Comparison of thyroid function tests between splenectomised and non-splenectomised β-thalassemia major patients

Wasan Ayad Hadeed[1] , Yusra Ahmed Hussein Alhially[2] , Ahmed Yahya Dallal Bashi[1]

[1] *Department of Biochemistry , College of Medicine , University of Mosul , Mosul , Iraq*

[2] *Department of Pediatric , Nineveh College of Medicine , University of Nineveh , Mosul , Iraq*

E-mails: dr_wasan2005@yahoo.com

Abstract:

This study was to evaluate and compare thyroid function tests and serum levels of ferritin in splenectomised and non-splenectomised β-thalassemic patients. This study is a case control study that was conducted in the Thalassemia Center in Ibn Al-Atheer Teaching Hospital in Nineveh Province/ Iraq during March-June 2014. Fifty patients of homozygous β-thalassemia major (TM) and twenty five apparently healthy controls were included in this study. The patients were divided into splenectomised and non-splenectomised patients (each 25 patients). Medical history and blood samples were collected from all participants and serum levels of Thyroid stimulating hormone (TSH), Thyroxine (T4), Free thyroxine (FT4), Triiodothyronie (T3), Free triiodothyronine (FT3), and ferritin in addition to body mass index (BMI) were measured.

There were significant decreases in BMI and serum FT4, while there were significant increases in serum TSH and ferritin in β-thalassemia major (in which 10% were diagnosed with hypothyroidism) in comparison with control participants. No significant differences were found between splenectomised and non-splenectomised patients in all parameters measured except a significant positive correlation between serum ferritin and TSH and a significant negative correlation between serum ferritin and T4 that reflects 16% hypothyroidism in splenectomised patients. In addition, significant increases were found in serum TSH and ferritin and a significant decrease in serum FT4 in splenectomised patients when compared with the control. Moreover, a comparison of non-splenectomised patients with control group showed no significant difference in all parameters measured except a significant increase in serum ferritin level. In conclusion, there were certain significant differences in thyroid function tests between β-thalassemia major patients and the controls, whereas there were no significant differences in the means of all studied parameters between splenectomised and non- splenectomised patients except for the positive significant correlation of serum ferritin with TSH level in splenectomised patients which reflect the hypothyroidism in splenectomised TM patients.

Key wards: Thalassemia, splenectomy, Thyroid function tests, ferritin.

Introduction

Beta-thalassemia major (TM) is a congenital hemolytic anemia caused by defects in β-globin chain synthesis and considered to be the most common autosomal single-gene disorder worldwide[1]. Treatment of TM consists mainly of periodic blood transfusion, chelation therapy and if possible bones marrow transplantation. Blood transfusion and iron chelation therapy have improved the quality of life [2]. However, frequent blood transfusions causes progressive iron overload, which is a major clinical complication of this treatment[3]. Iron overload can result in multiple progressive organ damage grouped together under a condition called hemosiderosis. The important complications of iron overload include growth retardation and delay of sexual maturation in children, and later involvement of the heart, liver, spleen and endocrine system leading some times to hypothyroidism[4,5]. The frequency of hypothyroidism in β-thalassemia major patients ranges from 6 to 30% among different countries depending on chelation regimens[6]. Splenectomy is often carried out to avoid complications associated with repeated blood transfusions and to minimize the need and frequency of blood transfusion[7,8]. However, it is now known that splenectomy increases the risk of sepsis and of thrombotic events[9]. Some physicians in Thalassemia Center in Mosul noticed increased frequency of hypothyroidism in splenectomised than in non-splenectomised thalassemia patients and they requested a scientific study to prove that. This study was conducted to evaluate and compare thyroid function tests, and serum levels of ferritin in splenectomised and non-splenectomised β-thalassemia patients and to support or not Mosul thalassemia physician claim.

