congenital hypothyroid patients, euthyroid controls and thyroidectomized patients. $R^2$, slope and $p$ values are reported in the graph.

hypothyroidism in infants.[25] On the other hand, an increased TSH secretion is present in 43% of CH infants and persists in 10% of late infants, suggesting a hypothalamus–pituitary resistance in these subjects.[9]

Studies evaluating the effect of either L-T4 or L-T3 on peripheral tissues did not find any difference between TP and CH adult patients in terms of cholesterol, triglycerides and SHBG levels.[24] Hence, it is reasonable to suppose that exposure to inappropriately low or high levels of thyroid hormones, before the hypothalamic–pituitary–thyroid axis maturation, may alter its set point leading to either increased or decreased sensitivity to thyroid hormone feedback, respectively.

Although studies evaluating the correlation between FT4 and TSH in CH at different ages are numerous, studies evaluating FT3 and TSH are scanty. In this report, similarly to a retrospective survey of the young Japanese population,[28] we observed a lower FT3/FT4 ratio in CH than in EU patients; nevertheless we also found higher FT3 levels and FT3/FT4 ratio in CH than in TP patients. These data suggest that CH patients may have different regulation of biochemical thyroid parameters under replacement therapy than TP patients. Several in vivo studies suggest that the lower FT3/FT4 ratio in TP patients may be due to a 'dissociation' of type two deiodinase (Dio2) activity between the peripheral tissues and hypothalamus–pituitary[29,30]: in the periphery ubiquitination/degradation activity of Dio2 is increased in response T4 exposure, leading to a reduced FT3 production; in hypothalamus–pituitary ubiquitination/degradation, the activity of Dio2 is reduced

independently of T4 exposure to allow an efficient TSH suppression.[31,32]

However, a certain degree of hypothalamus–pituitary Dio2 ubiquitination cannot be excluded in TP patients because the FT4/TSH correlation curve displays a lower slope than EU subjects.[11] This hypothesis is reinforced by the observation that, at variance with EU subjects that do not display an evident correlation between FT3 and TSH levels, TP patients show a significant inverse FT3/TSH correlation, suggesting a direct TSH suppression by T3 due to a defective T4 to T3 conversion at the hypothalamus–pituitary level.

At variance with TP patients, CH patients do not display FT3/TSH correlation, similarly to the EU subject. This different behaviour of TSH response to T3 between CH and TP patients may be explained by the increased hypothalamus–pituitary Dio3 expression in CH patients, which may cause a reduced TSH suppression by T3.[33] On the other hand, hypothalamus–pituitary Dio2 ubiquitination in CH may be similar to that observed in TP patients, thereby leading to a similar increase in FT4 levels and a reduced slope in FT4/TSH correlation curve.

In conclusion, at variance with TP patients, CH patients are apparently more resistant to thyroid hormones at the hypothalamus–pituitary level as observed by the FT4/TSH correlation curves. On the other hand, both FT3/FT4 ratio and FT3/TSH curves suggest better deiodination than TP patients, suggesting that combined T4/T3 therapy in CH adults patients may not be necessary, whereas a higher dose ofL-T4 is required to keep an adequate level of thyroid hormones. These results should be validated in larger CH patient groups and in tissue models by deiodinase expression/activity evaluation.

## AUTHOR CONTRIBUTIONS

Marco Russo, Pasqualino Malandrino, Dario Tumino, Daniela Leonardi, Damiano Gullo and Francesco Frasca treated the patients, gathered data and drafted the manuscript. Damiano Gullo and Francesco Frasca critically reviewed the manuscript. All authors contributed to the conception of the work and approved the final version of the manuscript.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## ORCID

*Marco Russo* http://orcid.org/0000-0001-5151-9417
*Dario Tumino* http://orcid.org/0000-0003-1021-6692

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