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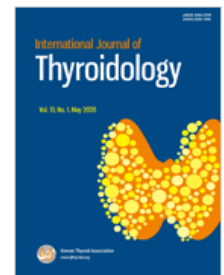
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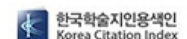
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pISSN 2384-3799  
eISSN 2466-1899

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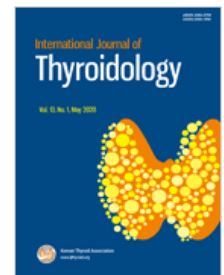
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# Pediatric Quality of Life in Congenital Hypothyroidism: an Indonesian Study

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**Background and Objectives:** Thyroxine is important for brain development. Improper hypothyroid treatment may lead to cognitive and motor impairment, thereby affecting the quality of life. We analyzed the correlation between age at first treatment, length of treatment, initial levothyroxine (LT4) dose, and serum levels of free thyroxine (fT4) and thyroid stimulating hormone (TSH) and pediatric quality of life in patients with congenital hypothyroidism (CH). **Materials and Methods:** This research was a cross-sectional study of 41 children with CH who consumed LT4 for at least 3 months during March 2019-December 2019. The quality of life was assessed from parents' reports using the Pediatric Quality of Life Inventory (PedsQL) generic scale. Spearman correlation analysis was carried out, and statistical significance was set at  $p < 0.05$ . **Results:** A total of 17 of the 41 children were girls. The mean PedsQL scores in physical and psychosocial functioning were 78.12 (68.75-100) and 233.30 (215-251.67), respectively. Age at first treatment was correlated with physical functioning ( $r = -0.501$ ,  $p < 0.05$ ) and psychosocial functioning ( $r = -0.440$ ,  $p < 0.05$ ). The initial LT4 dose was negatively correlated with physical functioning ( $r = -0.568$ ,  $p < 0.05$ ) and psychosocial functioning ( $r = -0.482$ ,  $p < 0.05$ ). The length of treatment showed a positive correlation with physical functioning ( $r = 0.776$ ,  $p < 0.05$ ) and psychosocial functioning ( $r = -0.852$ ,  $p < 0.05$ ). However, the serum fT4 and TSH levels were not correlated with quality of life in children with CH ( $p > 0.05$ ). **Conclusion:** Age at first treatment, initial dose of LT4, and length of treatment were correlated with quality of life in children with CH.

**Key Words:** Congenital hypothyroidism, Child, Quality of life, PedsQL

## Introduction

Thyroid hormone plays an important role in brain development. Hypothyroidism is a state of decreased or non-functioning thyroid gland to produce an appropriate amount of thyroid hormone to fulfil the body's metabolic needs.<sup>1)</sup> It can occur as a result of primary gland failure or inadequate stimulation of the thyroid gland by the hypothalamus or pituitary gland. Congenital hypothyroidism (CH) is one of the most common preventable causes of intellectual disability worldwide.<sup>2,3)</sup> Its symptoms are typically subtle in

infants.<sup>4,5)</sup>

The prevalence of CH is 1:4500 infants in the US, 1:3000 infants in Europe, 1:800 infants in Japan, 12, 6:1000 infants in Iran, and 1:257 in Pakistan.<sup>6-8)</sup> Newborn screening for hypothyroidism was passed by the Ministry of Health Republic of Indonesia in 2014 (PMK No. 78/2014),<sup>9)</sup> and 1:3000 infants was diagnosed with CH.<sup>10)</sup> The newborn baby screening program of CH from 2012 to 2013 at Cipto Mangunkusumo Hospital, Jakarta found that 14 of 3720 patients suffered from peripheral CH.<sup>11)</sup>

Research on factors correlated with quality of life in CH remains inconsistent. This study aimed to evaluate

Received April 28, 2020 / Revised June 19, 2020 / Accepted June 19, 2020

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correlations between age at first treatment, length of treatment, initial levothyroxine (LT4) dose, and serum free thyroxine (fT4) and thyroid stimulating hormone (TSH) levels and pediatric quality of life in patients with CH.

## Materials and Methods

We examined 41 children with CH attending the pediatric endocrinology outpatient clinic during March–May 2019. This study was approved by the ethical committee of the Dr. Soetomo General Hospital, Surabaya, Indonesia (1013/KEPK/III/2019). The diagnosis of CH was obtained at recall on the basis of abnormal serum TSH and fT4 values. The inclusion criteria included children less than 18 years old, with a treatment duration of more than 3 months, and those who agreed to be included in this study.

