β-Thalassemia intermedia: morbidity uncovered

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Chapter 5

Health-Related Quality of Life

Health-related Quality Of Life In Adults With Transfusion-independent Thalassaemia Intermedia Compared To Regularly Transfused Thalassaemia Major: New Insights

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Health-related quality of life in adults with transfusion-independent thalassaemia intermedia compared to regularly transfused thalassaemia major: new insights

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Abstract

Background: In patients with β thalassaemia intermedia (TI), the milder anaemia and transfusion independence imply better health-related quality of life (HR-QoL). However, the unbalanced pathophysiology of the disease allows for several serious clinical complications to manifest, which may have a negative impact on HR-QoL. *Methods:* This was a cross-sectional study on adult patients with transfusion- and iron chelation-independent TI and β thalassaemia major (TM) attending the Chronic Care Center, Hazmieh, Lebanon. A total of 80 patients agreed to participate in the study [32 TI (median age 24 yr) and 48 TM (median age 23 yr)]. The RAND SF-36 survey was used to assess HR-QoL. Data on patient demographics, clinical complications and socioeconomic status were collected. *Results:* Patients with TI and TM were comparable with age and gender, but patients with TM had a significantly longer median duration with a known thalassaemia diagnosis. Patients with TI had a higher proportion of multiple complications. Socioeconomic parameters were comparable, except for patients with TI being more commonly married. The mean Total, Physical Health and Mental Health Scores were significantly lower in patients with TI compared to TM, indicating poorer HR-QoL. There was a statistically significant positive correlation between the duration with a known thalassaemia diagnosis and a higher Mental Health Score (r_s = 0.73, P = 0.020). The mean Physical Health Score was significantly lower in patients with multiple clinical complications compared to patients with single or no complications (P = 0.012). Associations remained independently significant at multivariate analysis. *Conclusion:* Patients with transfusion-independent TI have lower HR-QoL compared to TM patients. At a comparable age, the shorter duration since diagnosis and the multiplicity of complications may explain these findings.

Key words thalassaemia intermedia; thalassaemia major; chronic disease; quality of life; clinical complications; health-related quality of life

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Extremely diverse phenotypes exist within the β thalassaemia syndromes. At one end of the spectrum is β thalassaemia minor, a clinically silent, mildly hypochromic and microcytic anaemia. At the other end is β thalassaemia major (TM) that refers to those patients whose clinical course is characterised by profound anaemia, who are presented to medical attention very early in life, and who subsequently require regular blood transfusions and iron chelation therapy for survival. The term β thalassaemia intermedia (TI) was first suggested to describe patients who have a milder anaemia compared to patients with TM, and who usually present to medical

attention later in childhood and remain largely transfusion independent (1).

Global public health efforts alongside advances in medical management, especially the introduction of safe blood transfusion practices and iron chelation therapy, surely translated into prolonged survival, lower morbidity and enhanced health-related quality of life (HR-QoL) in patients with TM (2–4). In patients with TI, however, the situation is far from ideal. Knowledge of the molecular and pathophysiological mechanisms underlying the disease process in TI has only recently started to evolve (5). It is now apparent that the diagnosis of TI carries higher morbidity than previously recognised, especially in the transfusion-independent patient where the mechanism of disease remains largely unbalanced (6–8). However, significant efforts are still needed before evidence-based management guidelines become available for this thalassaemia phenotype (9). Hence, both patient with the TI and the caring physician may be faced with challenges towards understanding the true burden of the disease and its optimal management. With these observations in mind, we evaluated reported HR-QoL of adults with transfusion-independent TI as compared to regularly transfused TM using a standardised instrument and further explored determinants of the observed differences.

