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## RESEARCH ARTICLE

## THE EFFECT OF FATIGUE ON SELF-PERCEIVED HEALTH IN PATIENTS WITH HEMOGLOBINOPATHIES IN A GREEK REPRESENTATIVE SAMPLE

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## Abstract

**Purpose:** The purpose of the present study was to measure the effect of fatigue in quality of life by measuring self-perceived health in patients with thalassemia.

**Methods:** 302 patients undergoing transfusion treatment from 5 hospitals around Greece participated in the study. Fatigue was measured with open access questions and quality of life with the Euro5D thermometer as self-perceived health. Statistical analysis was performed with SPSS21.

**Results:** 236 patients (78.7%) reported that they were suffering from fatigue while only 21.3 % (n=66) reported that they had no fatigue. Present health status had a mean of 69.9 with an SD 19.3. Almost half (48.2%) declared they had fatigue a few times over a months period, while 41.7% replied that daily activities were the cause for feeling fatigue. Females reported statistically significant higher existence of fatigue ( $\chi^2= 5.744$ ;  $p=0.017$ ). Education and marital status had no correlation with self-perceived health. Existence, frequency of fatigue, existence of fatigue during the last month, self-interpretation of the cause of fatigue and frequency of fatigue before transfusion all had significant differences with self-perceived health ( $p<0.05$ ).

**Conclusions:** Fatigue has been identified as a very common symptom in patients with thalassemia affecting the self-perceived health in this population. This result broadens the evidence regarding fatigue in hemoglobinopathies and leads us to the need for distinguishing the etiologies leading to fatigue in hemoglobinopathies since it is an important factor affecting HPQoL. Longitudinal studies are needed in order to understand the path of fatigue and the factors influencing the condition.

**Key words:** Fatigue, quality of life, thalassemia, adults, self-perceived health.

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## INTRODUCTION

Health related quality of life (HRQoL) has been defined from Patrick and Erickson as the value allocated to duration of life as it is modified by the functional states, impairments, perceptions and social opportunities that are inclined by disease, injury, treatment or policy.<sup>1</sup> One of the main topics in HRQoL includes patients' evaluation of their current level of functioning, as well as satisfaction with it, related to what they consider to be ideal. Under this spectrum, one of the significant aspects in HRQoL study is how the expression of an illness or treatment is experienced by an individual.<sup>2</sup>

Thalassemia is an inherited blood disease. It consists a serious public health problem throughout the Mediterranean region, Middle East, and Indian subcontinent, as well as in Southeast Asia<sup>3</sup> and as a chronic disease affects the HRQoL of individuals.

Fatigue, on the other hand, is a symptom with subjective significance and major consequence in an individual's life and Health Related Quality of Life (HRQoL). Many definitions have been used in order to describe fatigue, something that makes the identification of the symptom more difficult, as only few differentiating factors between causes exist, as well as taxation indicators regarding the effect of fatigue in human beings.<sup>4,5</sup>

Considerably, fatigue is mostly defined as a subjective symptom or as an objective reduction in an individual's everyday activity.<sup>6</sup> Literature distinguishes fatigue as a symptom that is mostly complex and multifactorial,<sup>7,8</sup> as it comprises of bodily and emotional factors, as well as occupational and life events.<sup>8-10</sup> In patients with hemoglobinopathies fatigue has been identified as a major symptom affecting both health and quality of life in patients with sickle cell disease while it has been found that fatigue was a major symptom affecting the quality of life in patients with thalassemia major as well,<sup>11</sup> but there is no study exploring the characteristics of fatigue in Thalassemia major patients and the correlation between the symptom and the health status of the patients.

The purpose of the present study was to investigate the symptom of fatigue in patients with hemoglobinopathies under transfusion therapy and its correlation with the self-evaluation of the present health of patients by measuring self-perceived health.

## MATERIAL AND METHODS

### Patients and settings

This is a descriptive study, which was conducted in 2 central hospitals in the rural area of Athens and 3 hospitals in the urban areas of Karditsa, Chania and Arta in Greece and lasted from February 2017 to April 2018. The study sample consisted of 302 patients undergoing

transfusion treatment.

Data collection was conducted only after having been granted the Ethical Approval from University of Peloponnesus and the ethics committees of the hospitals that their patients participated in the study. Individuals taking part in this research were clearly informed of the voluntary nature of their participation and their right to quit the study at any point they wish so and that study results would be confidential. A written informed consent was also obtained from all participants before the completion of the questionnaires that were used in the study. In order for a patient to be included in the study he or she should be a chronic patient under transfusion treatment for at least one year, to have a diagnosis of hemoglobinopathy (Thalassaemia major or minor, Sickle cell disease or sickle-beta thalassaemia), and to have the ability to speak and understand the Greek language. Exclusion criteria were to suffer from a psychiatric disease or serious cognitive impairment.

