Levothyroxine Treatment for Congenital Hypothyroidism Based on Thyroid Function: A 10-Year Clinical Cohort Retrospective Study

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Research Article

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Abstract

Objective

To explore the appropriate dosage of levothyroxine treatment for congenital hypothyroidism patients based on thyroid function.

Methods

116 patients who were regularly followed up in our endocrine clinic during January 2010 to December 2020 were allocated in 4 groups in terms of their thyroid function (group A: TSH ≥ 100mIU/L, group B: 20mIU/L ≤ TSH<100mIU/L, group C: 4.6mIU/L<TSH<20mIU/L while free thyroxine (FT4)<6.6pmol/L, group D: 4.6<TSH<20mIU/ while FT4>6.6pmol/L). The initial dosage of levothyroxine was individualized given to each patient based upon their TSH level and adjusted according to their thyroid function at every follow-up time point. The levothyroxine dosage at each time point of groups was compared, the thyroid function after treatment, physical and neurological development of different groups were also assessed.

Results

Except for the first month after initial levothyroxine treatment, there was a statistical difference in thyroid function between groups ($p < 0.05$), and some patients hadn't reached the normal level, in the following time points, after individualized dosage adjustment, all patients achieved the normal thyroid function, moreover, the difference of levothyroxine dosage was significant between four groups ($p < 0.05$) and positively correlated with the severity of disease. Although there were statistical differences in neurological development between groups ($p < 0.05$), they were all within the normal range.

Conclusion

Compared to recommend dosage, individualized Levothyroxine dosage could also obtain the same therapeutic effect while may reduce the risk of drug overdose.

Background

Congenital hypothyroidism (CH) is a common endocrine disease with an incidence of 1:2000 to 1:4000 in newborns, which is one of the most common preventable causes of intellectual disability worldwide(1). With respect to the growth and development of newborns and infants, thyroid hormones are indispensable, specifically for their neurological development(2, 3). Thyroid hormones participate various physiological processes like the formation and migration of neurons, the formation of axons and dendrons, the formation of medullary sheath, the development of synapses as well as the regulation of some specific neurotransmitters both in fetal period and childhood(2). Owing to thyroid hormones deficiency, CH patients could develop severe intellectual disability, there is an inverse relationship between age at treatment initiation and intelligence quotient (IQ) later in life, so that longer the condition goes undetected and untreated, the lower the IQ. Therefore, prompt identification and treatment of infants with CH is essential to assure normal growth and neurodevelopmental outcome. Oral levothyroxine is the first choice for CH treatment and the initial dosage is 10 ~ 15 μg/kg as recommended to make the serum FT4 (or T4) concentration in the upper one-half of the pediatric reference range and the serum TSH in the normal range of age as soon as possible(4). Neonates who have markedly elevated TSH (TSH > 40) in newborn screening should be treated with levothyroxine immediately that no need for confirmative test while patients with a TSH in a range of 20mIU/L ~ 40mIU/L or within 6mIU/L ~ 20mIU/L but with a low FT4 should also be treated with levothyroxine(5). However, for those infants who have a mild elevated TSH within a range of 6mIU/L ~ 10mIU/L and have a normal FT4 concentration, the intervention remains controversial(6–8). Although levothyroxine therapy has been considered as a safe, effective method for CH treatment, the drug overdose is an unavoidable issue in clinical practice. So far, there is no widely recognized guidelines or protocols for levothyroxine precise dosage based on CH severity and the research regarding the levothyroxine dosage adjustment during therapeutic phase are also rare. The present study aimed to explore the variations of levothyroxine dosage in patients with different TSH levels and to provide some help for clinical practice in CH management.

