Health-related Quality of Life and its Predictors Among Transfusion-dependent Thalassemia Patients

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Purpose: With regular blood transfusions and modern medical management strategies, transfusion-dependent thalassemia (TDT) patients are currently living into adulthood, but they still suffer from the chronicity of the disease and its complications. This study was aimed to assess the health-related quality of life (HRQoL) scores in pediatric TDT patients compared with healthy controls.

Patients and Methods: The PedsQL 4.0 Generic Core Scales were administered to 80 pediatric TDT patients (aged 5 to 18 y, child self-report) and their parents (parent-proxy report), as well as age-matched and sex-matched healthy controls (80 participants and their parents).

Results: Patients with TDT and their parents rated lower HRQoL scores in all domains (physical, emotional, social, and school functioning) compared with the healthy population ($P < 0.01$). The univariate analysis indicated that the total HRQoL score for children's self-reports was negatively predicted by high ferritin levels and the presence of any complication. The only negative predictor of the total HRQoL score in multivariate analyses was a high ferritin level (> 1800 ng/dL).

Conclusions: This study showed that thalassemia has a negative impact on HRQoL when compared with a healthy population. For a better quality of life, intensive treatment should be applied for complications and high ferritin levels.

Key Words: thalassemia, quality of life, blood component transfusion

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Thalassemia is one of the most common genetic disorders that can be fatal in the absence of treatment.[1] Each year, > 50 000 new patients are born with a severe form of thalassemia worldwide, especially in the Mediterranean Region, Middle East, Indian Peninsula, and Southeast Asia.[2,3] Despite an ongoing hemoglobinopathy prevention program since 2003,[4] thalassemia still remains a major public health problem, especially in middle-eastern, southern, and southeastern parts of Turkey.

With modern medical treatment in the last 2 decades, the mortality and morbidity of thalassemia have been reduced significantly and survival rates have improved.[5,6] However, frequent hospital visits, short stature, school absences, and delayed sexual development still affect the physical, psychological, social, and school performance of these patients.

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The World Health Organization defines health as being not only the absence of disease or infirmity but also a state of physical, mental, and social well-being.[7] Health-related quality of life (HRQoL) is a broad, multidimensional concept that includes domains related to physical, mental, emotional, and social functioning. In clinical practice, the PedsQL 4.0 Generic Core Scales is a modular approach to measuring HRQoL in healthy children and adolescents and those with acute and chronic health conditions.[8,9] It can be assessed in patients and in their parents by self-reports and proxy reports, respectively.[10]

Few studies have examined the factors associated with quality of life (QOL) in children with thalassemia.[11–14] These studies have focused on a heterogenous population affected by different globulin-chain defects and different thalassemia subtypes. Transfusion-dependent thalassemia (TDT) is a group of diseases wherein children are expected to have a much more unfavorable QOL due to iron load, transfusion complications, and disease severity. Publications related to this subject are scarce in the literature.

HRQoL studies on children with thalassemia are limited in Turkey.[15,16] To the best of our knowledge, no such study has been conducted in the southeastern part of Turkey until now. This area has lower socioeconomic status compared with west and north part of Turkey. Previous studies have shown that there might be differences in QOL according to the geographic, sociodemographic, and cultural properties of the area.[17] Therefore, we need to have a baseline evaluation for our patients; in this way we can develop strategies to improve their QOL. This study is designed to assess the HRQoL among TDT patients in southeastern part of Turkey compared with healthy controls. We also aimed to determine the factors that might affect QOL in these patients.