### Data collection

To measure fatigue, a questionnaire was created with close answer questions about the existence of fatigue during the last month, the frequency of fatigue, the cause of fatigue according to the participant and the existence of fatigue before the day of transfusion. HRQoL was evaluated with the second part of the EQ-5D, which is a 20-cm visual analogue scale (VAS), evaluating the current state of health according to the patient, asking the patient to evaluate his present health from 0 (the worst health status) to 100 (the best possible health), with intermediate values of the optical proportional scale, e.g. VAS = 50, indicating intermediate health status. This scale is based on the person's subjective assessments of his / her state of health.<sup>12</sup> The demographic characteristics of the patients (age, marital status, education level and place of residence) were included in the questionnaire with the fatigue evaluation.

### STATISTICAL ANALYSIS

Data analysis was conducted with the use of the statistical package IBM SPSS for Windows (version 21.0, Inc., Chicago, IL, USA). Both descriptive and inferential statistics were used in the analysis. More specifically, in order to examine prevalence of fatigue among our sample, descriptive analysis was conducted. The effect of gender, marital status and education on fatigue was examined through chi square test. The frequency distribution of all the variables measuring fatigue was estimated, as well as the position and dispersion parameters (mean, standard deviation, minimum and maximum value) of the quantitative variables of age and health. Independent samples t-test and one-way analysis of ANOVA were used for the assessment of possible

correlations between the present health status and the categorical variables measuring fatigue. All reported p-values were two-tailed, and only p values of  $<0.05$  were considered statistically significant.

## RESULTS

### Sample characteristics

The studied sample consisted of 172 females (57.1%) and 130 males (42.9%) while one did not state his or her gender. The age of the sample ranged from 19 to 72 years. The average age of the sample was 41.7 years with a standard deviation of 9.2 years, while the majority of participants were patients with a diagnosis of homozygous  $\beta$ -Thalassaemia (bT) (81.4%). The level of education, marital status, place of residence and a diagnosis characteristics are presented in table 1. Finally present health status had a mean of 69.9 with a SD 19.3, with minimum value 10 and maximum 100.

### Characteristics of fatigue

The majority of patients (78.7%) reported that they were suffering from fatigue (n=236) while only 21.3 % (n=66) reported that they had no fatigue.

In relation to the frequency with which participants experienced fatigue, out of the 247 participants who answered the question, 7.3% said fatigue is a common symptom, 23.1% is experiencing fatigue often during the week, 20.6% said they had fatigue one to two days a week and almost half (48.2%) said they had fatigue a few times over a months period.

In the question of what is thought to be the cause of fatigue, out of the 218 patients who answered, the largest percentage of respondents (41.7%) replied that daily activities were the cause for feeling fatigue, only 8.3% of them answered that fatigue is the result of their occupation, while, 12.4% said that fatigue was caused by their emotional state and, above all, the existence of depressed mood. Finally, the rest 17.9% of the sample linked the fatigue to the transfusion.

Regarding the onset of fatigue before transfusion, a large percentage of participants (N = 129-55.6%) replied that fatigue occurred less than a week before the scheduled transfusion, 9.9% that the onset of fatigue was from 6 days to 2 weeks before the transfusion, another 9.5% between 2 weeks to 1 month, while 25% said they had no fatigue before the transfusion.

In relation to the incidence of fatigue during the last month before the participation in the study, 6.4% said that they suffered from fatigue on a daily basis, 16.7% most days of the month, 16.7% fewer than half the days of the month, while 32.6% said that they had rarely experienced fatigue in the last month.