Materials and methods

Patients

This study is a case control study that was conducted in the Thalassemia Center in Ibn Al-Atheer Teaching Hospital in Nineveh Province/ Iraq during March-June 2014. The study included fifty patients of β-thalassemia major (TM) (25 males, 25 females) with age range 7-26 years. All patients were blood transfusion-dependent (15-20ml packed RBCs/kg at 2-4 weeks interval). All of the 50 patients in this study were on iron chelation therapy. The study consisted of three groups each of 25 subjects (of matched age and gender). Group 1 (non-thalassemic apparently healthy participants as a control group; group 2 (non-splenectomised TM patients); and group 3 (splenectomised TM patients) .

Approval as a volunteer from each subject enrolled in this study or his guardian was taken. The present study had approval from Regional Research Committee of Mosul Health Administration, and the

Scientific Research Committee of the College of Medicine, University of Mosul, Mosul, Iraq.

Methods

From each participant a medical history was taken and a complete physical examination was done, in addition to a questioner list given to each including; sex, age, weight, height, etc. and the BMI of each was calculated. Morning venous blood samples were collected (3ml) from all participants, and sera were obtained and stored at -20°C. Measurement of the serum ferritin by ELISA technique on semi-automated ELISA machine (Biokit model ELx 800, USA) using commercial kits (Accubind ELISA Microwells; Monobind Inc. Lake Forest, CA 92630. USA). Measurements of the thyroid function tests was done by using TOSOH AIA-360 immunoassay analyzer using commercial kits (TOSOH BIOSCIENCE 2012, INC. South San Francisco, CA94080, USA); ST AIA-PACK TSH is designed for the quantitative measurement of thyroid stimulating hormone (TSH); The ST AIA-PACK T4 is designed for the quantitative measurement of thyroxin (T4); The ST AIA-PACK FT4 is designed for the quantitative measurement of non-protein-bound (free) thyroxin (FT4); The ST AIA-PACK T3 is designed for the quantitative measurement of total triiodothyronine (T3); The ST AIA-PACK FT3 is designed for the quantitative measurement of free triiodothyronine (FT3).

Statistical analysis

All the data have been processed and analyzed by the use of the statistical package SPSS ver. 18 (Chicago Inc, Ill). A p-value ≤ 0.05 was considered statistically significant. Independent-samples T-test and one-way ANOVA test was used to compare the means differences of the variables among the groups of the study. When the result of ANOVA test was significant, post hoc tukey test was used. A Pearson correlation coefficient r was use to study the correlation of serum ferritin with different thyroid function tests.

Results

There were significant increases in the means of serum TSH, serum T3 and serum ferritin ($p<0.05$, $p<0.01$, $p<0.001$ respectively), also there were significant decreases in the means of BMI and serum FT4 ($p<0.01$, $p<0.05$ respectively), while no significant differences in FT3 and T4 in thalassemic patients in comparison with control participants (Table 1). As a result of an elevation of thyroid stimulating hormone (TSH) more than 4.3 µIU/ml the percentage of hypothyroidism is 10% of thalassemic patients group as demonstrated in Figure (1). In comparison between studied parameters in three groups (Table 2) there were significant increases in the means of serum TSH and T3, while a significant decrease in the mean of serum FT4 in group 3 when compared with that of group 1 ($P < 0.05$, $P < 0.01$, $p < 0.05$ respectively), in addition a highly significant increase in the mean of serum T3 in group 3 when compared with that of group 2 ($P < 0.001$). Moreover there were highly significant increases in the means of serum ferritin in both patients groups (2, 3) when compared with that of group 1 ($P < 0.001$ for both). On the other hand there were no significant differences in the other parameters (serum T4 and FT3) in the three studied groups ($P > 0.05$) as shown in Table (2). Finally, there was no a significant correlation between serum ferritin with thyroid function tests and age in group 2, while there was a significant positive correlation between serum ferritin and TSH (increase in serum ferritin associated with increase in serum TSH) (Figure 2) and a significant negative correlation between serum ferritin and serum T4 (increase in serum ferritin associated with decrease in serum T4) (Figure 3), whereas serum FT4, T3, FT3 and age showed no significant correlation with serum ferritin in group 3 patients. The results showed that there were 16% of patients in group 3 and 4% of patients in group 2 having hypothyroidism (Figure 4).