PATIENTS AND METHODS

This cross-sectional study was conducted in Diyarbakir Children's Hospital in the Pediatric Hematology and Oncology Clinic between August 2015 and November 2015. Our hospital is a large regional hospital, in southeast Turkey, providing regular blood transfusions, iron-chelation therapies, and follow-up care for thalassemia patients. TDT patients aged 5 to 18 years and one of their caregivers was enrolled in this study. Similar numbers of age-matched and sex-matched healthy peers with one of their caregivers (taken from the outpatient clinic among the children who had come in for minor ailments) were also enrolled as the control group. Inclusion criteria for patients were being on regular blood transfusions at intervals of 2 to 4 weeks for at least 2 years and having parents who were willing to give an informed consent form to participate. Patients were excluded, if: (a) they had a comorbid condition unrelated to thalassemia or its complications, (b) they were not able to

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communicate in Turkish, and (c) they had undergone stem-cell transplantation. The data were collected by means of a questionnaire when patients came to the hospital for a regular transfusion. The data collection was carried out from August 2015 to November 2015. A trained psychologist interviewed the participants face-to-face. Written informed parental consent and assent of the child were obtained prior to participation in the study after explaining the procedures. The investigation conformed to the principles outlined in the Helsinki Declaration.

The demographic features of the patients and the healthy controls were gathered from the interviews. Medical records and treatment results were reviewed from patients' files. The study was approved by the Ethics Committee of Gazi Yasargil Education and Research Hospital (July 30, 2015/9).

HRQoL was assessed using the PedsQL 4.0 Generic Core Scales (Turkish version) in both groups. Turkish version of this questionnaire was validated by Kabak et al.[15] The 23-item PedsQL 4.0 Generic Core Scales were designed to measure the core dimensions of health, as delineated by the World Health Organization, as well as role (school) functioning.[9,18] The 4 multidimensional scales are physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). The 2 summary scores are the total scale score (TSS) (representing the sum of items over the number of items answered in the physical, emotional, social, and school functioning scales; 23 items) and the psychosocial health summary score (representing the sum of items over the number of items answered in the emotional, social, and school functioning scales; 15 items). Health-related total QOL score were categorized as good (QOL score = 75 to 99.9) and low (QOL score <75) among study population.[19]

Statistical Analysis

The statistical software used for the data analysis in this study was the Number Cruncher Statistical System (NCSS) 2007 (Utah), which is a comprehensive, accurate, menu-driven statistical software package. During the evaluation of data, in addition to descriptive statistical methods (mean, SD), an unpaired t test was used on the comparison of 2 groups of variables with normal distribution. On the comparison of 2 groups of variables with abnormal distribution, the Mann-Whitney U test was used. The Pearson χ^2 test was used on the comparison of qualitative data, and on the comparison of self-reports and proxy reports of thalassemia patients, a paired t test was used. Logistic regression analyses were used to assess the factors that had an impact on HRQoL. A P-value of <0.05 was considered statistically significant.

RESULTS

In total, 80 patients who fit the inclusion criteria were approached during a scheduled visit to determine their interest in participating in the study. All of the patients and their parents accepted and completed the interview, resulting in a 100% response rate. In total, 80 healthy controls with their parents were also enrolled in the study as the control group. The characteristics of the patients/controls and their parents were comparable in both groups in terms of age, sex, education level, living area, family income, and parental education. Demographic values of patients, their parents, and the control group are shown in Table 1.

Patients were put on a regular transfusion schedule at 6 to 168 (median, 14.5) months of age, with a 2 to 4 week interval (median, 3.2). Their pretransfusion hemoglobin (Hb) level was in the range of 69 to 109 g/L (median, 9.1). Patients were put on chelation therapy between 18 and 168 months of age (median, 47.4). All of the patients were on regular chelation therapy with deferasirox. Ferritin levels were between 300 and 8149 (median, 2011) ng/mL. Although hepatomegaly (liver palpable 2 cm below the costal margin) was detected in 25 patients (31.2%), splenomegaly (spleen palpable 2 cm below the costal margin) was found in 24 (30%) of the patients. Of the 80 patients, only 7 (8.7%) of them had been splenectomized. Nineteen patients (23.7%) had ≥ 1 complications related to thalassemia, including severe osteoporosis (n = 12), growth retardation (n = 6), cardiac failure (n = 2), and hypoparathyroidism (n = 1).

