OPEN ACCESS
Freely Available Online

JOURNAL OF HEMATOLOGY AND ONCOLOGY RESEARCH
ISSN NO: 2372-6601

Research

DOI : 10.14302/issn.2372-6601.jhor-15-776

Reduced Physical Activity Patterns in Patients with Thalassemia Compared to Healthy Controls

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Abstract

Background: Patients with Thal (Thalassemia) are presumed to be inactive for many of the same reasons as healthy adults, though there are limited published data to support this claim. The primary aim of this study was to compare physical activity patterns in subjects with Thal to healthy controls as well as to explore the effects of transfusion therapy on physical activity in transfusion dependent patients with Thal.

Methods: 37 Thal (23 Thal major, 14 Thal intermedia, 21 Female, 27.3±10.1 years) and 30 healthy controls (17 Female, 28.0 ± 13.7 years) wore an ActiGraph accelerometer for one to two weeks.

Results: Thal subjects recorded a significantly fewer total number of steps per day and lower total energy expenditure compared to healthy controls ($p=0.001$). None of the adult Thal subjects met the recommended 10,000 steps/day as opposed to 27% of healthy adult controls ($p=0.004$). Thal spent significantly less time in moderate ($p=0.03$) to vigorous ($p=0.005$) activities and more time in sedentary activity ($p=0.006$).

Conclusion: It is now clear that Thal spend significantly less time in physically demanding activities than age-matched healthy controls, a result that has long been assumed though not previously documented. Further research is needed to define an appropriate physical activity regimen best suited for patients with Thal while examining its effect on mental and physical health.

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Citation: Ellen B. Fung, Jennifer Pinal, Michelle Leason (2015) Reduced Physical Activity Patterns in Patients with Thalassemia Compared to Healthy Controls. Journal of Hematology and Oncology Research - 2(1):7-21. https://doi.org/10.14302/issn.2372-6601.jhor-15-776'

Editor: Vijaya Bhatt, University of Nebraska Medical Center

Key Words

Thalassemia, physical activity, sleep, accelerometry, actigraph

Running Title

Physical Activity in Thalassemia

Received 13 Oct 2015; **Accepted** 4 Dec 2015; **Published** 10 Dec 2015;

Introduction

The 2008 Physical Activity Guidelines for Americans state that adults should participate in a minimum of 30 minutes of moderate level of physical activity per day, children a minimum of 60 minutes. Less than half of US adults meet this recommendation and it is estimated that fewer than 30% of adolescents participate in an hour per day of physical activity[1]. Patients with Thal are presumed to be inactive for many of the same reasons as healthy adults, though there are limited published data to support these claims. Additionally, there are a number of other factors that may contribute to inactivity in Thal. Chronically low hemoglobin (Hb) levels, either in non-transfusion dependent patients or prior to-transfusion have been associated with reduced exercise performance[2,3]. Along with reduced hemoglobin, pain[4], depression[5,6], and particularly for children, overprotective parenting can result in reduced physical activity for many patients with Thal. Additionally, patients with Thal major have various complications, which may inhibit or otherwise hamper participation in moderate to vigorous physical activity including iron overload associated cardiomyopathy, hepatitis, diabetes, osteoporosis and hypothyroidism.

While a small number of patients suffer from these co-morbidities, a larger percentage of relatively healthy patients, maintained on optimal chronic transfusion and chelation regimens could benefit from a regular low-intensity physical-activity program. In non-Thal populations, regular physical activity has been shown to decrease depression and improve mood[7], school performance[8,9,10], glucose tolerance[11,12,13], weight maintenance[14], body composition[15] and bone health[16,17,18].

There is a paucity of published literature examining physical activity patterns in hemoglobinopathies. Poor exercise performance and overall less activity have been observed in both adults and adolescent patients with sickle-cell disease[19,20]. Very few studies have examined physical activity in patients with Thal, and those that have focused primarily on the effect of iron overload on physical activity[2]. Thalassemic patients with heart failure and increased myocardial iron had reduced exercise tolerance compared to β-thalassemic patients without heart failure[21]. In general, those living with chronic illnesses that limit physical endurance have been shown to display lower levels of daily activity[22]. However, daily physical activity patterns amongst Thal patients, in particular, has yet to be explored. The primary aims of this study were to compare physical activity patterns in subjects with Thal to healthy controls, as well as to explore the effects of transfusion therapy on physical activity in transfusion dependent patients with Thal. Thal subjects were found to be significantly less active compared to age-matched healthy controls using a variety of measures, a result that has long been assumed though not previously documented.

Materials and Methods

A prospective case-control study design was used to evaluate physical activity among patients with Thal relative to healthy controls. Thal subjects and controls were asked to wear an ActiGraph (GT3X) accelerometer for week-long intervals, which measured their physical activity frequency and intensity. Twenty of the Thal patients included herein were also enrolled in a randomized trial testing the effect of vibration therapy on bone health[23]. The ActiGraph was worn only during non-vibrating periods of the protocol. Additional Thal case subjects were invited to participate from the Children's Hospital Research Center, Oakland (CHRCO) Hematology outpatient clinic. All case subjects were required to have a Thalassemia diagnosis to participate. They were categorized either as transfusion dependent (TM) if they received red blood cell transfusion therapy on a routine basis, typically every three weeks or a minimum of eight times per year, or non-transfusion dependent (TI) if they were non or intermittently transfused. Healthy controls of Asian or Caucasian decent were recruited from staff, friends and families of staff, and the University of California, Berkeley student body. Exclusion criteria for all subjects consisted of age ≤9 years and pregnancy. The protocol was approved by the Institution Review Board of CHRCO. Participants received information about the nature and purpose of the study and signed informed written consent. Adolescents under the age of 18 signed assent.