Patients and methods

This was a cross-sectional study of adult (≥18 yr) patients with TI and TM attending to the Chronic Care Center, Hazmieh, Lebanon, the national thalassaemia centre in the country. Over a period of 1 yr, all adult patients presenting to the centre on two specified days of every week (total of 52 TI and 85 TM) were approached for inclusion in the study, and 80 consecutive patients (32 TI and 48 TM) agreed to participate. The remaining patients refused to participate for being unable or unwilling to spend more time at the centre for completion of the questionnaire. The study was approved by the Institutional Review Board at the centre, and written informed consent was obtained from each patient. All patients with TI were diagnosed based on established criteria (10) and were transfusion and iron chelation independent, while all patients with TM were regularly transfused (every 2–3 wk) and iron chelated with desferrioxamine (started before the age of 7 yr, in a daily dose of 30–50 mg/kg, given 5–6 times weekly). Retrieved data included demographics (age and gender), age at diagnosis, splenectomy status, history of clinical complications (Table 1) (11–16), education level (illiterate, elementary school, middle school, high school, university), marital status, presence of dependents, employment status, personal monthly income, household monthly income, monthly expenditure on disease and any history of previous psychosocial support.

For each recruited patient, the RAND 36 item Short Form Health Survey (SF-36) was administered to assess the HR-QoL, by self-administration or face-to-face interviews (for illiterate persons or those with other difficulties). This instrument was previously translated to Arabic, adapted and validated on the Lebanese population using the International Quality of Life Assessment methodology (17). The SF-36 is suitable for self-administration, computerised administration or administration

Table 1 Definitions of evaluated clinical complications

Complication	Definition
EMH	Radiologic evidence of extramedullary haematopoietic foci with or without symptoms
Leg ulcers	An ischaemic or necrotic skin lesion on the lower extremity by general visual inspection
PHT	A systolic pulmonary artery pressure >35 mm Hg, which corresponds to a tricuspid regurgitant velocity on Doppler echocardiography of >2.8 m/s (11) + Exertional dyspnoea without evidence of left heart disease
Thrombosis	Compression ultrasonography, contrast venography or angiography evidence of thrombus
HF	Modified Framingham criteria (12)
Abnormal liver function	ALT >50 U/L
DM	A fasting blood sugar ≥126 mg/dL, or 2-h postprandial blood sugar ≥200 mg/dL, or Symptoms of hyperglycaemia and a casual (random) plasma glucose ≥200 mg/dL (13)
Hypothyroidism	TSH > 4.7 μU/L and a free T4 < 0.8 ng/dL (14)
Osteoporosis	Bone densitometry *T*-score – 2.5 SD (15)
Hypogonadism	Females: >13 yr, not yet Tanner B2 (i.e. prepubertal breast development) *or* >14 yr requiring oestrogen replacement therapy *or* >15 yr with primary amenorrhoea Males: >14 yr, not yet Tanner G2 (i.e. prepubertal genital development) *or* on androgen replacement therapy *or* >17 yr, not yet Tanner G4 (i.e. midpubertal genital development) (16)

EMH, extramedullary haematopoiesis; PHT, pulmonary hypertension; HF, heart failure; ALT, alanine transaminase; DM, diabetes mellitus; TSH, thyroid-stimulating hormone.

by a trained interviewer in person or by telephone to persons aged 14 and older. It is a generic questionnaire, widely used in various clinical conditions and populations (18). It consists of 36 questions that are clustered to yield eight health status scales: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. The health concepts described by the SF-36 range in score from 0 to 100, with higher scores indicating higher levels of function and/or better health. The subjects' responses are presented as a profile of scores calculated for each scale. Two summary measures aggregate these status scales, namely the Physical and Mental Health Scores (17).

Statistical analysis

Descriptive statistics are reported as medians (range), means ± standard deviation (SD) or percentages where appropriate. To evaluate for differences between patients with TI and TM, bivariate correlations were made using the independent samples Mann–Whitney *U* test or *t*-test for continuous variables and the chi-square or Fisher's exact tests for categorical variables. Spearman's correlation coefficient (r_s) was used to examine the relationship between SF-36 scores and any continuous variables. Multivariate linear regression analysis was carried out to evaluate for independent associations when needed. All *P*-values are two sided with the level of significance set at < 0.05.