Materials And Methods

Study design, population, and data collection

Patients during January 2010 to December 2020 who were regularly followed up in our endocrine clinic were enrolled in this study. All legal guardians had been informed and signed the informed consent; this study was approved by the research ethics committee of The First People's Hospital of Yunnan Province. The inclusion criteria were as follows: (1) Patients who were diagnosed with congenital hypothyroidism in terms of *Consensus statement on the diagnosis and management of congenital hypothyroidism* issued by the Subspecialty Group of Endocrinologic, Hereditary and Metabolic Diseases, The Society of Pediatrics, Chinese Medical Association(9) (2) with a gestational age between 37 to 42 weeks (3) having complete medical record and (4) follow-up regularly. The exclusion criteria were as follows: (1) Preterm infants; (2) incomplete medical record; (3) irregularly follow-up; (4) refuse to join this study and (5) being complicated with other inborn errors. The flow chart of study design is presented in Fig. 1.

Patient classification

Patients were categorized into four groups based on their thyroid function: Patients with a TSH level > 100mIU/L were as group A, 20mIU/L ≤ TSH < 100mIU/L as group B, 4.6mIU/L<TSH<20mIU/L while FT4<6.6pmol/L as group C and 4.6<TSH<20mIU/L while FT4≥6.6pmol/L as group D (which is defined as subclinical hypothyroidism, whose TSH persistent elevated after two consecutive recheck.)

Institutional regime of levothyroxine replacement therapy in our unit

For group A patients, whose TSH was above or equal to 100 mIU/L, were received 10–15μg/kg.das the initial dose which was at the lower limit of the recommended dosage, patients in group B with a moderate elevated TSH (20mIU/L ≤ TSH < 100mIU/L) were given a dosage of 4 ~ 8 μg/kg.d and the rest of two groups with a mild elevated TSH (4.6<TSH<20mIU/L) were administered 3 ~ 5μg/kg.d. Whereas, as the specification of levothyroxine is 50μg per tablet, for dividing convenient, it is usually prescribed as like "$1\frac{1}{2}$ Tab or $1\frac{2}{3}$ Tab…"

Data collection

The initial levothyroxine dosage of four groups was collected, whether the TSH level of four groups had reached to the normal range at 1 month after treatment was recorded as well as the difference of physical and neurological development at 1-, 2- and 3-year of life between groups were evaluated and compared.

Thyroid function test

Blood samples of patients were collected, serum was isolated and transferred to our lab for thyroid function test. Time-resolved fluorometry kit (Wallac, Finland) was adopted for TSH test following by manufacturer's manual while T4, T3, FT4 and FT3 were tested by time-resolved immunofluorescence assay (TRFIA) kit (Xin Bo BioTech, China) and analyzed by immunofluorescence analyzer (EFFICUTA, China) strictly following the manufacturer's instruction.

Physical and neurological development evaluation

Growth monitoring was performed at the age of 1-, 2- and 3-year-old conducted by qualified clinicians and the height, weight as well as the head circumference were documented. Gesell development scale score was adopted for neurological development assessment performed at the age of 1-, 2- and 3-year including the evaluation of gross and fine motor development, adaptability and sociability.

Statistical analysis

For continuous variables complying with normal distribution were expressed as mean and standard deviation and assessed by t test while skewed-distribution variables were summarized as medians and interquartile ranges and assessed by Mann-Whitney U test. Categorical variables were demonstrated by frequencies and proportions (%) analyzed by Pearson's chi-square

test or Fisher's exact test. SPSS 26.0 software (Chicago, IL, USA) was employed as statistical processing and two-tailed p value < 0.05 were considered to be statistically significant.

Results

The general characteristics of patients

There was no difference in gender distribution, birth weight, height at birth, head circumference at birth and cesarean section delivery rate between four groups (p > 0.05), the maternal thyroid function abnormal rate (maternal hypothyroidism or subclinical hypothyroidism) was much higher in group A compared to other groups (p < 0.05). The initial TSH screening of group A patients were significantly higher than other groups (p < 0.005) while the rest three groups had no such differences (Table 1).