The ActiGraph measures frequency and intensity of minute-by-minute body movements in three dimensions: anterior-posterior, medial-lateral, and vertical axis. For highest accuracy, patients wore the ActiGraph on their left hip, close to the body's center of mass. TM patients wore the ActiGraph for one week prior to and post transfusion. Controls and TI patients were asked to wear the ActiGraph for a complete week, at a pre-scheduled time convenient for them. Valid ActiGraph data was considered to include at least three week days and one weekend day[24]. All subjects were provided a calendar and asked to record any unusual physical activity patterns (e.g. time on rollercoasters, time off to shower or swim), their bedtime and waking time. Subjects were instructed to wear the ActiGraph only during non-sleeping hours. Readings were recorded throughout waking hours, except when infeasible (e.g. during showering, swimming). After subjects completed their wear-time, ActiGraph data was downloaded and saved using ActiLife version 5.10.0 software (Pensacola,FL).

Accelerometer Data Acquisition

The ActiGraph converts the magnitude of acceleration into activity "counts" per specified time interval (epoch). A sixty-second epoch was used. Storing counts over short epochs is critical to accurately assess physical activity patterns, particularly for subjects with minimal time spent in vigorous bouts of activity. Selected physical activity intensity categories were defined as sedentary, light, moderate, vigorous, and very vigorous, as specified by Freedson (1997). Categories were established by measuring healthy adults wearing ActiGraphs while exercising on treadmills. Subject physical activity was then presented as a percentage time spent in each category (out of 100% weartime). Activity counts were calibrated at different levels of intensity to derive the cut points provided in Table 1[25]. Cut points were similarly derived for pediatric populations[26].

The ActiGraph's multifunctional design captures both activity counts and simple step-count data provided by a pedometer. Validity of the step count function has been tested previously using the Actical accelerometer with similar 3-dimensional functionality and software design[27].

All subjects completed a 12-15 minute, self-administered Block Work and Home Activities Survey[28]. For the TM subjects, the survey was conducted during the pre-transfusion visit. The questionnaire encompasses the entire spectrum of behaviors from sleeping and sedentary activities to vigorous and intensive activities. This includes occupational activities, home and typical activities such as childcare and gardening, and various leisure activities, which were found to be important contributors to energy expenditure in the validation of the questionnaire[28]. Activities were categorized in the survey based on their metabolic expenditure levels (METs; 1 MET = 1 kcal/kg body weight/hour) developed by Dong et al (1999)[29]. Information on each subject's employment status and occupation were taken from the Block Work and Home Activities Survey. The subjects were placed into one of four categories based on their occupation type: 'office-work' (non-active, mainly sitting, desk work), 'non-office work' (more physically

Table 1. "Cut Point" Categories as Counts per Physical Activity Intensity Category

	Sedentary	Light	Moderate	Vigorous	Very Vigorous
9 Year Old	0-149	150-499	500-1770	1771-4360	4361-∞
10 Year Old	0-149	150-499	500-1910	1911-4588	4589-∞
11 Year Old	0-149	150-499	500-2059	2060-4832	4833-∞
12 Year Old	0-149	150-499	500-2220	2221-5094	5095-∞
13 Year Old	0-149	150-499	500-2393	2394-5375	5376-∞
14 Year Old	0-149	150-499	500-2580	2581-5679	5680-∞
15 Year Old	0-149	150-499	500-2781	2782-6007	6008-∞
16 Year Old	0-149	150-499	500-3000	3001-6363	6364-∞
Adult	0-99	100-759	760-5724	5725-9498	9499-∞

Values are in Absolute "Counts" determined from ActiGraph GT3X, Reference Ranges Taken from: [26]

demanding work involving standing, heavy lifting, and long hours standing), 'student' and 'unemployed.'

Weight and height were obtained and body mass index (BMI) was calculated for all subjects. Laboratory results, including liver iron concentration (LIC) assessed by Super conducting Quantum Interference Device (SQUID), pre-transfusion Hb, and serum ferritin were obtained from case subjects' medical records. Dates of transfusion were abstracted from medical records in order to accurately document the time periods around ActiGraph recordings.

Data Analysis

Adults were defined as individuals ≥18 years of age [similar to definitions in the activity studies by Freedson, 1997]. Subject's race was recorded and categorized based on the NIH Policy on Reporting Race and Ethnicity (2001)[30]. Specific calculations were made as follows: step-count data recorded by the ActiGraph were compared amongst groups (Thal vs. controls, Pre/ Post Tx) and to current recommendations. Adults meeting the recommendations were defined as those with steps ≥10,000 steps/day or subjects <18 years steps ≥ 12,000[31,32,33].

Data were first plotted and normality tests run to check for outliers, ranges and distribution assumptions. Summary statistics were then computed including means, standard deviations (SD) or standard error of the mean (SEM) and 95% confidence intervals (CI) for variables at each time point within each group. Categorical variables were analyzed by chi-square test, and continuous variables by Student's t-test, with pooled (for equal variances) or Satterwaite (for unequal variances) p-value. Analysis of variance models with repeated measures over time (ANOVA) were run for pre-post transfusion data, controlling for baseline as necessary. Statistical analyses were conducted using Stata 9.2 (Stata, Inc., College Station, TX). A significance level of $p<0.05$ was used for all statistical tests, with a p value of <0.1 considered a trend.