Results

Patient characteristics

A total of 80 patients (32 TI and 48 TM) were included in this analysis. Table 2 summarises characteristics of patients. Patients with TI and TM were comparable in median age at study and gender distribution. However, patients with TM had a significantly younger median age at diagnosis and subsequently a longer median duration with a known thalassaemia diagnosis compared to patients with TI (median of 22.3 vs. 16 yr, $P < 0.001$). There was no statistically significant difference in the proportion of patients who had undergone splenectomy between the two groups. Similarly, the proportions of patients who had any history of clinical complications, as defined in this study, were similar in both groups. However, patients with TI had a higher proportion of patients with multiple complications compared to TM (50.3% vs. 30.4% among those who had complications in TI and TM, respectively). Patients with TI were more commonly married, but a comparable proportion of patients had received an education or were employed in the two groups. There were no significant differences in financial income or expenditure on disease between both groups.

Table 2 Characteristics of patients

Parameter	Thalassaemia intermedia (n = 32)	Thalassaemia major (n = 48)	*P*-value
Median age at study (range), yr	24 (18–46)	23 (18–42)	0.734
Median age at diagnosis (range), yr	5 (0.1–31)	0.6 (0.2–5.5)	<0.001
Median duration with diagnosis (range), yr	16 (1–39)	22.3 (16.5–41.5)	<0.001
Male, %	37.5	45.8	0.460
Splenectomised, %	64.5	64.6	0.995
History of clinical complications, %	46.9	47.9	0.927
Single, %	21.9	33.3	
Multiple, %	25	14.6	
Educated, %	100	97.9	0.411
Elementary school, %	9.4	16.7	
Middle school, %	28.1	22.9	
High school, %	18.8	25	
University, %	43.8	33.3	
Married, %	29	10.4	0.034
With dependents, %	29	12.5	0.067
Employed, %	45.2	40.9	0.714
Median personal monthly income (range), USD	50 (0–3300)	75 (0–3000)	0.417
Median household monthly income (range), USD	1750 (450–3300)	1500 (350–3000)	0.176
Median monthly expenditure on disease (range), USD	47.5 (0–500)	150 (0–500)	0.238
Previous psychosocial support, %	0	6.2	0.149

Health-related quality of life

The mean Total SF-36 Score was significantly lower in patients with TI compared to TM (66.5 ± 16.1 vs. 75.8 ± 18.8, $P = 0.021$), indicating poorer HR-QoL. Data for the eight scales of the SF-36 were also analysed. Looking at summaries, both the mean Physical Health Score (TI: 66.2 ± 16.8 vs. TM: 77.1 ± 18.1, $P = 0.008$) and the Mental Health Score (TI: 62.8 ± 17.3 vs. TM: 71.7 ± 21.2, $P = 0.042$) were significantly lower in patients with TI compared to TM. The most notable differences were in the Physical Functioning, General Health and Vitality scales (Fig. 1).

For the whole study group, there was a statistically significant positive correlation between the duration with a known thalassaemia diagnosis and the Mental Health Score ($r_s = 0.73$, $P = 0.020$) but not the Physical Health Score ($r_s = 0.34$, $P = 0.256$). There were no statistically significant differences in the mean Physical ($P = 0.188$) or Mental Health Scores ($P = 0.260$) between married and single patients. However, the mean Physical but not the Mental Health Score was significantly lower in patients with multiple clinical complications compared to patients with single or no complications ($P = 0.012$) (Fig. 2).

A stepwise multivariate linear regression model was built with Physical or Mental Health Scores as the dependent variables and: thalassaemia diagnosis (TM or TI), marital status (married or single), duration with a known thalassaemia diagnosis and multiplicity of clinical complications (yes or no) as the independent variables. A longer duration with a known thalassaemia diagnosis was the only independent variable correlating with higher Mental Heath Scores ($P = 0.039$) while multiplicity of clinical complications was the only independent variable correlating with lower Physical Heath Scores ($P = 0.032$).