Table 1
The general characteristics of patients

	Group A	Group B	Group C	Group D	p
Gender					
male (%)	18(48.6)	14(53.8)	8(47.1)	24(37.5)	0.387*
Cesarean section (%)	9(24.3)	4(15.4)	6(35.3)	8(22.2)	0.507*
Maternal thyroid function					
abnormal (%)	14(37.8)	2(7.7)	3(17.6)	3(8.3)	0.004*
Birth weight					
mean ± SD(kg)	3.09 ± 0.23	2.98 ± 0.23	3.17 ± 0.27	2.99 ± 0.28	0.058$
Height at birth					
mean ± SD(cm)	50.1 ± 1.04	50.0 ± 0.77	49.8 ± 1.36	50.02 ± 1.14	0.830$
Head circumference at birth					
mean ± SD(cm)	34.16 ± 0.65	33.98 ± 0.54	33.9 ± 0.71	33.83 ± 0.85	0.269&
Initial TSH screening(mIU/L)					
median (range)	100 (15.5,333)	23.4(8.49,420)	11(4,9)	15(4,237)	0.000&
*Fisher's exact test					
$ One-Way ANOVA					
& Kruskal-Wallis test					

The diagnostic time and thyroid function of patients

All patients were diagnosed at around 1 month of life and there was no difference in diagnostic time point. There was statistical difference in TSH, FT4 between four groups (p < 0.05), what's more, the FT4 level of group A patients were also

significantly lower than other groups (Table 2)

Table 2
Age, TSH and fT4 level of patients at diagnosis

	Group A(37)	Group B(26)	Group C(17)	Group C(36)	F	P
Age(days)	30(20,40)	30(20,37)	30(30,40)	30(22.5,50)	1.8902	0.5955*
TSH (mIU/L)	100(100,111.94)	49.845(30.49,78.36)	11.8(9.8,16.5)	10.6935(7.875,14.8)	100.5532	< .0001*
FT4(pmol/L)	4.01(2.08,5.09)	6.585(4.657,9.15)	5.5(5,5.91)	10.83(9.585,14.3)	72.5549	< .0001*
*Kruskal-Wallis test						

The dosage of levothyroxine at each follow-up point

After being given initial dosage of thyroxine based on the TSH level one month, there were some patients still hadn't reached the normal thyroid function in each group. The levothyroxine dosage at each time point was positively correlated the TSH level and the sequence from high to low was A group > B group > C > D group ($p < 0.05$) (Table 3)

Table 3
The levothyroxine doses at different time points of four groups (μg/kg. d)

Time	Group A	Group B	Group C	Group D	F	p
Diagnosis	9.12 ± 2.43	7.9 ± 2.19	6.28 ± 2.40	4.47 ± 2.03	28.17	< .0001
2-week	8.76 ± 2.68	7.6 ± 2.18	5.19 ± 2.03	4.24 ± 1.93	21.77	< .0001
1-month	7.35(5.81,9.15)	6.96(6.1,8.33)	4.72(4.72,4.72)	3.3(2.47,4.91)	51.4976	< .0001
3-month	5.7(3.99,7.43)	5.15(3.85,5.77)	3.11(3.11,3.11)	2.86(2.08,3.39)	50.793	< .0001
6-month	4.14(3.11,4.9)	3.43(2.94,4.17)	2.67(2.67,2.67)	2.17(1.43,3.01)	40.3017	< .0001
12-month	3.2(2.53,3.89)	2.5(2.31,2.87)	2.21(2.21,2.21)	1.69(1.1,2.5)	38.6064	< .0001
18-month	2.9(2.2,3.57)	2.23(1.64,2.46)	2.07(2.07,2.07)	1.6(1.19,2.12)	28.1057*	< .0001
24-month	2.95 ± 0.92	2.27 ± 1	1.97 ± 0.8	1.58 ± 0.51	10.43	< .0001
36-month	2.5(2.24,3.6)	1.68(1.12,2.99)	1.69(1.69,1.69)	1.22(1.08,1.8)	15.4036	0.0015

The thyroid function restoration of each group

At two weeks after intervention, the TSH level of group A was still higher than the rest three groups otherwise at the following time points, there was no difference between four groups ($p > 0.05$) (Fig. 2a). The FT4 concentration of four groups had no significant difference after treatment ($p > 0.05$), they all gradually increased and stabilized at the normal range in the following follow-up time points (Fig. 2b).