Sample Size Determination

Prior to this study, there were no objective studies of physical activity patterns in patients with Thal. To judge the adequacy of the proposed sample size for testing the level of physical activity in comparison with healthy subjects without Thal, we considered pilot data gathered from our center (unpublished) along with published NHANES data from healthy individuals in the US[26]. For time spent in sedentary activity, we observed an average of 11.6±2.1 hours for those with Thal compared to 7.5±0.5 hours for healthy individuals. Using these data, assuming a 5% Type 1 error rate, with 5 patients per group, we estimated a 95% power to detect a difference between the Thal and Controls. For the average number of counts per minute, we observed Thal patients averaged 238±67 counts/min compared to published controls: 390±50. Using these data, assuming a 5% Type 1 error rate, with 6 patients per group we would have 95% power to detect a difference between the Thal and controls. Given the protocol was designed to include older and younger subjects, pre/post transfusion, we estimated we would need at least 27 subjects (6 * 4 groups plus 10% overage) in order to detect statistical differences in most of the physical activity variables observed. Our plan was to recruit 30 healthy controls and up to 40 Thal subjects to meet our aims.

Results

Forty-three subjects with Thal and 31 healthy controls were initially invited to participate in the study. Three adult Thal subjects (2 Male, 1 Female) either moved or expired prior to consenting to the study. Additionally, three adult male Thal subjects dropped after consenting due to scheduling difficulties. One healthy control was excluded after consenting when it was discovered he had a diagnosis of Thal trait. Therefore, a total of 37 Thal (23 transfusion dependent, 14 non-transfusion dependent or intermittently transfused) and 30 healthy controls were included in the analysis. Data was summarized from the ActiGraph for an average of 7.0 ± 1.6 days for Thal and for 7.9 ± 1.7 days for the healthy control groups. The genotypes of the transfused and non-transfused subgroups are provided in Table 2. There were no significant differences observed between the Thal and healthy control groups in terms of age, gender, height, weight, BMI or race.

Employed Thal subjects, both TM and TI, were more likely to have 'non-office work' jobs, which included factory work, traveling sales, retail clerks and other physically demanding jobs. All employed controls were involved in 'office-work' type jobs, which primarily consisted of sitting at a desk for most of the workday. Employment status and occupation by group are provided in Table 2.

As expected, TM subjects presented greater pre-transfusion hemoglobin and serum ferritin levels compared to TI subjects (Table 2). However, LIC, reflecting total body iron stores, were similar between TM and TI subjects.

Overall, Thal subjects recorded a significantly fewer total number of steps per day compared to healthy controls (Table 3, p=0.001). This observation was significant for both Thal age groups, adults and adolescents (Figure 1). Further analysis revealed that none of the adult Thal subjects met the recommended number of steps/day (10,000) as opposed to a little over one quarter of the healthy adult control group. Similar trends were observed for the sub-group of Thal adolescents (Table 3).

Thal subjects had a significantly lower total energy expenditure (Kcal/day) measured by ActiGraph (p=0.001), a result which appeared to be driven primarily by the adult sub-group. Though when energy expenditure was calculated from the *self-reported* Physical Activity Survey Questionnaire, there were no significant differences between groups.

Compared with controls, overall subjects with Thal spent significantly less time in moderate (p=0.03), vigorous (p=0.005) and very vigorous (p=0.02) activity and more time in sedentary activity (p=0.006). However, in sub-group analysis it became clear that there were no significant differences observed between adult controls and adult Thal subjects in most activity intensities, other than the small amount of time spent per day in vigorous activities (p=0.007). The distinctive activity patterns for the adolescent Thal compared to healthy controls are illustrated in Figure 2.

Confirming their increased time spent in sedentary activities, Thal subjects reported engaging in their combined time spent watching TV, surfing the internet, driving and other sitting-type-activities in the Self-Assessment Survey Questionnaire.

There were no differences in total hours of sleep per night for adult Thal subjects compared to healthy controls when subjects estimated their usual sleeping habits in the Survey Questionnaire (Table 3). However, when asked to record actual sleeping and waking time on a calendar, Thal adults spent significantly more total hours sleeping, on average spending 1 more hour asleep each night compared to healthy adult controls (p=0.046).

Transfused subjects began recording data from their ActiGraph on average 6.0 ± 2.9 days prior to transfusion, and again following, starting to record on average 2.3 ± 2.9 days after their transfusion day (Table 4). There was no significant difference in steps per day when comparing TM subject's physical activity patterns pre versus post transfusion. Of interest, none of these subjects met the U.S. recommendations for steps per day (10,000 steps/day for adults and 12,000 steps/day for adolescents) prior to their transfusion date, while three subjects met the recommendations post transfusion. Gender, BMI, Hb and serum ferritin were not significant modifiers to step count during the transfusion cycle for these subjects.

Despite the noteworthy trend in overall number of steps taken following a transfusion, results indicated that TM subjects had no significant difference in energy expenditure and time spent in various activity intensities prior to and following their transfusion (Table 4).

Discussion

This is the first study to have measured the activities of daily living in Thal subjects using ActiGraph technology**.** The results indicated that when compared to age-matched controls, Thal subjects took significantly fewer total number of steps per day. This result was corroborated with the total energy expenditure, as Thal subjects also had significantly lower total kilocalories

Table 2. Basic demographics, anthropometry, socioeconomic and clinical characteristics of subjects with Thal (TM and TI) and healthy controls