### Differences between demographic variables with Self-perceived

### health

Considering gender differences, females reported statistically significant higher existence of fatigue ( $\chi^2 = 5.744$ ;  $p=0.017$ ) compared to males, while no other statistically significant difference was found with chi square test for the rest of the variables exploring fatigue. (Table 2)

Regarding the correlation between Self-perceived health as it was measured with the Euro5D and the demographic variables, independent sample t test did not manage to reveal any significant differences between rural and urban residences ( $t=0.017$   $p>0.05$ ) or between males and females ( $t=0.460$   $p>0.05$ ) in Self-perceived health. (Table 3)

Finally, one way analysis of variance ANOVA, which was used to identify significant differences in Self-perceived health between the four different marital status categories and the five different education categories of the sample, revealed that no significant overall differences were existing as  $F=0.221$ ,  $p>0.05$  and  $F=1.783$ ,  $p>0.05$  respectively. (Table 3)

### Correlation between fatigue characteristics and Self-perceived health

In order to explore significant differences in Self-perceived health between the patients that were suffering from fatigue and those that didn't have fatigue, independent sample t test was used. Analysis revealed that those that had fatigue had statistically significant lower Self-perceived health than those that had no fatigue ( $t=3.420$   $p<0.001$ ). (Table 4)

Finally, one way analysis of variance ANOVA was also used to identify significant differences in the present Self-perceived health between the four different variables describing fatigue. Analysis showed significant overall differences in how often a patient was experiencing fatigue between the five different groups as  $F([4,246] = 8.407$ ,  $p=0.001$ ). Post hoc analyses with the Dunnett's t-test after Bonferroni correction revealed that patients experiencing fatigue only few times in a month have significantly higher self-perceived health from patients experiencing fatigue everyday (mean Difference=-22,164,  $p=0,001$ ), and patients experiencing fatigue frequently in the week (mean Difference=-10,956,  $p=0,001$ ). Significant overall differences were also found in the cause of fatigue as  $F([3,227] = 2,736$ ,  $p=0.020$ ). Post hoc analyses with the Dunnett's t-test after Bonferroni correction revealed that patients who thought that the reason for feeling fatigue was their depressing mood had significantly lower self-perceived health than those that there was no reason for feeling fatigue (mean Difference=-17,595,  $p=0,005$ ). Analysis also showed significant overall differences in the self-perceived health with the

variables "Frequency of fatigue before transfusion" as  $F ([5,246] = 2.796, p= 0.041)$ , and existence of fatigue during last month, as  $F ([6,246] = 7.403, p= 0.001)$  respectively. In the first variable (Frequency of fatigue before transfusion), post hoc analyses with the Dunnett's t-test after Bonferroni correction revealed that patients experiencing fatigue for a period of time between 2 weeks and 1 month before the transfusion had significantly lower self-perceived health than those experiencing no fatigue (mean difference=-11,864,  $p=0.03$ ). Almost the same differences were found for the second variable, with patients experiencing fatigue every day (mean difference=-21.667,  $p=0.002$ ), or most of the days (mean difference=-20,105,  $p=0.001$ ) during the last month before the transfusion, reporting significantly lower health status than those with no fatigue during the last month. (For means see table 4)

## DISCUSSION

This was one of the first studies exploring the symptom of fatigue in regard to HRQoL in thalassemia major patients, since until now most of the published research concerns fatigue in patients with sickle cell disease.<sup>13-16</sup> Only in one study fatigue was measured as a symptom of fibromyalgia in patients with thalassemia minor using 40 patients where they detected an increased prevalence of fatigue in those patients.<sup>16</sup>

Our results reveal that in the majority of patients (almost 80%) with Thalassemia major and minor, under transfusion treatment are suffering from fatigue. This is a very interesting finding since until now fatigue was mainly found in with patients with iron deficiency anemia<sup>17,18</sup> and sickle cell anemia<sup>13-16</sup> but had not been explored in Thalassemia patients, since in the one study that fatigue was examined as a symptom, it was connected with pain and reduced quality of life and not as a unique symptom.<sup>13</sup>

In relation to the frequency with which participants experienced fatigue, almost half of the sample reported that they experienced fatigue a few times over a month's period and one quarter of the patients reported that they were experiencing fatigue often during the week. Slightly lower was the amount of patients that reported they were suffering from fatigue one to two days through the week, while the rest 7.3% reported that fatigue was a common symptom in their lives.

Trying to identify the patient's beliefs about the cause of fatigue, a very large number of patients reported that daily activities were the cause for feeling fatigue. The second most important factor was not having been transfused, something that connects fatigue with low hemoglobin, a result that is consistent with other reports in the

literature,<sup>17</sup> since fatigue is universally considered a key symptom of anemia, for example, in cancer.<sup>19, 20</sup> The third factor causing fatigue was emotional status, with the existence of depressing symptoms. This finding was expected as well since there is extensive evidence of a significant relationship between depression and fatigue in chronic illnesses.<sup>21-23</sup> Finally, 8.3% of them answered that fatigue was the result of their occupation, a result which is consistent with literature about job fatigue.<sup>24</sup>