Table 2 shows mean scores of the 4 multidimensional PedsQL 4.0 subscales and their summarized TSS and the psychosocial health summary for the thalassemia patients, their parents, and the healthy controls (children and parents). All QOL scores from the patients were statistically significantly lower than those of healthy controls ($P = 0.0001$). The QOL scores of the patients as reported by their parents were also lower compared with those of the healthy controls ($P = 0.001$). The PedsQL 4.0 mean total score, psychosocial functioning score, and subscales score of patient self-report and parent-proxy report were similar ($P = 0.2$ to 0.9).

In univariate analysis, high ferritin levels and presence of any complication related to thalassemia were the variables that associated with low QOL scores (Table 3). In multivariate analysis, high ferritin level was the only variable associated with low QOL scores ($P = 0.014$).

DISCUSSION

The findings of this study showed that patients with TDT had significantly lower HRQoL in all domains when compared with healthy controls. The patients suffered from long-term side effects of anemia, repeated transfusions, and chronic illness, which negatively affected their HRQoL. The mean total score and subscale scores of patients ranged from 70.7 to 83.3 (on a 0 to 100 point scale) in our study. The physical score, followed by school functioning, was the lowest among all. The low physical score could have been due to growth retardation and the negative effect of chronic illness on physical appearance, leading to low performance in daily activities. The patients in this study had school absences at least 1 to 2 times in a month to receive regular transfusions, and more hospital visits were warranted for blood tests and the treatment of complications related to the diseases. These school absences and subsequent lack of energy while performing academic activities had a negative impact on the school functioning domain of patients' HRQoL, as was previously shown in the literature.[11,20] Arranging for transfusions during the evening, overnight, and on weekends would reduce absences from school and would enhance social integration and better school functioning.

Our findings in patients with TDT were in concordance with those found in other children with

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TABLE 1. Demographic Characteristics of Patients With Thalassemia and Their Parents Compared With Healthy Controls

	n = 80		
	Thalassemia Patients	**Healthy Controls**	***P***
Age (month, SD)	123.23 ± 40.17	121.34 ± 42.43	0.773
Sex (n [%])			
Boy	43 (53.75)	45 (56.25)	0.752
Girl	37 (46.25)	35 (43.75)	
Living place (n [%])			
City	15 (18.75)	20 (25.00)	0.616
District	52 (65.00)	49 (61.25)	
Village	13 (16.25)	11 (13.75)	
Duration of education (month, SD)	44.95 ± 33.34	43.76 ± 35.63	0.828
Family income (TL) (n [%])			
0-850	65 (81.25)	64 (80.00)	0.942
850-1700	11 (13.75)	11 (13.75)	
> 1700	4 (5.00)	5 (6.25)	
Caregiver education level (n [%])			
Literate	21 (26.250)	18 (22.50)	0.636
Primary school	57 (71.25)	58 (72.50)	
High school	2 (2.50)	4 (5.00)	

thalassemia[11,12,21] in that the HRQoL was reported to be lower when compared with a healthy population. Ismail et al[11] reported lower QOL in thalassemia patients regardless of sex, age, and ethnicity when compared with healthy population. A study of thalassemia patients in adolescent period by Boonchooduang et al[12] showed lower HRQoL scores in all dimensions compared with healthy counterparts. Ansari et al[13] compared the outcomes of HRQoL obtained from 250 thalassemia patients with 51 controls and found similar results. The median HRQoL scores in all domains were somewhat higher in our patients compared with these studies in the literature,[11–13,21] where the median scores ranged from 55 to 85. In our opinion, this is related to the following factors: first, all our patients were on oral chelator therapy with deferasirox. This means there was no burden from nightly subcutaneous injections of desferrioxamine (eg, painful insertion of the needle, long infusion periods that limit one's activity while using the pump), which was shown to be a risk factor for poor HRQoL in previous studies.[7,22] Second, due to strict quality control of transfused erythrocyte suspensions, none of our patients were suffering from any chronic viral hepatitis, HIV, or other transfusion-derived viral infection. Third, in all the clinical visits, our patients were welcomed by a group of dedicated thalassemia caregivers (a trained pediatric hematologist, a thalassemia nurse, and a trained psychologist whenever needed) who allocated enough time for listening to complaints and providing good communication, taking in the account that, in the literature,[22] HRQoL has been shown to be influenced by the quality of communication of the caregivers in a thalassemia center.