Table (1): Comparison of studied parameters between the controls and the thalassemic patients.

Parameters	***Mean ± SD***		***P-value***
	Control	**patients**	
TSH µIu/L	1.635±1.095	2.475±1.737↑	<0.05
T4 nmol/l	73.12±16.84	70.86±16.65↓	NS
FT4 pmol/l	16.73±4.00	14.50±3.26↓	<0.05
T3 nmol/l	1.69±0.22	1.94± 0.40↑	<0.01
FT3 pmol/l	4.07± 0.70	4.40±0.77↑	NS
Ferritin ng/ml	37.56±24.08	4205±2513.13↑	<0.001
BMI Kg / m^2	20.92±3.74	18.64±2.50↓	<0.01
Age years	17.66±5.30	15.28±4.62↓	<0.05

Table (2): Comparison between studied parameters in the three groups.

Serum Parameters	*Mean ± SD*			*P-value*
	Group 1 N=25	*Group 2 N=25*	*Group 3 N=25*	
TSH µIu/L	1.635±1.095[b]	2.110 ± 1.287	2.856 ± 2.067	<0.05
T4 nmol/l	73.12±16.8	71.240 ± 16.20	70.49 ± 17.41	NS
FT4 pmol/l	16.73 ± 4.00[b]	14.67 ± 2.45	14.33 ± 3.96	<0.05
T3 nmol/l	1.69 ±0.22[b]	1.80 ±0.29[c]	2.09 ± 0.44	<0.001
FT3 pmol/l	4.07±0.70	4.46 ± 0.61	4.43 ± 0.91	NS
Ferritin ng/ml	37.56±24.08[a b]	3546.80±1827.05	4863.20±2941.8	<0.001
Age years	30[a] .5±17.66	14.24±4.17	16.32±4.88	<0.05

* Significant difference at p≤0.05. [a] significant difference between group 1 and group 2, [b] significant difference between group 1 and group 3, [c] significant difference between group 2 and group 3.

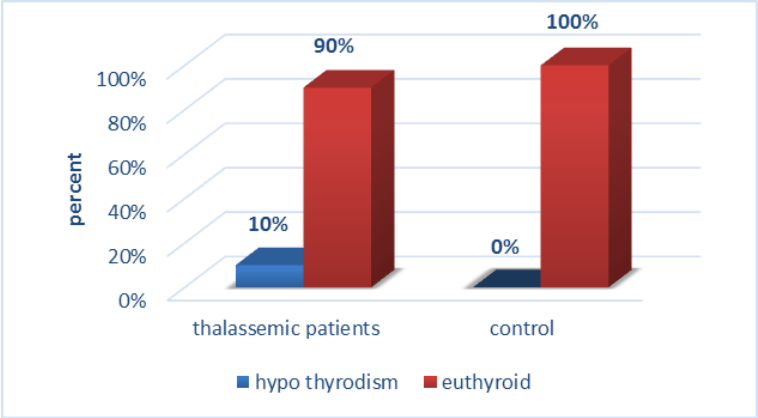

Figure (1): Column chart showing Percentage of thyroid status in patients and Control groups

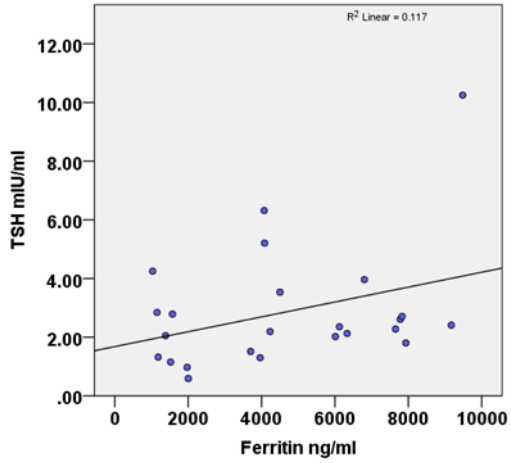

Figure (2): showing linear positive (direct) correlation between serum ferritin and serum TSH in group 3.