Regarding the onset of fatigue before transfusion, more than half of the participants replied that fatigue occurred in a time less than a week before the scheduled transfusion, almost 10% that the onset of fatigue was from 6 days to 2 weeks before the transfusion, another 10% between 2 weeks to 1 month, while one out of five patients reported that they had no fatigue before the transfusion. Once again these results are consistent with the literature connecting fatigue with anemia and low hemoglobin like the one by Ameringer and colleagues who reported that lower levels of hemoglobin were significantly correlated with higher levels of fatigue,<sup>14</sup> even though results are controversial in this matter and more research is needed in order to explore all possible factors contributing to this correlation.<sup>13</sup>

In relation to the incidence of fatigue during the last month before the participation in the study, 6.4% of the patients reported that they suffered from fatigue on a daily basis, 16.7% most days of the month, 16.7% fewer than half the days of the month, while 32.6% said that they had rarely experienced fatigue in the last month. These results indicate that almost one in five patients are living with fatigue leading to reduced health and quality of life since fatigue has been found to be a factor affecting quality of life.<sup>14</sup>

Considering gender differences, females reported statistically significantly higher existence of fatigue compared to males, result that is similar to other reports concerning hemoglobinopathy patients.<sup>14</sup>

Regarding the correlation between health status and demographic variables, Independent sample t-test found no significant difference between rural and urban residence or between males and females in health status as expected since health status is correlated with the disease severity which is not affected by demographic variables or gender.<sup>13,14</sup>

No differences were found in the present health status between the four different marital status categories and the five different education categories of the sample as well, result that is consistent with previous results in Greece.<sup>11</sup>

Our results concerning the correlation between fatigue and the self-perceived health as an indicator of HRQoL, revealed that those that had fatigue had statistically significant lower self-perceived health

than those that had no fatigue. Our results supports the evidence presented from the rest of the studies in the field of hemoglobinopathies that fatigue has a significant correlation with quality of life,<sup>14</sup> and disease complications<sup>15</sup> that lowers the existing health status of the patients.

Finally in order to explore the correlation between self-perceived health and fatigue characteristics one way analysis of variance was used. Analysis showed significant overall differences in how often a patient was experiencing fatigue, with patients experiencing fatigue only few times in a month having significantly higher self-perceived health from patients experiencing fatigue every day, and patients experiencing fatigue frequently in the week. Significant overall differences were also found in the cause of fatigue, with patients who thought that the reason for feeling fatigue was their depressing mood having significantly lower self-perceived health than those that there was no reason for feeling fatigue. Regarding the frequency of fatigue before transfusion and existence of fatigue during last month, patients experiencing fatigue for a period of time between 2 weeks and 1 month before the transfusion had significantly lower self-perceived health than those experiencing no fatigue and patients experiencing fatigue every day or most of the days during the last month before the transfusion, reported significantly lower self-perceived health than those with no fatigue during the last month. Our findings are confirming the results of other studies which found that symptom frequency is one of the strongest predictors of deficits in the physical domain of HRQoL.<sup>25</sup>

#### Limitations

There are a number of limitations to our study. First of all, the participants in our study were recruited to represent a convenience sample of patients undertaking transfusion therapy which excluded the majority of patients with sickle cell disease that are not transfused. Thus, our sample was not a probability sample and findings cannot be generalized to the broader hemoglobinopathies population. This selection strategy and the correlational nature of the study design possible reduced our ability to identify any differences associated with the different diagnosis of hemoglobinopathies but give us robust evidence about Thalassemia major and minor patients in Greece.

#### CONCLUSIONS

Concluding, fatigue has been identified as a very common symptom in patients with thalassemia affecting the present status of health in this population. This result broadens the evidence regarding fatigue in hemoglobinopathies and leads us to the need for distinguishing the etiologies leading to fatigue in hemoglobinopathies. Clinically, since a

strong correlation was evidenced, fatigue could be used to measure health. If fatigue is existing, it is important to screen for the conditions that lead to it. So, it is critical to identify the cause/s of fatigue in determining appropriate interventions. Longitudinal studies are needed in order to understand the path of fatigue and the factors influencing the condition.