	Thalassemia (Tx) *(n=23)*	Thalassemia (Non-Tx) *(n=14)*	Control *(n=30)*	p-value
Age, years	29.8 ± 10.5 (25.3, 34.3)	22.9 ± 8.0 (18.2, 27.5)	28.0 ± 13.7 (22.8, 33.1)	NS
% <18 years	17.4	42.9	26.7	NS
% ≥18 years	82.6	57.1	73.3	NS
Race (n, %)	White (6, 26.1) Asian (16, 69.6) Pacific Islander (0) Other (1, 4.4)	White (3, 21.43) Asian (11, 78.6) Pacific Islander (0) Other (0)	White (2, 6.7) Asian (20, 66.7) Pacific Islander (5, 16.7) Other (3, 10.0)	0.09
Gender				
Male (n, %)	8 (34.8)	8 (57.1)	13 (43.3)	NS
Female (n, %)	15 (65.2)	6 (42.9)	17 (56.7)	NS
Employment				
Employed (n, %)	Employed (14,60.9) Unemployed (3, 13.0) Student (6 26.1)	Employed (5, 35.7) Unemployed (3 ,21.4) Student (6 ,42.9)	Employed (12, 40) Unemployed (0) Student (18, 60)	0.019
Occupation (n, %)	Office Work (9,39.1) Non-Office Work (7, 30.4) Student (6, 26.1) Unemployed (1, 4.4)	Office Work (2,14.3) Non-Office Work (4, 28.6) Student (6, 42.9) Unemployed (2,14.3)	Office Work (12, 40) Non-Office Work (0) Student (18, 60) Unemployed (0)	0.001
Thalassemia Genotype, (n)	B-thalassemia (16) E-B-thalassemia (6) HbH (0) HbHCS (1)	B-thalassemia (4) E-B-thalassemia (1) HbH (1) HbHCS (8)		0.001
Liver Iron Concentration, ug/g wet weight^	1480 ± 1161 (965, 1995)	1753 ± 1282 (977, 2528)		NS
Ferritin, ng/mL*	1871 ± 1288 (1314, 2428)	570 ± 588 (214, 925)	n/a	0.002
Hemoglobin, g/dL*	10.1 ± 1.2 (9.6, 10.6)	8.8 ± 1.5 (7.9, 9.7)	n/a	0.006
Height, cm	156.0 ± 8.1 (152, 159)	155.0 ± 11.9 (148, 161)	161.0 ± 13.1 (156, 166)	NS
Weight, kg	50.5 ± 8.7 (46.7, 54.2)	53.5 ± 15.4 (44.6, 62.3)	58.1 ± 16.5 (52.0, 64.3)	NS
Body mass index, kg/m^2	20.8 ± 3.2 (19.4, 22.2)	22.1 ± 5.0 (19.2, 25.0)	21.9 ± 3.9 (20.4, 23.4)	NS

Continuous variables: Mean ± SD (95% CI), Categorical variables: n (%)

*All laboratory values for transfused patients drawn pre-transfusion, ^Liver Iron concentration determined by Super conducting Quantum Interference Device (SQUID) p-values for categorical values determined from chi-square with Fischer exact follow up tests, p-value for continuous values determined from either non-paired Students t-tests, or ANOVA.

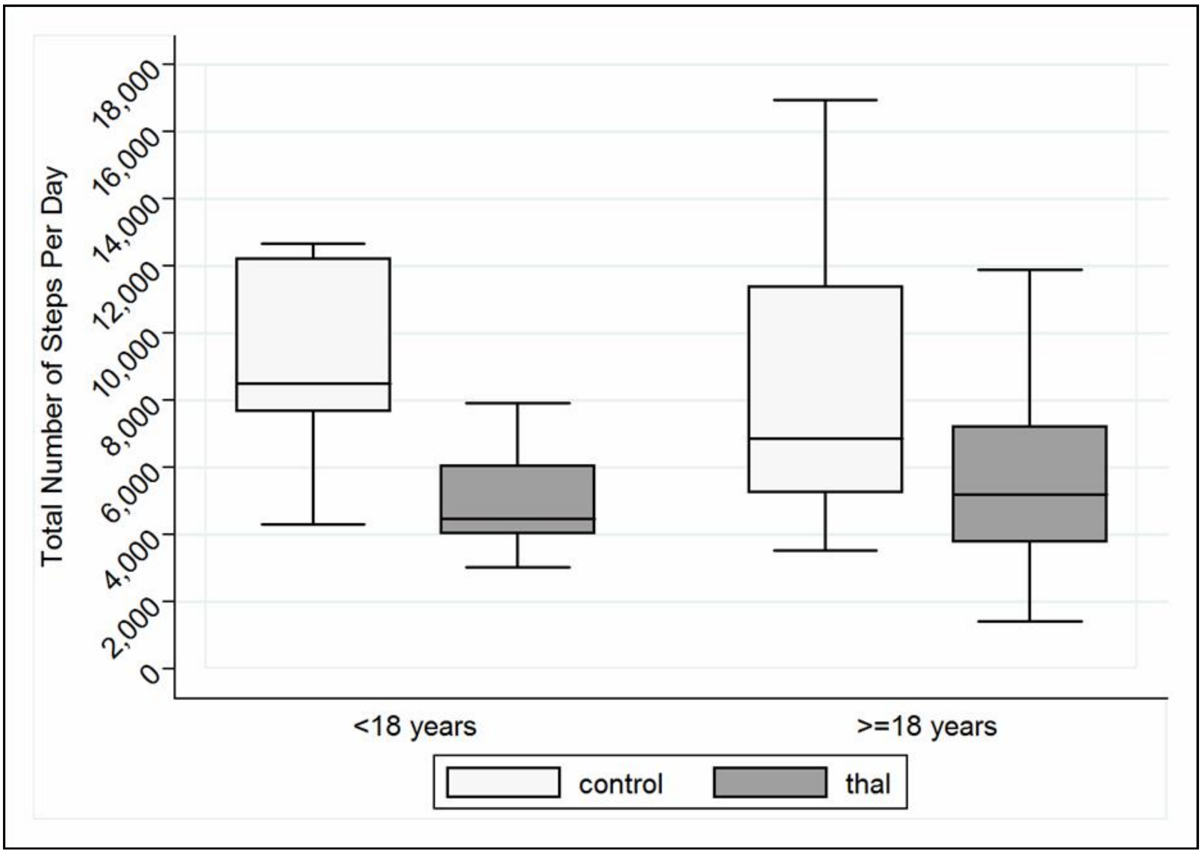

Figure 1. Total Number of Steps Per Day Assessed by ActiGraph in Patients with Thal (n=37) Compared to Healthy Controls (n=30) divided by Age Group.