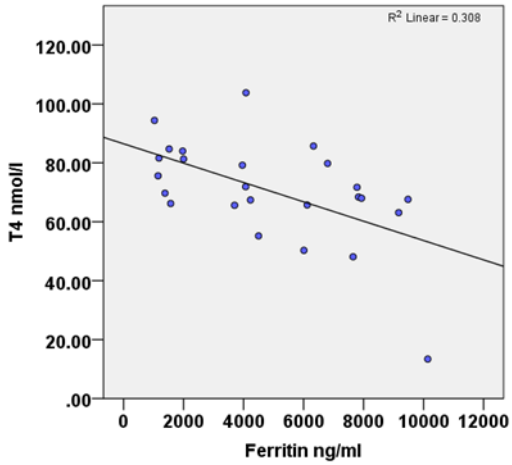

Figure (3): showing linear negative (indirect) correlation between serum ferritin and serum T4 in group 3.

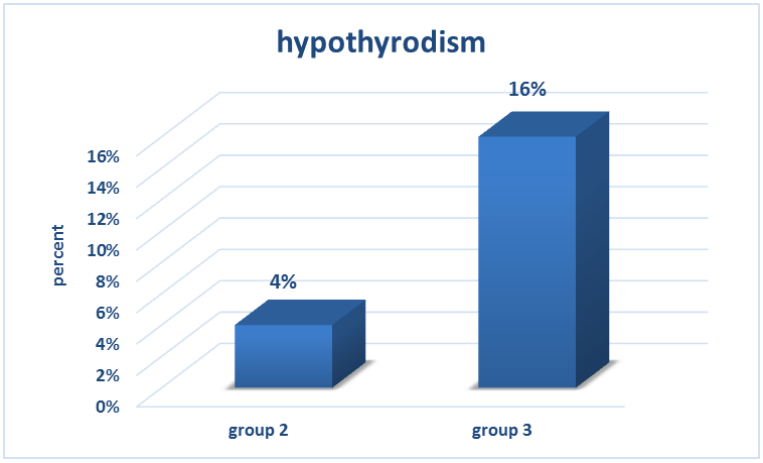

Figure (4): Column chart showing Percentage of hypothyroidism in non-splenectomised (group2) and splenectomised (group 3) β- thalassemia patients.

Discussion

The results of this study demonstrated that there was a significant increase in the mean of serum TSH level in thalassemic patients as compared with the controls. While the mean of serum FT4 was a significantly lower in thalassemic patients as compared with the controls (Table 1). These results might refer to the decline in the function of thyroid gland (as a result of thyroid damage from iron infiltration) and subsequent increase in the secretion of TSH from pituitary gland to compensate that reduction in thalassemic patients group[10]. The results of this study was in accordance with the results of other studies[11,12] . In this study hypothyroidism was found in 10% of thalassemic patients depending on the elevation of thyroid stimulating hormone (TSH) more than 4.3 µIU/ml (Figure 1). This result was in agreement with the results obtained by Salih *et. al*. who found 20% hypothyroidism in their study on thalassemia major patients in the Children's Teaching Hospital in Karbala Province[12]. Moreover, in another study thyroid dysfunction had been reported in 6 to 30% of patients with thalassemia among different countries depending on chelation regimens[5]. However, lower prevalence of hypothyroidism was found in patients who had evidence of lower iron overload as measured by ferritin levels[13]. Moreover, this study demonstrates that there was a significant decrease in the BMI in thalassemia major patients when compared with that of the control group (Table 1). This decrease in BMI might be due to the developed endocrinopathies secondary to iron overload, and also possibly due to the side effects of chelating therapy in long term which are major contributing factors [14,15]. This result agree with the results of others who found that the thalassemic patients had low BMI in their study on thalassemia major patients[12]. In this study all the results of the parameters measured in group 3 when compared with that of group 2 showed no significant difference except for serum T3 (Table 2) which might be accounted to be due the non-significant difference in serum ferritin levels in both patient's groups. This result was in agreement with the results obtained by other investigators who found insignificant differences between splenectomised and non-splenectomised thalassemic patients in thyroid function tests and serum ferritin[12,16].