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#### Compliance with ethical standards

**i. Conflict of Interest:** The authors declare that they have no conflict of interest.

**ii. Ethical approval:** Ethical approval was granted by the scientific boards of General Hospital of Nikaia and Aghia Sophia" Children's Hospital ". All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

**iii. Funding:** No fund has been given for this review

**iv. Informed consent:** Informed consent was obtained from all individual participants included in the study.

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## ANNEX

**Table 1.** Descriptive summary scores for the demographic characteristics of the sample

Variable	N	%
<b>Sex</b>		
Males	130	42,9
Females	172	57,1
Total	301	99,7
<b>Educational level</b>		
Primary school	23	9,3
Elementary school	21	7,0
High school	102	33,8
University or college	138	45,7
MSc- PhD	12	4,0
<b>Marital status</b>		
Single	143	47,5
Married	136	45,2
Divorced	19	6,3
Widow	4	1,0
<b>Place of residence</b>		
Athens	195	64,6
Rural area	107	34,8
<b>Diagnosis</b>		
Thalassemia major	246	81,4
Thalassemia minor	36	12,0
Sickle -beta Thalassemia	16	5,3
Hemoglobin H	4	1,3

N:number of participants; %:percent of total sample

**Table 2.** Differences between males and females in fatigue

		Gender		Test
		Males	Females	( $\chi^2$ , p value)
Existing fatigue	Yes	90	142	$\chi^2=5,744$
	No	37	30	<b>p=0,017</b>
How often do you experience fatigue	Everyday	5	13	$\chi^2=6,643$
	Frequently in the week	16	40	P=0.156
	1-2 days per week	23	28	
	Few times in the month	55	64	
Cause of fatigue	Transfusion	19	20	$\chi^2=9.439$
	Everyday activities	30	61	P=0.093
	Job fatigue	11	7	
	Depressive mood	13	13	
	Other reason	9	10	
Frequency of fatigue before transfusion	Less than one week	52	77	$\chi^2=3.753$
	between 6 days to 2 weeks	12	10	P=0.289
	Between 2 weeks and 1 month	13	9	
Fatigue during last month	Never	9	10	$\chi^2=3.894$
	Everyday	7	8	P=0.421
	Most days of the month	13	26	
	Less than half of the days	34	49	
	Rarely	39	37	
Increased fatigue	Yes	19	25	$\chi^2=0.068$
	No	83	100	P=0.795

In bold statistically significant p values with  $p < 0.05$  in chi-square test

**Table 3.** Differences between health status and demographic characteristics of the sample

Dependent variable	Category	N	Mean	SD	test/ p value
Health status	Males	127	70,45	21,05	t=0.460
	females	172	69,38	17,99	p= 0.646
Health status	Primary school	27	64,04	19,25	F=1.783
	Elementary school	21	65,38	20,81	p=0.132
	High school	102	69,33	19,04	
	University or college	138	71,39	19,50	
	MSc- PhD	12	78,75	13,51	
Health status	Single	142	69,16	19,713	F=0,221/
	Married	136	70,85	18,529	p=0,882
	Divorced	19	68,42	23,514	
	Widow	3	71,67	12,583	
Health status	Athens	194	69,00	19,44	t=-1.017
	Rural area	105	71,38	19,10	p=0.310

N= number of participants for the category; SD: Standard Deviation;

In bold statistically significant p values with  $p < 0.05$

**Table 4.** Differences between health status and fatigue variables

Variable	Category	N	Mean	SD	Test / p value
Existing fatigue	Yes	233	67,89	19,256	T=-3.420
	No	67	76,90	18,014	<b>P=0.001</b>
How often do you experience fatigue	Never	52	70,00	18,284	F=8.407
	Everyday	18	50,44	21,829	<b>P=0.001</b>
	Frequently in the week	57	61,65	16,557	
	1-2 days per week	51	71,65	15,564	
	Few times in the month	119	72,61	19,112	
Cause of fatigue	None	24	77,71	15,602	F=2.736
	Transfusion	39	67,38	18,378	<b>P=0.020</b>
	Everyday activities	91	72,11	18,496	
	Job fatigue	18	73,06	21,292	
	Depressive mood	27	60,11	19,234	
	Other reason	19	68,42	23,724	
Frequency of fatigue before transfusion	Never before transfusion	57	76,00	15,324	F=2.796
	Less than one week	129	70,15	19,327	<b>P=0.041</b>
	between 6 days to 2 weeks	23	66,22	22,167	
	Between 2 weeks and 1 month	22	64,14	22,630	
Fatigue during last month	Never	19	80,00	13,744	F=7.403
	Everyday	15	58,33	24,398	<b>P=0.001</b>
	Most days of the month	38	59,89	18,936	
	Less than half of the days	84	71,18	16,138	
	Rarely	76	75,20	19,819	

N= number of participants for the category; SD: Standard Deviation; in bold statistically significant p values with  $p < 0.05$