

Health-related Quality of Life in Children and Adolescents with Graves' Disease

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Background: Graves' disease is the most common cause of hyperthyroidism in children. In adults, it influences physical and mental health as well as health-related quality of life (QoL) of the patients. However, study of QoL in children has been limited.

Objective: To measure QoL in children with Graves' disease by means of the PedsQL™ and EQ-5D-Y by using Thai version questionnaires.

Materials and Methods: A cross-sectional descriptive study examined 21 Graves' disease patients with the mean age 13.6 ± 3.1 years. All of the participants and their care givers reported the PedsQL™ questionnaires and 20 participants older than eight years completed the EQ-5D-Y questionnaires.

Results: The total mean QoL scores by child- and parent-report PedsQL™ questionnaires were 85.4 ± 17.8 and 82.1 ± 16.3 , respectively. Both reported the lowest scores in the emotional functioning domain. The scores by child and parent reports were not different except in the school domain, in which parents reported lower scores. For the EQ-5D-Y questionnaires, 40% of the children reported problems in the domain of having pain or discomfort and 40% reported problems in the domain of feeling worried, sad, or unhappy. Mean (\pm SD) EQ-5D visual analogue scale value was 86.5 ± 12.0 .

Conclusion: Children and adolescents with Graves' disease reported their lowest QoL life scores in the domain of emotional functioning, followed by the physical functioning domains. However, the total QoL score was not lower than the total QoL scores in the previous studies of general healthy populations.

Keywords: Health-related quality of life; Quality of life; Children, Graves' disease

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Graves' disease is the most common cause of hyperthyroidism in children. It is an autoimmune disorder caused by thyrotropin receptor antibodies (TRAb) stimulating thyrotropin receptors on the thyroid gland, leading to increased production of thyroid hormone. Children with Graves' disease usually present with goiters or symptoms of hyperthyroidism such as palpitation, weight loss, tremor, or anxiety. Unlike adults, children with Graves' disease are usually diagnosed late because some of them present with non-specific symptoms⁽¹⁾.

Health-related quality of life (QoL) is the impact of a disease and its treatment on individual's

life in relevant dimensions⁽²⁾. It has emerged as an informative measure of the treatment outcome of chronic diseases that are not life threatening. The pediatric quality of life questionnaire PedsQL™ was developed to measure children's well-being in domains from their own perception at specific ages^(3,4).

Graves' disease influences physical and mental health as well as QoL^(5,6). Studies in adults showed impaired QoL at diagnosis of patients with Graves' disease and improved QoL after restoration of euthyroidism⁽⁷⁾. However, Swedish and Danish prospective studies showed persistent QoL impairment months and years after euthyroidism^(8,9). Moreover, ophthalmopathy affected QoL negatively, especially in patients with severe or active ophthalmopathy^(10,11).

QoL studies of patients with Graves' disease are usually conducted in adults. There are specific thyroid QoL questionnaires for adults, however there is no specific thyroid QoL questionnaire for children. To date, there is limited data of QoL in children with either hyperthyroidism or Graves' disease⁽¹²⁾. There is only one study showing that children with Graves'

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disease age 8 to 18 years had lower psychosocial and emotional scores than young adults with Graves' disease and lower school functioning scores than healthy population⁽¹²⁾.

The objective of the current study was to measure QoL in children with Graves' disease by means of the Thai versions of PedsQL™ and EQ-5D-Y questionnaires.

Materials and Methods

The present study was a cross-sectional study conducted between September 2020 and February 2021. The authors enrolled 21 children with Graves' disease, aged 5 to 18 years treated at Thammasat University Hospital and were followed up more than one visit. Children who had underlying disease that significantly interfered with QoL, such as cardiovascular disease, asthma, and diabetes mellitus, were excluded. Informed consents were obtained from children's legal guardians and from children aged 12 years or older. The PedsQL™ 4.0 SF-15 Generic Core Scales questionnaires (Thai version) were presented to the patients and their guardians by a study coordinator and completed before clinical examinations. The patients and their guardians completed the questionnaires by themselves or interviewed by the study coordinator. Patients aged eight years or older completed the EQ-5D-Y questionnaires.

Family and social history were obtained from the patients or caregivers. History of hyperthyroidism, duration of disease and treatment, as well as thyroid function tests were reviewed in the medical records.