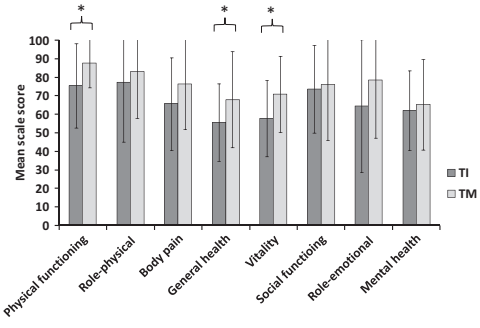

Figure 1 Bar chart showing the mean (bars) and standard deviation (whiskers) of the eight SF-36 health status scales in patients with thalassaemia intermedia (TI) and thalassaemia major (TM). *Statistically significant difference ($P < 0.05$) by the independent samples *t*-test.

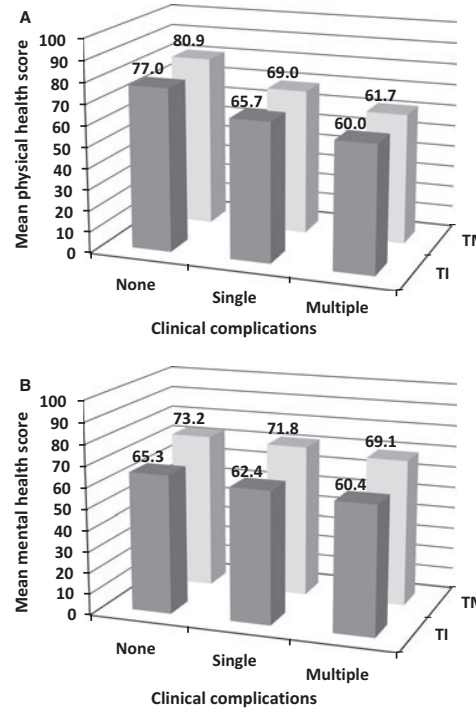

Figure 2 Bar charts showing mean (A) Physical Health Score and (B) Mental Health Score, for patients with thalassaemia intermedia (TI) and thalassaemia major (TM) according to history of clinical complications.

Discussion

Our study demonstrates that patients with transfusion-independent TI have impaired HR-QoL compared to patients with regularly transfused TM of similar age and gender. This finding is contrary to what one would normally assume and echoes recent evidence that highlights the true burden of TI (9).

Several studies evaluated HR-QoL in children (19–23) and adults (24–28) with TM. Reported HR-QoL in patients with TM has markedly improved over the years, especially with the introduction of safe blood transfusions and iron chelation therapy (2, 4). However, several challenges continue to exist, especially for the thalassaemic child transitioning into adulthood (29), allowing the HR-QoL in patients with TM to remain lower than that reported for normal individuals (19–28). Data on

patients with TI are scarce (30). Our study is the first to evaluate reported HR-QoL, using a standardised instrument, for adult patients with TI. Although normative data for the SF-36 using a Lebanese population are not available for comparison, a clinically meaningful gap (~10 scale points) was noted between patients with TI and TM for both the mean Physical and Mental Health Scores. The difference becomes even more meaningful knowing that patients with TM evaluated in this report were receiving the subcutaneous iron chelator desferrioxamine, which may be associated with lower HR-QoL as compared to the newer oral chelators deferiprone and deferasirox (31–34). Only one previous report evaluated HR-QoL in patients with TI. In a cohort of children and adolescents, Pakbaz *et al*. (30) compared 19 TI to 29 TM patients using the Dartmouth Care Cooperative Chart System questionnaire. Similar to our findings in adults, a higher proportion of TI children reported impaired HR-QoL compared to their TM colleagues.