The physical and neurological development of four groups after treatment

After treatment, there was no difference in height, weight and head circumference of four groups ($p > 0.05$) (Fig. 3) Although there was a statistical difference in neurological development between groups ($p < 0.05$) yielded from the Gesell score, they were all within the normal range (Table 4).

Table 4
The Gesell Developmental Score at different ages of four groups

	Group A	Group B	Group C	Group D	F	p
1-year						
Gross motor	89.65 ± 6	90.5 ± 6.85	93.06 ± 5.83	91.42 ± 5.6	1.37	0.2552**
Fine motor	91.08 ± 8.29	93.15 ± 6.69	96.35 ± 5.89	94.42 ± 5.77	2.71	0.0485**
Adaptability	91(86,97)	93(88,98)	96(96,96)	90(89,97)	4.6743	0.1973*
Language	88(82,90)	86(80,90)	95(95,95)	90(87,94)	14.6561	0.0021*
Sociability	90(88,98)	95(88,98)	98(98,98)	92.5(89,98)	8.9311	0.0302*
2-year						
Gross motor	94(90,99)	96(91,98)	92(92,92)	96.5(90,101)	2.7147	0.4377*
Fine motor	94(88,98)	93(89,98)	92(92,92)	97.5(93,98)	5.443	0.1421*
Adaptability	95(89,99)	90.5(87,99)	93(93,93)	99(95,102)	7.9004	0.0481*
Language	84(79,89)	85.5(83,92)	96(96,96)	93(90,96)	24.4284	< .0001*
Sociability	97.5(89.5,101)	94(89,99)	98(98,98)	98.5(92,102)	1.196	0.7540*
3-year						
Gross motor	97.5(89.5,101)	94(89,99)	98(98,98)	98.5(92,102)	10.6981	0.0135*
Fine motor	91.42 ± 8.7	96.5 ± 4.22	96.86 ± 5.71	97.76 ± 5.01	3.8	0.0146**
Adaptability	90(88,94)	97.5(92,99)	95.5(95.5,95.5)	98(93,100)	15.2357	0.0016*
Language	90(88,97)	93(90,93)	95(95,95)	93(90,98)	2.2074	0.5305*
Sociability	93.38 ± 7.19	97.45 ± 5.85	95.93 ± 5.44	95.82 ± 4.53	1.38	0.2576**

*Kruskal-Wallis test

** ANOVA

Discussion

CH is one of the most common preventable causes of intellectual disability worldwide and the first choice of treatment is oral levothyroxine. Thyroid hormones play a critical role in brain and somatic development, specifically for children under 2 years old, their neurological development is highly thyroid hormones dependent(10). Research revealed that thyroid hormones are key factors in the formation and differentiation of neurons that must be constantly available to perform these functions. Therefore, many clinical guidelines recommend using high initial dosage of levothyroxine (10 ~ 15 μg/kg.d) regardless of the causes and severity of congenital hypothyroidism, in order to make the serum FT4 (or T4) concentration in the upper one-half of the pediatric reference range and the serum TSH in the normal range of age as soon as possible(4, 11, 12). However, few researches showed that lower thyroxine dosage than recommended could also obtain the same goal while reduce the risk of thyroxine overdose(11, 13). Some previous studies revealed that excessive serum FT4 level may lead to craniosynostosis (the premature fusion of one or more cranial sutures), developmental-behavioral impairment and attention deficit hyperactivity (ADHD)(13–15). Moreover, it might also cause negative effect on intelligence quotient in puberty(16, 17).