Questionnaire

Children's quality of life was measured using the Thai version of PedsQL™ 4.0 SF-15 Generic Core Scales and the EQ-5D-Y scale. The PedsQL™ 4.0 SF-15 Generic Core Scales were provided by the Mapi Research Trust. It was an age-specific questionnaire and divided into six age groups. In the current study, child and parent reported for young children of ages five to seven years, children of ages eight to 12 years, and teens ages 13 to 18 years were selected. Parallel questionnaires were completed separately by the children and by their guardians. The PedsQL questions covered the following four areas, physical, emotional, social, and school functioning. The children and their guardians rated how much of a problem each item had been during the past one month. The questionnaires scale using a 5-point Likert scale from 0 for never to 4 for almost always,

except for a 3-point scale with 0 for not at all, 2 for sometimes, and 5 for a lot, for the young child self-report. The scores were reversed and linearly transformed into a 0 to 100 scale in each area. The maximum score, 100 points, indicated good QoL with no problems, while 0 points indicated QoL with nearly constant problems. The total scores for each functional area were the average scores from the answered questions. The scores were not calculated if more than 50% of the questions were unanswered. The total QoL score was the average of the total scores of the four functional areas. The psychosocial health score was the average of the emotional, social, and school functioning scores.

Permission to use the Thai EQ-5D-Y, a child-friendly version of the EQ-5D, was granted by the EuroQol Group. The EQ-5D-Y has two parts, the EQ-5D-Y descriptive system and the EQ visual analogue scale (EQ VAS)⁽¹³⁾. The EQ-5D-Y descriptive system consists of five dimensions as mobility for "walking about", self-care for "looking after myself", usual activities for "doing usual activities", pain or discomfort for "having pain or discomfort", and anxiety or depression for "feeling worried, sad, or unhappy". Each dimension has three levels, with no problems, some problems, and a lot of problems. The EQ VAS records the self-rated health on a vertical, visual analogue scale that takes values between 100 for the best imaginable health and 0 for the worst imaginable health. The respondents were asked to describe today's health in both EQ-5D-Y descriptive system and EQ VAS. The EQ-5D-Y was completed by children aged eight years and older. The authors applied this tool for children up to 18 years, as suggested by the developer, in order to have only one EQ-5D version in the study and to avoid the discontinuity as the adult and child versions are two different instruments.

All analyses were conducted using Stata, version 14.2 (StataCorp LP, College Station, TX, USA). Descriptive statistics were used for demographic data. Paired t-test and Wilcoxon signed-ranks test were used to compare QoL scores between children and parent reports. It was considered to be statistically significant at p-value of less than 0.05.

The present study was approved by the Human Research Ethics Committee of Thammasat University No. 1 (Faculty of Medicine), Project code MTU-EC-PE-1-174/58.

Results

Of the 21 patients enrolled with Graves' disease,

Table 1. Characteristics of the participants (total n=21)

Characteristics	
Sex (male); n (%)	7 (33)
Age (years); mean±SD	13.6±3.1
Type of family; n (%)	
Biparental	15 (71)
Monoparental	6 (29)
Primary care giver; n (%)	
Mothers and/or father	19 (90)
Grandparents	2 (10)
Age at diagnosis (years); mean±SD	10.8±2.3
Duration of disease (years); median (IQR)	2.5 (0.9 to 4.2)
Presenting symptoms; n (%)	
Goiter	17 (81)
Palpitations	16 (76)
Fatigue	16 (76)
Weight loss	14 (67)
Sweating	14 (67)
Tremor	13 (62)
Nervousness	12 (57)
Diarrhea	5 (24)
Ophthalmopathy	4 (19)

SD=standard deviation; IQR=interquartile range

seven were male. Mean age was 13.6±3.1 years and ranged from 7.4 to 17.7 years. Eleven of the patients had been diagnosed at another hospital and referred to the present study hospital for follow-up.

Fifteen patients or 71% had a family history of thyroid diseases. Mean age at diagnosis was 10.8 years. The most common presentation was goiter, followed by palpitations, fatigue, weight loss, and sweating. Ophthalmopathy was presented in four participants. TRAb was analyzed in ten patients during the course of treatment and elevated TRAb was found in nine patients.

All participants had been treated with anti-thyroid drugs. No patients received radioactive iodine ablation nor surgery. Two participants received propylthiouracil before being referred

to the authors' hospital. At the time of the present study, 20 participants were on methimazole, and a participant was medication-free. Medication had been stopped for three of the patients, however, two of them relapsed and anti-thyroid medication was reintroduced. After diagnoses, one-third of the patients were followed up for less than one year, one-third were followed up for one to three years, and one-third were followed up for more than three years. Table 1 shows the characteristics of the participants.

At the time of the present study, 16 patients had euthyroidism, three patients had subclinical hypothyroidism, and two patients had subclinical hyperthyroidism.

Quality of life

The PedsQL and EQ-5D-Y questionnaires were conducted among 21 and 20 children, respectively. The 21 caregivers completed the PedsQL questionnaires.