Age at first treatment, length of treatment, initial dose of LT4, and serum fT4 and TSH levels at diagnosis were evaluated. The parents were interviewed about their child's quality of life using the Pediatric Quality of Life Inventory (PedsQL) 4.0 generic scale, for parents report questionnaire sectors.<sup>12)</sup> The PedsQL 4.0 generic scale consists of 23 items that assess physical functioning (eight items), emotional functioning (five items), social functioning (five items), and school/nursery functioning (five items). The PedsQL

scale evaluated physical and psychosocial (sum of emotional, social, and school) functioning. The score was assessed by summing all the number of items answered on the scales and linearly transformed to 0–100 as follows: 0=100, 1=75, 2=50, 3=25, and 4=0.<sup>13)</sup> The reference range value for thyroid function test was based on age, while doses of LT4 also based on age and body weight.<sup>14,15)</sup> The correlation among age at first treatment, length of treatment, initial LT4 dose, fT4 and TSH serum levels, and PedsQL scale was analyzed by using Spearman's test. p-value less than 0.05 was considered statistically significant. All the statistically significant results were analyzed by SPSS 17.0 software (IBM SPSS).

## Results

The baseline characteristics of the patients are presented in Table 1. Of the 41 subjects, the median of age at first treatment was 12 months, while the length of treatments was 20 months. We had 85% patients with central congenital hypothyroid, while 15% was peripheral congenital hypothyroid. Among our subjects, congenital heart disease and Down syndrome occurred in 11 and 3 children with CH, respectively.

Pediatric quality of life every sector in our patients was shown in Table 2. Our patients have a mean quality of life score of more than 70 points in each sector

**Table 1.** Baseline characteristics

Characteristics		Congenital hypothyroidism (n=41)
Gender	n (%)	
Boy		24 (58.5)
Girl		17 (41.5)
Age of initial treatment (month)	Median (IQR)	12.0 (1.0–80.0)
Length of treatment (month)	Median (IQR)	20.0 (6.0–54.0)
Initial LT4 doses	n (%)	
≤10 mcg/kgBW		12 (29.3)
>10 mcg/kgBW		29 (70.7)
Type of hypothyroidism	n (%)	
Peripheral		6 (14.6)
Central		35 (85.4)
Comorbid	n (%)	
Congenital heart disease		11 (26.8)
Down syndrome		3 (7.3)
Without comorbid		27 (65.9)

IQR: interquartile range

with the highest score in the aspect of psychosocial functioning. The correlation among age at first treatment, length of treatment, initial dose of LT4, serum fT4 and TSH levels and PedsQL are described in Table 3. Age at first treatment, length treatment, and initial LT4 dose were positive correlated to five sectors of PedsQL.

## Discussion

The correlation between age at first treatment and PedsQL in our study was significant. Early diagnosis and treatment yielded a better PedsQL score than late diagnosis and treatment (Table 3). Thus, early treatment (<13 days) with initial LT4 more than 9.5 mcg/kgBW/day could prevent the severity of psychomotor disorders.<sup>16)</sup> By contrast, Pulungan et al.<sup>11)</sup> and Ordooei et al.<sup>17)</sup> reported that the age at first treatment is not significantly correlated with PedsQL. Neonatal CH screening programs allow early detection and treatment.<sup>18,19)</sup> Late diagnosis and improper treatment

may cause serious permanent cognitive and motor deficits, thereby affecting the quality of life, social life, emotions, behavior, and self-esteem of a patient.<sup>3,6,20)</sup>

The length of treatment was found to be correlated with PedsQL in this study, making it the most significant variable that affected the quality of life. Some studies supported this finding.<sup>21,22)</sup>

As shown in Table 1, most of our patients received LT4 dosage >10 mcg/kgBW/day. The correlation between an initial dose of LT4 and PedsQL was significant. There was a controversial issue is the optimal initial dose of levothyroxine (LT4) for avoiding mental retardation with the minimum side effects. Several studies conclude that a high initial dose is beneficial and harmless.<sup>23-26)</sup> Salerno et al.<sup>26)</sup> comparing initial LT4 dose 6.0-8.0 mcg/kgBW/day with 8.1-10.0 mcg/kgBW/day; and 10.1-15.0 mcg/kgBW/day. The results showed that there were no significant differences in height, weight, head circumference, and bone age maturation among the three groups of CH patients. There was no clinical signs nor symptoms of overtreatment observed during follow-up in higher LT4 dosage group. However, high LT4 starting doses rapidly normalize serum TSH concentrations thus resulting in an improvement of the IQ at 4 years of age, even in patients with severe CH at diagnosis.<sup>26)</sup> Another study showed that optimal treatment with LT4 dose above 9.5 mcg/kgBW/day before 13 days of life, achieving euthyroid before third week of life then maintenance FT4 concentrations during the first year

**Table 2.** Pediatric quality of life sectors

Parameters	Median (interquartile range)
Physical functioning	78.1 (68.7-87.5)
Social functioning	75.0 (70.0-80.0)
Emotional functioning	75.0 (65.0-80.0)
School/nursery functioning	83.3 (75.0-91.6)
Psychosocial functioning	233.3 (215.0-251.6)