In early studies, children consistently reported their HRQoL to be better than that described by their parents.[14,23] Caocci and colleagues performed a cross-sectional study on a group of 60 thalassemia children and their parents, and reported lower scores in emotional functioning, psychosocial health summary score, and TSS in parent-proxy reports.[14] In our study, parent-proxy reports were in close agreement with patient self-reports. This can be attributed to strong family support strategies in

TABLE 2. Quality of Life in Patients With Transfusion-dependent Thalassemia Compared With Healthy Population (Self-Report and Proxy Report)

	n = 80				
	Thalassemia Patients		**Healthy Control**		
	Mean	**SD**	**Mean**	**SD**	***P***
Self-report					
Psychosocial health summary score	77.69	12.83	93.79	2.87	0.0001
Physical functioning	70.7	18.09	96.64	2.21	0.0001
Emotional functioning	77.5	17.5	96	3.5	0.0001
Social functioning	83.31	19.06	94.75	3.89	0.0001
School functioning	72.25	16.76	90.63	4.01	0.0001
Total scale score	75.94	12.59	94.5	2.38	0.0001
Proxy report					
Psychosocial health summary score	78.21	12.26	92.02	5.38	0.0001
Physical functioning	71.91	20.75	97.19	2.61	0.0001
Emotional functioning	77.69	16.55	93.63	3.56	0.0001
Social functioning	82.69	16.46	94.25	3.57	0.0001
School functioning	74.25	18	88.18	14.36	0.0001
Total scale score	76.63	12.64	93.31	4.21	0.0001

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TABLE 3. Univariate Analyses Related With Low Quality of Life Scores in Thalassemia Patients

	Good QOL (n = 39)	Low QOL (n = 41)	*P*
Age (month; median, SD)	129.1 ± 35.97	117.63 ± 43.49	0.204
Sex (n [%])			
Boy	23 (58.97)	20 (48.78)	0.361
Girl	16 (41.03)	21 (51.22)	
Living area (n [%])			
City	6 (15.38)	9 (21.95)	0.461
District	28 (71.79)	24 (58.54)	
Village	5 (12.82)	8 (19.51)	
Education duration (month, SD)	49.29 ± 30.92	41.29 ± 36.69	0.292
Family education level (n [%])			
Literate	11 (28.21)	10 (24.39)	0.925
Primary school	27 (69.23)	30 (73.17)	
High school	1 (2.56)	1 (2.44)	
Family income (TL) (per month; n [%])			
0-850	32 (82.05)	33 (80.49)	0.972
850-1700	5 (12.82)	6 (14.63)	
> 1700	2 (5.13)	2 (4.88)	
Presence of complication (n [%])			
Yes	34 (87.18)	27 (65.85)	**0.025**
No	5 (12.82)	14 (34.15)	
Age at first transfusion (month; median, SD)	18.38 ± 28.61	10.95 ± 11.07	0.130
Age at start of iron chelation (month; median, SD)	52.72 ± 36.29	42.3 ± 19.86	0.116
Transfusion frequency (per week; median, SD)	3.15 ± 0.63	3.32 ± 0.65	0.258
Pretransfusion hemoglobin value (median SD) (g/dL)	8.88 ± 1.66	8.98 ± 1.19	0.755
Ferritin level (median, SD)	1660.79 ± 1887.18	2520.98 ± 1765.52	**0.038**
Hepatomegaly (> 2 cm below costal margin) (n [%])	11 (28.21)	14 (34.15)	0.567
Splenomegaly (> 2 cm below costal margin); (n [%])	12 (32.43)	12 (32.43)	1
Being splenectomized (n [%])	7 (17.95)	4 (9.76)	0.288

A *P* value < 0.05 is statistically significant are in bold.
QOL indicates quality of life.

our hospital, which increase parents' awareness of the chronicity of their children's disease, including thalassemia camps and public thalassemia education conferences.