*Step recommendations for adolescents (12,000 steps/day[33]) and for adults (10,000 steps/day[32])

expended per day, measured by the ActiGraph, compared to controls. Major differences were recorded in the patterns of the activities in Thal subjects versus controls. Of these, amount of time spent in sedentary and vigorous activities stood out as the most prominent. Unexpectedly, these differences were most notable in Thal youth. Thal youth spent 72% of time in sedentary activity, compared to age-matched control youth (only 56%, Figure 2). It is now clear that physical activity is reduced during activities of daily living in patients with Thal, a result that has long been assumed though not yet documented.

Though no other studies have examined general physical activity patterns among Thal patients, others have explored exercise capacity and performance, focusing on the effects of iron overload and its' subsequent comorbidities. Mavrogeni et al[34] assessed exercise in patients with B-Thal and heart failure using a treadmill protocol. They observed reduced values of exercise indexes associated with myocardial T2*, a magnetic resonance parameter indicating elevated iron concentration in the heart. Sohn and colleagues[2] also studied the influence of somatic and cardiac iron overload on exercise performance in a large (n=71) TM patient cohort. They found decreased aerobic capacity in Thal patients and concluded that the observed exercise limitation is related to systemic inflammation, degree of anemia and cardiac iron burden. Geordie and colleagues[35] examined cardiorespiratory response to exercise on a cycle ergometer in Thal and found a significantly lower peak oxygen consumption during incremental exercise compared to control subjects. Abnormally high heart rate and cardiac output (associated with hypoventilation) were also recorded in Thal subjects during exercise. This study re-tested Thal patients 3 to 8 days after transfusion and found no significant improvement in ventilation or circulation, a result that is consistent with our findings.

The reason for the inactivity observed in patients with Thal in this study may be similar to healthy adults without Thal, though there are limited published data to support these claims. These restrictions may include

Table 3. Physical activity patterns and energy expenditure assessed by ActiGraph compared with self-assessment in subjects with Thal and healthy controls

	Thalassemia n=37	Control n=30	*p-value*
Total steps/day			
All Subjects	5321 ± 1972	8323 ± 3377	0.001
Kids (<18 years)	4766 ± 1507	9220 ± 2944	0.001
% met recommendations*	0%	25%	0.09
Adults (≥18 years)	5526 ± 2107	7997 ± 3527	0.004
% met recommendations*	0%	27%	0.004
Energy Expenditure (Kcal/day) measured from Actigraph			
All subjects	1227 ± 765	2450 ± 1798	0.001
Kids (<18 years)	844 ± 341	1288 ± 838	0.14
Adults (≥18 years)	1369 ± 832	2872 ± 1878	0.001
Energy Expenditure (Kcal/day) estmated from Block PA Survey Questionnaire**			
All subjects	1914 ± 791	1940 ± 694	NS
Kids (<18 yrs)	1328 ± 388	1333 ± 693	NS
Adults (≥18 yrs)	2117 ± 798	2160 ± 560	NS
% Time Spent in Different Activities			
% time in sedentary activity			
All subjects	72.1 ± 9.2	65.6 ± 9.3	0.006
Kids (<18 yrs)	72.0 ± 6.5	56.6 ± 9.5	0.001
Adults (≥18 yrs)	72.1 ± 10.1	68.8 ± 6.9	NS
% time in light activity			
All subjects	17.3 ± 8.0	19.1 ± 5.4	NS
Kids (<18 yrs)	13.1 ± 2.5	16.3 ± 3.3	0.036
Adults (≥18 yrs)	18.9 ± 8.8	20.1 ± 5.8	NS
% time in moderate activity			
All subjects	10.2 ± 4.5	12.8 ± 5.0	0.03
Kids (<18 yrs)	13.4 ± 4.3	18.9 ± 4.3	0.015
Adults (≥18 yrs)	9.1 ± 4.0	10.6 ± 3.1	NS
% time in vigorous activity			
All subjects	0.5 ± 0.7	2.3 ± 3.8	0.005
Kids (<18 yrs)	1.4 ± 0.7	7.5 ± 4.0	<0.001
Adults (≥18 yrs)	0.1 ± 0.2	0.4 ± 0.5	0.007
% time in very vigorous activity			
All Subjects	0.1 ± 0.1	0.3 ± 0.5	0.02
Kids (<18 yrs)	0.1 ± 0.2	0.8 ± 0.8	0.016
Adults (≥18 yrs)	0.0 ± 0.0	0.1 ± 0.2	NS

(Continued on page 15)

limited time, lack of motivation, fatigue or lethargy and competing interests. Additionally, they have a myriad of other factors, which may deter from an active lifestyle. One of the most evident reasons is chronic pain, which is increasingly common among Thal patients[36]. Pain can restrict daily physical activity and dissuade incentives to exercise. Chronic pain can lead to fear of injury: another important reason Thal subjects can be more inactive than their healthy counterparts. Incessant fear of exacerbating their symptoms can lead to a more sedentary lifestyle. Many patients are fearful of cardiomyopathy. Having witnessed fellow patients suffer and on occasion die of heart failure, they find themselves reluctant to stress their hearts with rigorous

(Continuation of table 3)

Hours of Sleep, Subject Estimated from Survey Questionnaire^			
Adults (≥18 yrs)	7.0 ± 1.4	6.8 ± 0.9	NS
Reported time watching television, hours	4.4 ± 1.5	3.7 ± 1.9	0.075
Reported time in all sedentary activities, hours	6.1 ± 3.3	4.3 ± 2.6	0.015
METminutes, including all activities by self-assessment questionnaire			
Total Sample	2308 ± 844	1973 ± 564	0.068
Kids (<18 yrs)	1975 ± 945	2319 ± 620	NS
Adults (≥18 yrs)	2437 ± 784	1848 ± 499	0.004
METminutes, including all non-job activities by self-assessment questionnaire			
Total Sample	1472 ± 876	1209 ± 553	NS
Kids (<18 yrs)	1448 ± 912	1482 ± 545	NS
Adults (≥18 yrs)	1482 ± 880	1110 ± 534	0.09
Subjects Met Physical Activity Guidelines_ Healthy People 2010 (%) ^^	58.3%	70.0%	NS

Continuous variables: Mean ± SD (95% CI); Categorical variables, (%)

p-values for categorical values determined from chi-square with Fischer exact follow up tests, p-value for continuous values determined from either non-paired Students t-tests, or ANOVA.