In the study by Pakbaz *et al*. (30) the authors could not evaluate the association between clinical complications and HR-QoL. However, in our study, the report of poor physical health status in patients with TI seems to be attributed to a higher proportion of patients having multiple clinical complications. Severity of the disease and multiplicity of clinical complications have been associated with compromised HR-QoL in patients with TM (19, 24, 28) and sickle cell anaemia (35). Recent evidence continues to highlight that a substantial proportion of patients with TI suffer from serious cardiovascular (namely venous thromboembolism or pulmonary hypertension with secondary right heart failure), endocrinological, hepatic or skeletal complications (7). These complications were mostly evident in patients who never received transfusion or iron chelation therapy (7). In TI, the prevailing approach has been avoidance of early blood transfusions and the concomitant requirement for chelation therapy. However, in a recent study on 584 patients with TI, subjects who were placed on transfusion regimens suffered fewer complications relevant to chronic anaemia, ineffective erythropoiesis and haemolysis (7). Other observational studies have also confirmed that patients with transfused TI suffer fewer thromboembolic events, pulmonary hypertension and silent brain infarcts as compared to transfusion-independent patients (36–39). We herein provide further evidence that multiplicity of complications in the non-transfused patient is also associated with compromised HR-QoL. As such, the introduction of transfusion therapy aimed at preventing the consequences of chronic haemolytic anaemia may benefit patients with TI and improve HR-QoL. Rather than enforcing the regular transfusion regimens implemented in TM, blood transfusion in TI should be individually tailored to meet patient needs. Although earlier introduction of blood transfusions will increase the rate of iron accumulation, effective methods of iron chelation are now available, and the benefits of transfusion therapy may greatly outweigh the cost and inconvenience of iron chelation therapy (7, 40).

There was a negative correlation between mental health status and duration with a known thalassaemia diagnosis, which may explain the lower Mental Health Score observed in patients with TI compared to TM. When comparing a TI to a TM patient of similar age, the patient with TI would have lived a shorter duration of time carrying a diagnosis of thalassaemia, because patients with TI usually present to medical attention and get diagnosed later in childhood (1). Thus, it may be worthwhile proposing that the patient with TM could have had a longer duration of time and greater opportunity to adapt to the disease, its complications and treatment (41). Moreover, as many patients get diagnosed in late childhood or adolescence, it may be harder for them to adjust to the disease because adolescence is a challenging period by itself even without the illness, and this will make them feel even more different than their peers while all they want is to be able to fit in (29, 42, 43). Although patients with TI and TM are usually treated at the same comprehensive care centre, the more frequent presence of TM patients at the centre, to receive blood transfusions, allows them to establish stronger bonds with the health care staff and to get more involved in educational activities aimed at expanding their knowledge about the disease. The health care system has also traditionally been biased towards displaying TM as the more serious condition requiring considerable attention, although this notion is gradually starting to change as the severity of TI is starting to unfold (9). Because broad knowledge about TI and its management has only recently started to become available (9), during initial stages following diagnosis, the patient with TI may be a victim of clinical misinterpretations or inappropriate management, allowing for confusion about the taught and observed nature of the disease to develop. In other words, the patient may personally start to realise that the disease carries more complications than he or she had anticipated or been taught. All the aforementioned factors may have negatively impacted the HR-QoL in patients with TI, especially the reported mental health status.

The study was limited by the small sample of patients recruited for each thalassaemia group. The lack of SF-36 measurement for a sample of healthy Lebanese controls did not allow comparison of HR-QoL for both thalassaemia groups to normal values. Moreover, our findings may not be generalizable to thalassaemia patients in other countries, because HR-QoL may be influenced by standards of health care and other environmental factors.

Contrary to previous belief, patients with TI report substantially impaired HR-QoL. We recommend that all patients with TI undergo frequent HR-QoL assessment, preferably by a standardised instrument like the SF-36. This should also be supported with proper utilisation of psychological interventions and relevant patient education in line with current understanding of the disease. Such efforts should be introduced directly after diagnosis and be maintained throughout patient follow-up. Prospective clinical trials are also urgently needed to evaluate the role of transfusion and other interventions in preventing clinical complications in TI, which are associated with compromised HR-QoL.

Disclosures

The authors have no conflicts of interest to disclose. The study did not receive external funding.

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