By the PedsQL, the mean total QoL score from the child reports was 85.4 out of 100, with a range from 49 to 100, and a standard deviation of 14.8. The mean physical and psychosocial health scores from the child reports were 82.6 and 86.3, respectively. The highest score was the mean social functioning score at 91.7, followed by the school and emotional functioning scores. By parent-proxy, the mean total QoL score was 82.1. The mean physical and psychosocial health scores by parent reports were 87.6 and 80.3, respectively. There was no difference in PedsQL scores between child- and parent-reports in any domains except school. The parents reported lower school functioning scores than the patients did. Table 2 shows the QoL results of the participants by self and parents-report using the PedsQL 4.0 generic core scales.

Twenty patients did the EQ-5D-Y and the results are shown in Figure 1. No patients reported a lot of problems in any dimension of EQ-5D-Y. Forty percent of the patients reported having pain or discomfort and 40% reported feeling worried, sad, or

Table 2. Pediatric quality of life (PedsQL) assessment scores in children with Graves' disease by child- and parent-report

PedsQL assessment scores	Child-report; mean±SD	Parent-report; mean±SD	Mean difference; mean±SD	p-value
Total	85.4±14.8	82.1±16.3	3.3±14.2	0.30
Physical	82.6±20.2	87.6±16.4	-5±17.4	0.20
Psychosocial health	86.3±14.1	80.3±17.1	6.1±15.8	0.09
Emotional	79.2±23.2	75.3±20.8	3.9±14.7	0.24
Social	91.7±11.2	91.7±14.2	0.0±18.3	0.99
School	88.1±18.4	73.8±25.9	14.3±26.8	0.02

SD=standard deviation

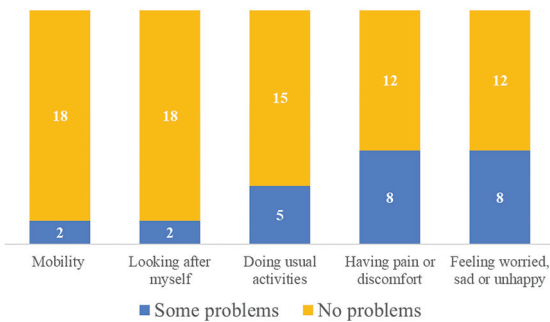


Figure 1. Distribution of EQ-5D-Y dimensions from child-report (n=20).

unhappy. Children younger than 12 years were more likely to report problems in some dimension of EQ-5D-Y. Mean EQ-5D-Y VAS value was 86.5 with 12.0 standard deviation. Mean EQ-5D-Y VAS in children aged 8 to 11 years, 12 to 15 years, and 16 to 18 years were 84.4 ± 14.5 , 89 ± 13.4 , and 87.1 ± 9.0 , respectively.

No influences of gender, type of family, parental marital status, family economy, current thyroid function status, and presence of ophthalmopathy on the total PedsQL scores and ED-5D-Y VAS. Lower emotional functioning scores were reported by parents if their child was younger than 12 years or diagnosed for less than two years at 63.2 ± 21.8 versus 84.4 ± 15.2 and 65.6 ± 21.9 versus 84.1 ± 15.9 .

Age, gender, family economy, and presence of ophthalmopathy were not associated with difficulty in ED-5D-Y dimensions. Patients diagnosed for less than one year reported more difficulties in mobility than patients diagnosed for more than one year. Younger children, aged 8 to 11 years, tended to report more difficulties in EQ-5D-Y dimensions and reported the lowest mean EQ-5D-Y VAS in comparable with the other age groups, but not statistically significant.

Discussion

Studies of adults have shown that Graves' disease leads impairment of physical and mental health and of QoL^(5-7,9). However, the impact of Graves' disease on QoL in children and adolescents is limited⁽¹²⁾. To the authors' knowledge, this is the first single-institution study using both PedsQL and EQ-5D-Y for evaluating QoL in children and adolescents with Graves' disease.

In the current study, the children's average total QoL score by PedsQL was 85.4, which is close to the 82.5 points in the previous report of healthy Thai pupils⁽¹⁴⁾. In addition, the present study had slightly higher psychosocial score at 86.3 versus 80.5, but slightly lower physical score at 82.6 versus 86.2, than

the study of healthy Thai children⁽¹⁴⁾. The differences between the previous study⁽¹⁴⁾ and the present study may be influenced by factors such as study settings in school versus hospital based, and socioeconomic status, which can affect QoL.