*Recommendations for steps per day for adolescents are 12,000 steps/day[33], and for adults 10,000 steps/day[32].

**Estimated from the Validated Block Physical Activity Survey[28]

^Hours of evening sleep recorded during the week(s) when the Actigraph was worn to assess physical activity. Missing and unreliable data was obtained from many of the younger Thal and healthy control subjects, therefore summary statistics are only presented for the adult cohorts. Average number of hours of evening sleep was also estimated by each subject during the first week the actigraph was worn using the validated Block Physical Activity Survey.

Activities were categorized in the validated physical activity survey based on their metabolic expenditure levels (METs; 1 MET = 1 kcal/kg body weight/hour) developed by Dong et al (1999)[29].

^^Healthy People 2010 Guidelines: "Engage in moderate physical activity for at least 30 minutes on at least five days a week, or engage in vigorous physical activity for 20 minutes on at least three days per week," or a combination adding up to five days.

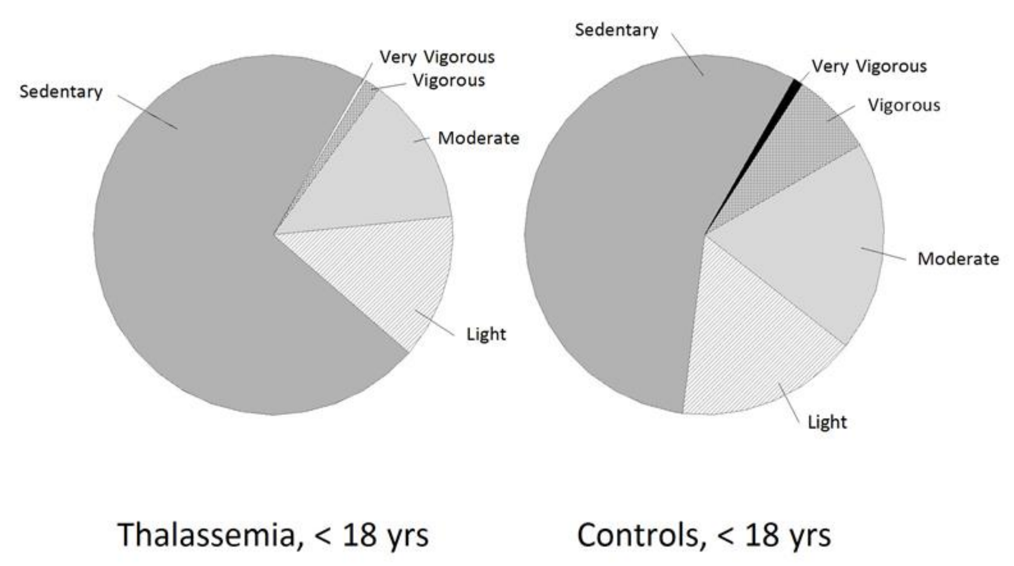

Figure 2. Activity Patterns of Daily Living in Young Subjects with Thal Compared to Young Healthy Controls.

Thal youth (<18 years) spent significantly less time in light, moderate, vigorous and very vigorous activity and more time in sedentary activity compared to healthy controls (<18).

Table 4. Physical activity patterns and energy expenditure assessed by ActiGraph in subjects with Thal prior to and following red blood cell transfusion.*

	Pre-Transfusion n=20	Post-Transfusion n=20	*p-value*
Total Steps/day	4715 ± 1714	5550 ± 2616	NS
% Recommendations met	0%	15%	0.08
Total Steps/day Active Subjects Only^	4399 ± 1943	6108 ± 3027	0.11
% Time spent in different intensity exercises			
% Sedentary	72.3 ± 8.5	70.1 ± 11.3	NS
% Light	18.5 ± 7.4	18.3 ± 9.4	NS
% Moderate	8.9 ± 3.9	11.1 ± 7.3	NS
% Vigorous	0.4 ± 0.6	0.5 ± 0.1	NS
% Very Vigorous	0.0 ± 0.1	0.0 ± 0.1	NS
Total Energy Expenditure (Kcal/day)	1045 ± 531	1015 ± 487	NS
Total Energy Expenditure Active Subjects Only^	995 ± 592	1090 ± 527	NS

* Subjects were asked to begin recording ActiGraph data one week prior to the day of transfusion, and again immediately following transfusion for an additional week of data collection.

Three subjects were missing post-transfusion data and therefore were not included in the analysis above.

^ For subjects who were considered more "Active" which included those categorized as either "non-office workers", "students" or "unemployed", n=12.

exercise, whether or not the fear is unfounded. These types of fears may not only come from the patient; parents of Thal children are commonly found to constrain their child's physical activity.

High rates of depression[37] and fatigue found in Thal subjects can also limit a patient's incentives to stay active. An orthogonal factor to these disincentives to exercise are the set of physical limitations that present with Thalassemia. In particular, Thal subjects have reportedly higher percentage body fat per body weight (that is, they are less lean for body weight)[38]. Less lean cell mass results in less overall muscle mass to propel and/or sustain an individual during exercise. Lower lean cell mass could equate to fatigue combined with anemia and lead to limited exercise capacity.