In our retrospective observation, after being individualized given levothyroxine according to their TSH level one month (9.12 ± 2.43□/□.d for A group, 7.9 ± 2.19□/□.d for B group, 6.28 ± 2.40□/□.d for C group and 4.47 ± 2.03□/□.d for D group), among four

groups, there were four patients (10.8%) in group A, one patient (3.8%) in group B, four patients (23.5%) in group C and three patients (8.3%) in group D, hadn't reached the normal TSH level while there were eight patients (21.6%) in group A, one patient (3.8%) in group B and one patient (2.7%) in group D, had a FT4 level beyond the upper limit of normal value. At the following follow-up time point, the dosage of levothyroxine of each patient was individualized adjusted according to their thyroid function, then, their thyroid function was all back to the normal range eventually. Our study indicates that for reducing the risk of levothyroxine overdose, it would necessitate individualized adjustment of levothyroxine dosage. There is no exact dosage for patients with different TSH level by now, but for most patients with mild elevated TSH, low dose thyroxine could make their TSH level back to normal one month after treatment. It is critical to follow up regularly during treatment and monitor thyroid function, adjust the thyroxine dosage as well, to maintain thyroid function in the normal range.

In a research performed by Soliman *et al.* revealed that in forty-five patients, after receiving a high dose of levothyroxine (10 ~ 15μg/kg. d), one fourth developed hyperthyroidism consequently(18). Craven and Frank found that high initial levothyroxine dosage (> 12.5μg/kg.d) may cause hyperthyroidism, after a period of follow-up, more than one half patients had to reduce dosage, so they suggested reducing the initial dosage to avoid overtreatment(19). Nevertheless, with respect to the comparison between individualized treatment and high initial dosage treatment, the relative researches are so rare. By means of clinical retrospective study, we have explored the correlation between levothyroxine dosage and patients' thyroid function as well as the thyroid function restoration time of different TSH level patients after individualized treatment.

An identical high initial dose of levothyroxine for all CH patients has been challenged by Mathai *et al* and they retrospectively explored the variable strategy of the initial dosage of levothyroxine. In their work, they had categorized CH patients by etiology and administered levothyroxine by a dose of 10, 12 and 15□/□.d for patients who were diagnosed with thyroid hormones synthesis disorder, ectopic thyroid and thyroid agenesis respectively. After treatment, they successfully normalized the serum FT4 of all patients within 14 days. What's more, they also demonstrated that lower initial thyroxine dose (9.98 ± 3.19□/□.d) could also make FT4 back to normal within 16 days(20). Another research performed by Bakker *et al.* was carried out in 30 CH newborns who received a dosage of thyroxine range from 4.8 to 11.1μg/kg. d and they found that there was no association between initial dosage and the time of the FT4 normalization, either low dose group(6.4 ± 2.1□/□.d) or high dose group(11.8 ± 1.4□/□.d) had obtained the normal FT4 and TSH at a similar time frame(21). Tuhan *et al* had set three different dosages (6-9.9 □/□.d, 10-11.9□/□.d and 12–17□/□.d) for CH treatment turned out that there was no difference in TSH level at 1 month after treatment(22).

In the present study, all patients had been treated within two months of life and being adjusted the levothyroxine dosage at each follow-up to maintain their thyroid function staying the normal range and there was no difference in physical and neurological development between groups ($p > 0.05$), however, we are unable to tell if these results were due to small sample size, therefore, further prospective, multicenter control study is needed. Although there was statistical difference in the result of Gesell development scale score between groups ($p < 0.05$), they were all within the normal range. As a flood of literature reported, if CH patients are treated within one month of life, they could gain a normal IQ and the longer the hypothyroidism goes undetected and untreated, the lower the IQ(4, 23–25).

In our study, even for those patients who with significantly elevated TSH, the initial dosage of levothyroxine they had received was still lower than recommended whereas they eventually achieved the normal thyroid function and with no any physical or neurological developmental impairment. In summary, the key factor of success treatment for CH is early detection and intervention, rather than high levothyroxine dosage.