The present study findings, which was contrast with the findings from the studies of adults, support the results of a previous study⁽¹²⁾ that suggested that in pediatrics, Graves' disease did not significantly interfere with QoL. A previous subgroup analysis of pediatric Graves' disease patients aged 8 to 18 years in the UK found no more impairment of QoL than in healthy children except in the school domain, but a whole group analysis of persons aged 8 to 30 years showed that Graves' disease decreased QoL in comparison with healthy controls⁽¹²⁾. Children do not share the opinions of adults about the effects of illness on their lives⁽¹⁵⁾.

Previous report of Thai children with chronic diseases such as heart disease, asthma, and thalassemia had mean PedsQL scores of 69 ± 14.8 ⁽¹⁶⁾. While this might appear unsurprising, children with Graves' disease may have potentially better clinical course. Moreover, the present study children reported higher mean total QoL scores than Thai children with respiratory allergic diseases including asthma and allergic rhinitis^(14,17). In comparison to a previous QoL study in Thalassemic patients in the present study hospital conducted in 2019, the children had slightly higher total QoL scores in both child- and parent-reports at 85.3 versus 81.0 and 82.1 versus 78.8, respectively⁽¹⁸⁾.

PedsQL scores in the present study showed minimal impairment due to many factors. Firstly, the majority of the present study children had euthyroidism. Therefore, they might have non-severe disease at the time of QoL assessment. In a previous study, patients with euthyroidism presented less impairment in QoL than a hyperthyroidism group⁽⁵⁾. Moreover, patients with Graves' disease in the euthyroidism phase had higher QoL scores compared with those in the hyperthyroidism phase at the time of diagnosis⁽⁶⁾. Despite no difference in QoL between patients with and patients without euthyroidism was documented in the present study, if the study were large enough, the analysis would be valuable. Secondly, there were only four patients with ophthalmic involvement, and all had mild symptoms. Although ophthalmopathy is a factor involving serious QoL decline, especially if it was severe⁽¹⁰⁾, the present study did not show lower QoL scores in patients with ophthalmopathy.

Looking into specific areas of QoL, the lowest score in the child report was the emotional domain and followed by physical domain. However, emotional and school domains were the two lowest scores by parent-proxy report. These three domains were also found to be low in a previous report⁽¹²⁾. This may be due to emotional instability and limitation of physical function leading to restriction of physical activity, which are common symptoms of thyrotoxicosis. Moreover, frequent school absences, limited activities at school, pain from venipuncture, or even lower self-esteem might influence QoL. Moreover, all except one of the participants was on methimazole at the time of the study. Thionamides usage was a factor affecting lower physical functioning scores in both hyperthyroidism and euthyroidism patients⁽⁵⁾.

PedsQL scores by parent proxy reports correlated with child reports in total, physical, and psychosocial scores, which is consistent with prior research⁽¹⁹⁾. However, no correlation was found in social and school domains. Moreover, parents reported lower QoL in the school domain. The authors speculated that parents and proxies may be more concerned about their children's school performance.

EQ-5D-Y, a simple and easy to use QoL questionnaire, is a valid and reliable tool for both healthy and chronically ill children. The authors could not find any research using EQ-5D-Y for children with Graves' disease. The present study Graves' patients reported more difficulties in pain or discomfort, and worried, sad, or unhappy compared to other dimensions. These mirrored the previous study⁽¹⁸⁾. It might be assumed that the main problems interfering with QoL were emotional challenges.

The present study has limitations. The sample was small, with only 21 children and adolescents. Therefore, it only represented QoL in a particular group of patients with non-severe and short duration disease. It would be of significant use to see if studies of large numbers of patients had similar or varied QoL scores. Another limitation is that there was no standard norm at the time of the present study, therefore, the authors cannot compare QoL between patients and a healthy population. It would be better to have longitudinal QoL data in pediatric Graves' disease. Furthermore, there is a lack of relevant socioeconomic factors and pubertal status. Lastly, the authors used a general QoL questionnaire instead of a thyroid specific questionnaire.

Conclusion

The present study is the first study using the

EQ-5D-Y and PedsQL with Thai pediatric Graves' disease patients. The results showed that children and adolescents with Graves' disease reported the lowest scores in the emotional domain followed by the physical domains. However, the total scores were not inferior to the previous studies of healthy children in Thailand. Physicians must be aware of emotional suffering during diagnosis and follow-up, especially in younger children and in the recently diagnosed children.

What is already known on this topic?

Graves' disease has negative influence on QoL in adult especially during hyperthyroidism phase.

What this study adds?

This study showed that QoL in children and adolescent with Graves' disease was closed to the general healthy children. The lowest QoL scores was in emotional functioning domains, followed by the physical functioning domains.

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Conflicts of interest

The authors declare no conflict of interest.

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