Our findings have important implications: they point to potential health benefits for Thal subjects if physical activity levels are increased. A physical activity regimen would be most effective if implemented early on, and in small steps. As with most exercise intervention programs, they are most effective if incorporated when an individual is young, when they can integrate the routine as part of daily schedule. Further, Thal adults more commonly have exercise limiting co-morbidities. For example, a promising potential outcome is increased bone density/strength with a concomitant decreased risk of osteoporosis, a co-morbidity observed in up to 70% of adults with Thal[39]. A systematic review of the literature on physical activity and bone strength supports the positive association between weight-bearing exercise and the buildup of bone mass in the growing years[40].

A negative association between Thal and physical activity can carry implications beyond patients' physical health. Regular physical exercise has been associated with positive mental health benefits[41], and better sleep. Etiology of this includes endorphin release, increase in cortical blood flow, reduced emotional strain, buffer against stress, distraction from negative preoccupations, and increase self-esteem[41]. Subjects with Thal slept one hour more per night compared to the controls, though we did not assess the quality of sleep. Recent research suggests that both too much and too little sleep are associated with adverse health outcomes[42]. The optimal amount of sleep appears to be between 6 to 8 hours per night. In this study, a number of patients with Thal slept more than 9 hours per night, which Cappucio and colleagues suggest is can be used as a diagnostic tool related to long-term health consequences. Further research is needed to assess the importance of these mechanisms to improve overall quality of life among those suffering from Thal.

This study was limited in its sample size, particularly for the cohort of transfused subjects. Consequently, our assessment of the effect of transfusion therapy on physical activity patterns may be imprecise. We were also limited by the inability to match occupational status in the case and control subjects. However, if anything, this worked to our disadvantage in that the Thal group participated in more physically demanding jobs, where one might expect overall energy expenditure to be higher. Moreover, given we did not assess pain or mood in this study, we were limited by the inferences we could draw linking physical activity to overall quality of life.

Additionally, we found it interesting that measured activity (by ActiGraph) and those by self-report did not corroborate, particularly for the Thal subjects. Perhaps subjects with Thal perceive themselves to be more active, or desire to be more active than they currently are. Whatever the etiology, this topic requires further exploration in future research.

Conclusion

In conclusion, Thal subjects recorded significantly less total number of steps per day compared to healthy controls. Additionally, substantial differences in daily activity patterns were observed, with Thal subjects taking part in less vigorous activities and more sedentary activities. These findings suggest a substantial degradation in overall physical activity as a result of the various ailments associated with Thal. This provides needed grounding to the common perception that Thal patients exhibit significantly less exercise than their healthy counterparts. Further research is needed following Thal patients in a physical activity regimen best suited to their needs while examining any changes in mental and physical health.

Acknowledgements

The authors would like to thank the patients and their families for their time in volunteering for the study, as well as Catherine Gariepy for her initial assistance and enthusiasm for the project, Elizabeth Scott, who assisted with data management and quality control of the ActiGraph data and Ginny Gildengorin, PhD who provided statistical support and expertise during the data analysis phase.

Financial Support

This publication was supported in part by the Cooley's Anemia Foundation and by the National Center for Advancing Translational Sciences, National Institutes of Health, through the UCSF-CTSI Grant Number UL1 TR000004. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Conflict of Interest

The authors have no competing interests to report

References

1. 2008 physical activity guidelines for Americans. In: Physical activity Guidelines advisory committee: *physical activity guidelines advisory committee report, 2008* Washington, D.D. U.S. Department of Health and Human Services; 2008. http://health.gov/paguidelines/pdf/paguide.pdf. Accessed 15 May 2015.

2. Sohn EY, Kato R, Noetzli LJ, et al. Exercise performance in thalassemia major: correlation with cardiac iron burden. Am J Hematol. 2013;88:193-197.

3. Marinov BI, Terziyski KV, Sapunarova KG, Kostianev SS. Exercise performance in children with severe beta-thalassemia before and after transfusion. Folia Med (Plovdiv). 2008;50(4):48-54.

4. Oliveros O, Tracthenberg F, Haines D, et al. Pain over time and its effects on life in thalassemia. Am J Hematol. 2013;11:939-43.

5. Yengil E, Acipayam C, Kokacya MH, et al. Anxiety, depression and quality of life in patients with beta thalassemia major and their caregivers. Int J Clin Exp Med. 2014;7(8):2165-72.

6. Yahia S, El-Hadidy MA, El-Gilany AH, et al. Predictors of anxiety and depression in Egyptian thalassemic patients: a single center study. Int J Hematol. 2013;97(5):604-9.

7. Chu AH, Koh D, Moy FM, Muller-Riemenschneider F. Do Workplace physical activity interventions improve mental health outcomes? Occup Med. 2014;64(4):235-245.

8. Fox CK, Barr-Anderson D, Neumark-Sztainer D, Wall M. Physical activity and sports team participation: associations with academic outcomes in middle school and high school students. J Sch Health. 2010;80(1):31-37.

9. So WY. Association between physical activity and academic performance in Korean adolescent students. BMC Public Health. 2012;12:258.

10. Wang PS, Huang YC, Wu SF, et al. Effects of daily energy expenditure on academic performance of elementary students in Taiwan. Japan Journal of Nursing Science. 2014;11:1-9.

11. Yates T, Davies M, Gorely T, et al. Effectiveness of a pragmatic education program designed to promote walking activity in individuals with impaired glucose tolerance: a randomized controlled trial. Diabetes Care. 2009;32(8):1404-10.