Limitations

The present study was retrospective and the sample size was small either, which may lead to unreliable conclusions, furthermore, we had only enrolled the term infant, whereas the prevalence of CH is higher in preterm infants compared to the term neonates thus our work was not universally representative. Given to the importance of precise levothyroxine treatment, more prospective studies are required.

Conclusion

The results of our study are consistent with many similar studies indicating the levothyroxine dosage for CH treatment needs to be reconsidered. We suggest that the initial dosage of levothyroxine should be stratified according to TSH level at the diagnostic time and adjusted align with the dynamic thyroid function of each patient.

Abbreviations

TSH**:** Thyroid stimulating hormone; FT4: Free thyroxine; CH: Congenital hypothyroidism; IQ: Intelligence quotient; T3: Triiodothyronine; T4: Thyroxine

Declarations

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Author contributions

L,L conceptualized this study and reviewed the manuscript; S,H and XL,M wrote the original draft; XL,M collected the clinical data; JH,Y provided the funding support and processed the data statistically.

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Availability of data and materials

The original data sets and materials are not publicly available due to patient's privacy protection purpose but are available from the corresponding author on reasonable request.

Ethics statement

This is a retrospective study and all methods were carried out in accordance with the institutional guidelines and regulations of The Fist People's Hospital of Yunnan Province. The informed consent was signed by legal guardians/parents. The studies involving human participants were reviewed and approved by the Medical Ethics Committee of The First People's Hospital of Yunnan Province (ethical examination approval number: 2013LW001).