**Table 3.** Correlation among factors associated with congenital hypothyroidism

Factors	PedsQL				
	Physical functioning	Social functioning	Emotional functioning	School/nursery functioning	Psychosocial functioning
Age at first treatment*	(r=-0.568, p=0.000)	(r=-0.343, p=0.028)	(r=-0.315, p=0.045)	(r=-0.315, p=0.045)	(r=-0.440, p=0.004)
Length treatment*	(r=0.776, p=0.000)	(r=0.719, p=0.000)	(r=0.603, p=0.000)	(r=0.757, p=0.000)	(r=0.852, p=0.000)
Initial dose of LT4*	(r=-0.568, p=0.000)	(r=-0.492, p=0.001)	(r=-0.337, p=0.031)	(r=-0.296, p=0.061)	(r=-0.482, p=0.001)
fT4	(r=0.169, p=0.291)	(r=0.109, p=0.499)	(r=0.202, p=0.206)	(r=0.097, p=0.546)	(r=0.153, p=0.338)
TSH	(r=-0.286, p=0.070)	(r=-0.308, p=0.050)	(r=0.005, p=0.976)	(r=-0.221, p=0.166)	(r=-0.225, p=0.158)

fT4: free thyroxine, LT4: levothyroxine, PedsQL: Pediatric Quality of Life Inventory, TSH: thyroid stimulating hormone  
Statistics were carried out using Spearman's test.

\*Statistically significant correlated.

will achieve normal psychomotor development at 10 to 30 months, irrespective of the severity of CH.<sup>23)</sup> Nonetheless, other authors have shown a dual effect of an initial high dose. A higher starting dose level of LT4 also contributed to more behavior problems in spite of better learning ability.<sup>27)</sup>

Our study showed that patients have high mean of quality of life (Table 2). It may be caused by more patients treated with initial high doses than low doses. Early LT4 treatment (dose >9.5 mcg/kgBW/day) is correlated with mental and psychomotor development.<sup>13,23)</sup> Rovet et al.<sup>27)</sup> showed that underdosage of thyroxine may cause learning disabilities and psychoeducational problems. In addition, Alvarez et al.<sup>28)</sup> and Craven et al.<sup>29)</sup> and Vaidyanathan et al.<sup>30)</sup> reported that LT4 over-treatment may cause attention disorder and inhibitory control at school age and biochemical hyperthyroidism at follow up.

Higher score of quality of life may be due to the subtle clinical manifestations of central CH frequently observed in our study. Central CH is more difficult to diagnose than peripheral CH, and it is commonly diagnosed late.<sup>18)</sup> This finding differed from a previous report, which stated that peripheral CH is more prevalent than central CH.<sup>31)</sup> This difference may be due to the status of our hospital being a national tertiary referral hospital in the east Indonesian region.

In this study, the correlation of the initial serum fT4 and TSH levels with quality of life in CH based on parents' reports was not significant. Klaver et al.<sup>32)</sup> and Kelderman-Bolk et al.<sup>33)</sup> also revealed that TSH and fT4 values do not significantly affect the quality of life. Unlike our results, the findings of other studies indicated a correlation between serum TSH and fT4 levels and PedsQL.<sup>21,22)</sup> The improvement of TSH and fT4 was influenced by treatment compliance, initial doses of LT4, age at first treatment, and severity of the disease.<sup>22)</sup> Several studies showed the decreased quality of life in hypothyroidism.<sup>34,35)</sup> Therefore, newborn screening of CH and regular visits for patients with CH are critical. Regular monthly visits (infants under 6 months of life) are recommended, continued with regular visits every 2 months until 1 year old and every 3-4 months until 3 years old.<sup>2,14)</sup>

Children with CH in our study had some comorbidities. Of the 41 subjects in our study, there were congenital heart disease (26.8%) and Down syndrome (7.3%) co-occurring CH. Razavi et al.<sup>36)</sup> showed congenital anomalies in 20% of 150 infants with CH. Down syndrome, congenital heart disease and developmental dysplasia of the hip were the most congenital malformations co-occurring CH.

We conclude that age at first treatment, initial dose of LT4, and length of treatment are correlated with quality of life in children with CH. Our study had some limitations. We had small sample size in single pediatric endocrinologist out patients clinic centre. We did not evaluate IQ of the CH patient and correlated with QoL. Therefore, multicenter studies are needed to determine the QoL of CH in long term outcomes of treatment.

## Acknowledgments

The authors thank to the patients who participated in the study and the endocrine teams of Dr. Soetomo General Hospital, Surabaya, Indonesia, for the support.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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