12. Ross R, Hudson R, Stotz PJ, Lam M. Effects of exercise amount and intensity on abdominal obesity and glucose tolerance in obese adults: a randomized trial. Ann Intern Med. 2015;162(5):325-334.

13. Popp Switzer M, Elhanafi S, San Juan ZT. Change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance. Curr Cardiol Rep. 2015;17(3):562.

14. Drenowatz C, Jakicic JM, Blair SN, Hand GA. Differences in correlates of energy balance in normal weight, overweight and obese adults. Obes Res Clin Pract. 2015;8:S1871-403X.

15. Guo W, Bradbury KE, Reeves GK, Key TJ. Physical activity in relation to body size and composition in women in UK Biobank. Ann Epidemiol. 2015;25(6):406-

413.

16. MacKelvie KJ, McKay HA, Petit MA, Moran O, Khan KM. Bone mineral response to a 7-month randomized controlled, school-based jumping intervention in 121 prepubertal boys: associations with ethnicity and body mass index. J. Bone Miner. Res. 2002;17:834–844

17. Mackelvie KJ, McKay HA, Khan KM, Crocker PR. A school-based exercise intervention augments bone mineral accrual in early pubertal girls. J. Pediatr. 2001;139:501–508.

18. Hind K, Burrows M. Weight-bearing exercise and bone mineral accrual in children and adolescents: a review of controlled trials. Bone. 2007;40:14–27.

19. Vincent L, Feasson L, Oyono-Enguelle S, et al. Skeletal muscle structural and energetic characteristics in subjects with sickle cell trait, a-thalassemia, or dual hemoglobinopathy. J Appl Physiol. 2010;109:728-734.

20. Buchowski MS, Chen KY, Byrne D, Wang WC. Equation to estimate resting energy expenditure in adolescents with sickle cell anemia. Am J Clin Nutr. 2002;76:1335-44.

21. Mavrogeni S, Gotsis E, Verganelakis D, et al. Effect of iron overload on exercise capacity in thalassemic patients with heart failure. Int J Cardiovasc Imaging. 2009;25:777-783.

22. Tudor-Locke C, Craig CL, Aoyagi Y et al. How many steps/day are enough for older adults and special populations. J Behavioral Nutr Physical Activity. 2011;8:80:1-19.

23. Fung EB, Gariepy CA, Sawyer AJ, et al. The effect of whole body vibration therapy on bone density in patients with thalassemia: a pilot study. Am J Hematol. 2012;87 (10):E76-9.

24. Trost SG, Pate RR, Freedson PS, et al. Using objective activity measures with youth: how many days of monitoring are needed? Med Science Sports Exercise. 2000;32:2:426-31.

25. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. Accelerometer. Med Sci Sports Exerc. 1997;30(5):777-781

26. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc. 2008;40:181-188.

27. Eslinger DW, Probert A, Conner Gorber S, et al. Validity of the Actical Accelerometer Step-Count Function. Med Sci Sports Exerc. 2007;39(7):1200-4.

28. Block G, Jensen CD, Block TJ, et al. The work and home activities questionnaire: energy expenditure estimates and association with percent body fat. Journal of Physical Activity and Health. 2009;6:S61-S69.

29. Dong L, Block G, Mandel S. Activities contributing to total energy expenditure in the United States: Results from the NHAPS survey. IJBNPA. 2004;1(4):1-11

30. NIH policy on reporting race and ethnicity data: subjects in clinical research. In: National institutes in health. 2001. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html. Accessed 12 April 2015.

31. Tudor-Locke C, Craig CL, Aoyagi Y et al. How many steps/day are enough for older adults and special populations. IJBNPA. 2011;8:80:1-19.

32. Tudor-Locke C, Craig CL, Brown WJ, et al. How many steps/day are enough: for Adults. IJBNPA. 2011;8:79:1-17.

33. Tudor-Locke C, Craig CL, Brown WJ, et al. How many steps/day are enough: for Children and Adolescents. IJBNPA. 2011;8:78:1-14.

34. Mavrogeni S, Gotsis E, Verganelakis D, et al. Effect of iron overload on exercise capacity in thalassemic patients with heart failure. Int J Cardiovasc Imaging. 2009;25:777-783.

35. Grant GP, Graziano JH, Seaman C, Mansell A. Cardiorespiratory Response to Exercise in Patients with Thalassemia Major. Am Rev Respir Dis. 1987;136:92-97.

36. Oliveros O, Tracthenberg F, Haines D, et al. Pain

over time and its effects on life in thalassemia. Am J Hematol. 2013;11:939-43

37. Shafiee A, Nazari S, Jorjani S, et al. Prevalence of depression in patients with B-thalassemia as assessed by the Beck's Depression Inventory. Hemoglobin. 2014;38 (4):289-91

38. Fung, EB, Xu Y, Kwiatkowski J, et al. Relationship between Chronic Transfusion Therapy and Body Composition in Subjects with Thalassemia. Journal of Pediatrics. 2010;157:4:641-7.

39. Vogiatzi MG, Macklin EA, Fung EB, et al. Bone disease in Thalassemia: a frequent and still unresolved problem. J Bone Miner Res. 2009;24(3):543-557.

40. Tan VP, Macdonald HM, Kim S, et al. Influence of physical activity on bone strength in children and adolexcents: a systematic review and narrative synthesis. J Bone Miner Res. 2014;29(10):2161-81.

41. Camacho TC, Roberts RE, Lazarus NB, et al. Physical activity and depression: evidence from the Alameda county study. Am J Epidemiol. 1991;134:220-231.

42. Cappucio FP, D'Elia L, Strazzullo P, Miller MA.Sleep Duration and All-Cause Mortality: A Systematic Review and Meta-Analysis of Prospective Studies. Sleep. 2010;33(5):585-592.