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Figures

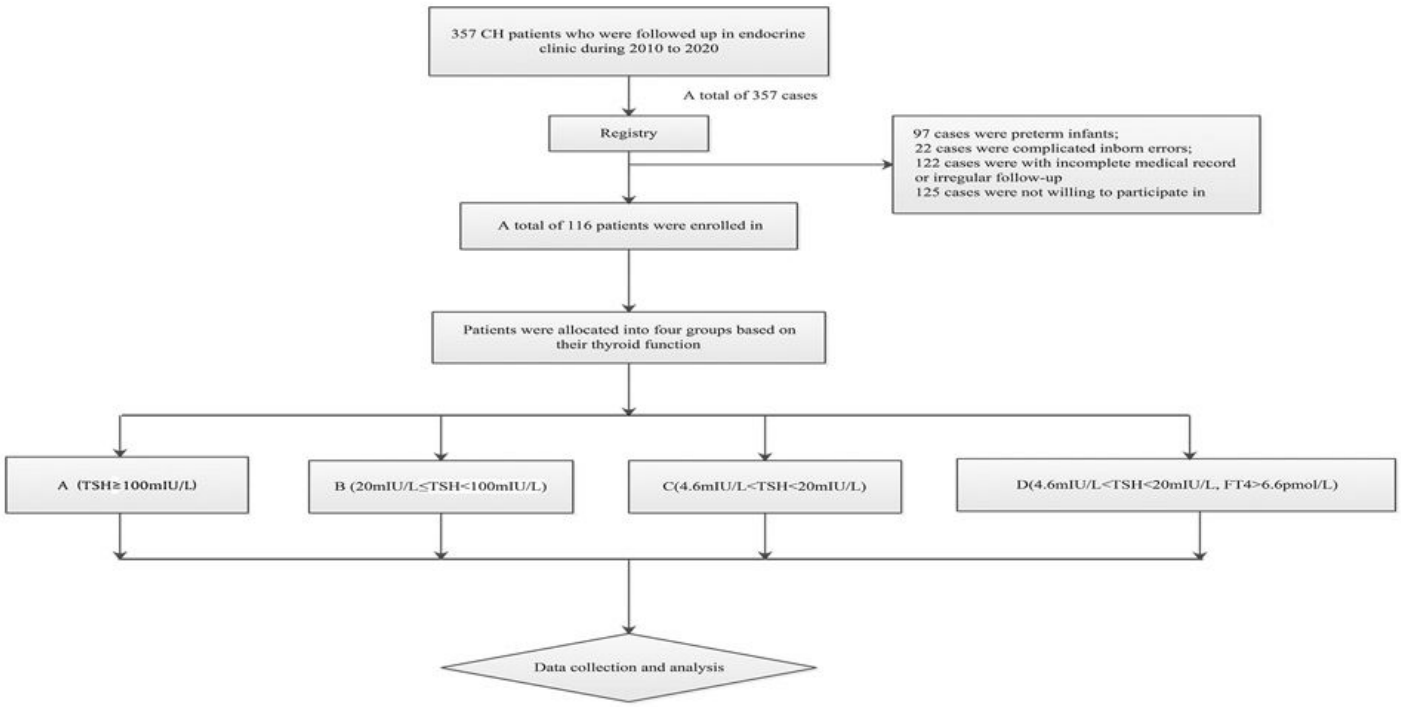

Figure 1

The flow chart of study design

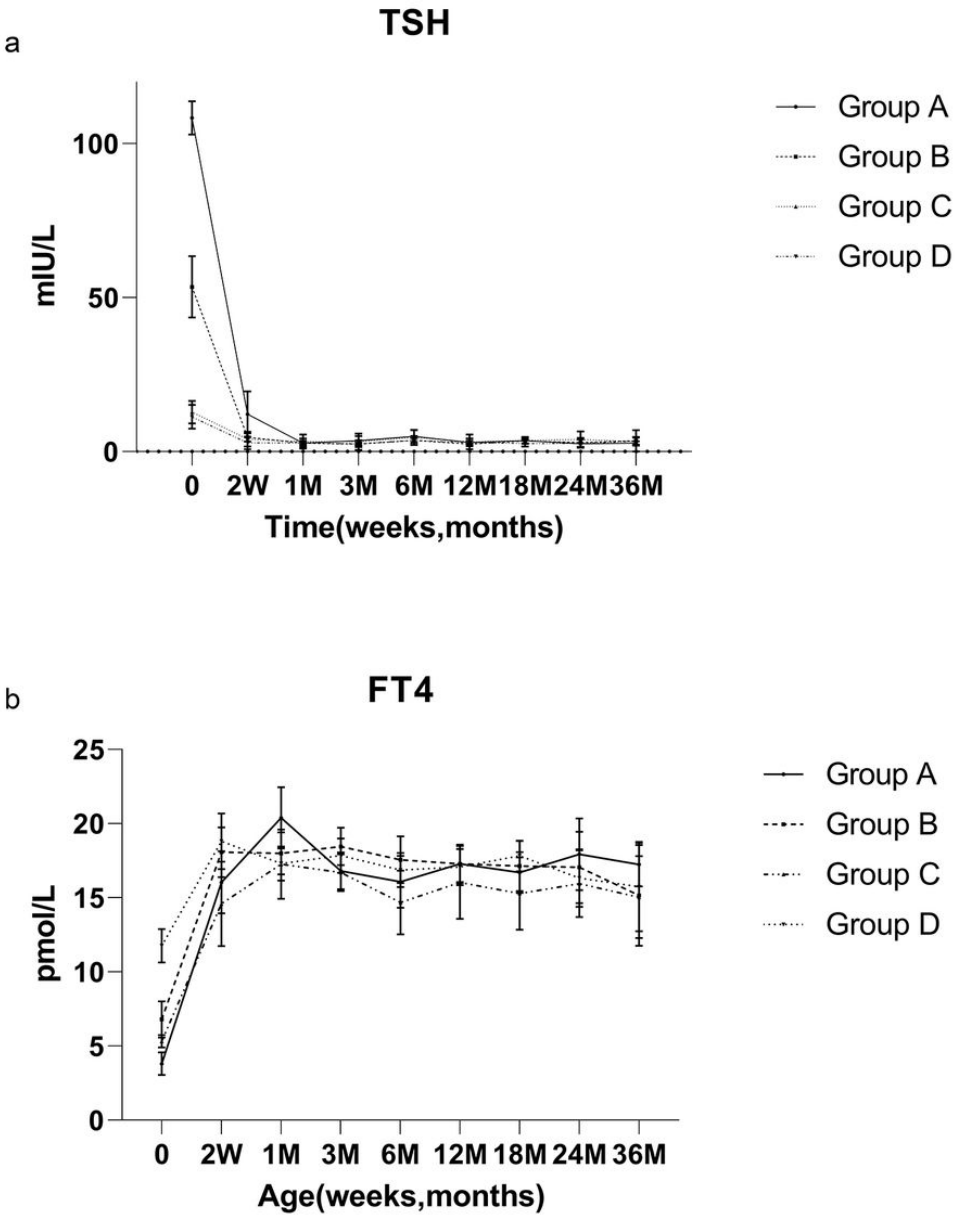

Figure 2

The thyroid function restoration of each group: a. the changes of TSH level of