Previous studies have shown a correlation between a low Hb level (< 7 g/dL) and impaired HRQoL scores.[19,24] Saha et al[19] conducted a cross-sectional study over 365 thalassemia patients and reported better QOL scores in patients with pretransfusion Hb levels above 7 g/dL. A study of 315 thalassemia patients by Thavorncharoensap et al[24] showed similar results. In our study, the pretransfusion Hb level was not related to the HRQoL level. This could be because the number of patients who had a low Hb level was too small (n = 2, only 5%) to detect a significant difference.

Consistent with the findings from previous studies conducted on children with thalassemia,[11,24] sex was not associated with HRQoL in this study.

The frequency of blood transfusions per year was also not related to HRQoL in this study, as was shown in the literature before by Thavorncharoensap et al.[24] However, this was contradicted by Saha et al[19] and Surapolchai et al,[25] who reported total HRQoL scores were worse among children receiving more regular transfusions.

Although existing evidence indicates that living area, family income, and the education level of caregivers has an impact on the HRQoL of thalassemia patients,[25] this study found no relationship between family socioeconomic features and HRQoL. This contradictory result could possibly be due to the fact that we had a very homogenous population, comprising families with similar sociodemographic features of low income and education.

We found that disease severity, age at disease onset, and age at onset of chelation treatment were not significantly related to HRQoL scores. Similar results have been shown in other studies.[26–28] Ali et al[26] evaluated HRQoL in 43 thalassemia patients and showed that age, splenectomy status, disease severity, or desferrioxamine use were not statistically associated with QOL scores. Torcharus and colleagues conducted a study over 43 thalassemia patients and reported that age at disease onset, pretransfusion Hb level, age, or sex had no significant difference on QOL in these patients. However, Thavorncharoensap et al[24] showed that age at first transfusion, pretransfusion Hb level, and disease severity significantly affected the HRQoL of thalassemia patients in their study.

In our study, patient age was investigated as an influential factor in QOL, but no significant correlation was found, in agreement with the studies by Kaheni et al[29] and Tahmasbi et al.[30] However, in a study by Thavorncharoensap et al,[24] older patients had a significantly better QOL compared with their younger counterparts.

We also did not find any significant correlation between splenectomy and QOL, in agreement with the previous literature.[29,30]

Our results for both univariate and multivariate analyses showed that a high ferritin level was correlated with poor QOL in all domain scores, which was consistent with the literature.[31,32] A higher ferritin level might be indicative of serious iron deposition in vital organs such as the heart, liver, and pituitary glands, leading to severe morbidity and mortality, as have been shown in the literature. The findings of our study showed that a serum ferritin level higher than 1800 ng/mL was associated with a low HRQoL.

Finally, in univariate analyses, in agreement with results reported by Thavorncharoensap et al[24] and Shaligram et al,[33] the presence of complications was correlated with low overall HRQoL scores, but the correlation was lost in multivariate analyses.

CONCLUSIONS

In this study, we showed that patients with TDT and their parents reported all HRQoL subdomains lower than age, sex, and education-matched healthy peers. These findings are important in planning treatment through a

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national thalassemia program and providing social and school support to patients with TDT. To avoid the school absences of these patients, thalassemia clinics should reorganize their schedules for blood transfusions on weekends or at night for school children and help them to overcome this problem. Also, psychosocial interventions such as counseling, play therapy, and assistance with schoolwork should be implemented to improve the HRQoL in this group of patients.

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