patients after treatment. b. the changes of FT4 level of patients after treatment.

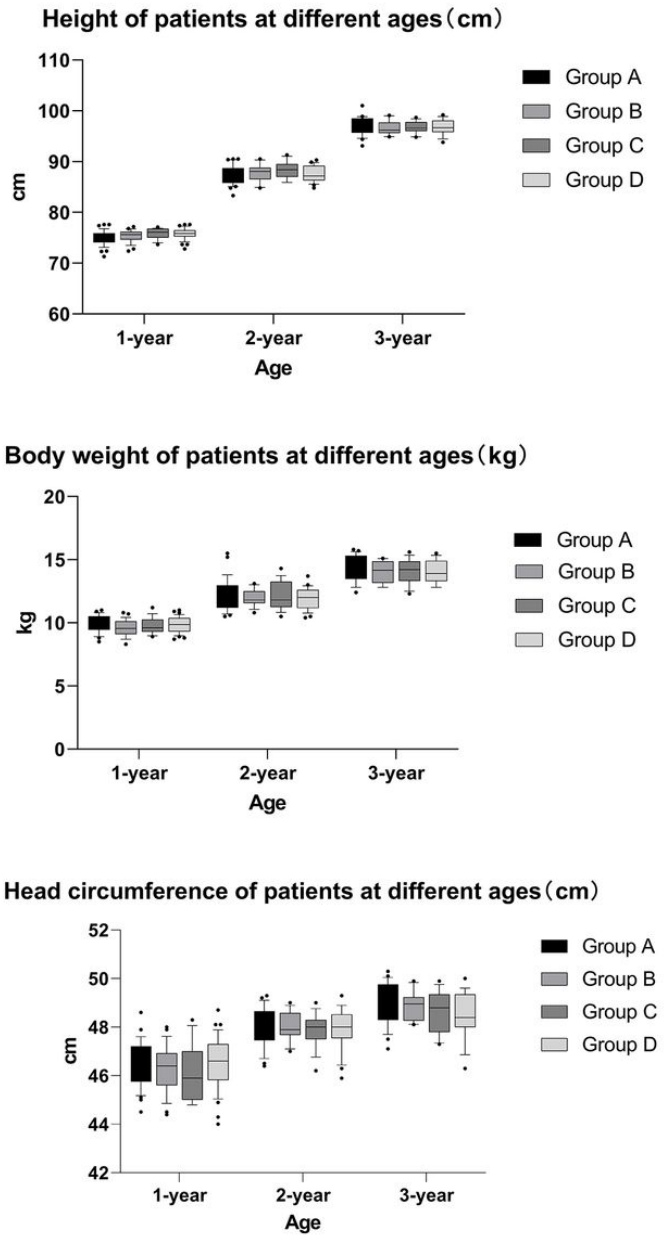

Figure 3

The physical development of patients: There was no difference in weight, height and head circumference between four groups after treatment (p>0.0