On the other hand the direct significant correlation of serum ferritin with serum TSH level and indirect significant correlation of serum ferritin with serum T4 (Figure 2&3) in splenectomised patients (group 3) which reflected the high incidence of hypothyroidism (16%), while in non-splenectomised patients (group 2) there was no significant correlation between serum ferritin and the parameters for thyroid function and only 4% had hypothyroidism (Figure 4). The intact spleen might be a reservoir of excess iron and might have a possible scavenging effect on iron free fractions including non-transferrin bound iron[17]. Nonetheless, splenectomy was associated with high rates of endocrinopathy in patients even with low serum ferritin levels, suggesting that other contributing factors might be involved, splenectomised patients showed higher levels of haemolysed, prothrombotic red blood cells and subsequent thrombin generation [18,19]. This result was in consistence with that of Belhoul *et. al*. who diagnosed hypothyroidism in 26% of splenectomised thalassemic patients and 4.5% of non-splenectomised thalassemic patients[20]. A similar results also obtained in other studies[21,22,23].

When comparing the results of the parameters in group 3 with that of group 1, significant increases in the means of serum TSH and serum ferritin and a significant decrease in the mean of serum FT4 were found (Table 2). In fact, splenectomised patients were characterized by a decreased extra hepatic iron buffering capacity, with an accelerated iron deposition in several tissues, including thyroid gland [24]. Whereas, when comparing the results of the parameters in group 2 with that of group 1 there was no significant difference in all parameters studied except serum ferritin. Significant increases in the means of serum T3 was found in group 3 when compared with that of group 1 and group 2. Anyhow, measuring of total serum T3 is inaccurate screening test of thyroid status, because serum T3 concentration fluctuated rapidly in response to stress and other non-thyroidal factors[25].

References

1. Angastiniotis, M. and Modell, B. (2006). Global epidemiology of hemoglobin disorders. In: Cohen AR, ed. Cooley's anemia: Seventh Symposium. New York, NY: New York Academy of Sciences, USA pp 251–69.

2. Telfer, P.T.; Warburton, F.; Christou, S.; Hadjigavriel, M.; Sitarou, M. and Kolnagou, A. (2009). Improved survival in thalassemia major patients on switching from desferrioxamine to combined chelation therapy with desferrioxamine and deferiprone. Haematologica 94(12): 1777-8.

3. Abdulzahra, M.S.; Al-Hakeim, H.K. and Ridha, M.M. (2011). Study of the effect of iron overload on the function of endocrine glands in male thalassemia patients. Asian J Transfus Sci. 5: 127–31.

4. Vichinsky, E.P. (2005). Changing patterns of thalassemia worldwide. Ann N Y Acad Sci 1054: 18-24.

5. Galanello, R. and Origa, R.(2010). Beta-thalassemia. Orphanet Journal of Rare Diseases 5:112.

6. De Sanctis, V.; Eleftheriou, A. and Malaventura, C. (2004). Prevalence of endocrine complications and short stature in patients with thalassaemia major: a multicenter study by the Thalassaemia International Federation (TIF). Pediatr Endocrinol Rev. Suppl 2 : 249-55.

7. Al-Salem, A.H. and Nasserulla, Z. (2002). Splenectomy for children with thalassemia. Int Surg 87: 269-73.

8. Graziano, J.H.; Piomelli, S.; Hilgartner, M.; Giardina, P.; Karpatkin, M. and Andrew, M. (1981). Chelation therapy in beta thalassemia major. III. The role of splenectomy in achieving iron balance. J Pediatr 99: 695-9.

9. Pecorari, L.; Savelli, A.; Cuna, C. D.; Fracchia, S. and Pignatti, C. (2008). The role of splenectomy in thalassemia major. An update. Acta Pediatrica Mediterranea 24: 57-65.

10. Al-Hakeim, H.K. and Al-Hakany, M.F. (2013). The Effect of Iron Overload on the Function of Some Endocrine Glands in β-Thalassemia Major Patients. Magazin of Al-Kufa University for Biology 5(2): 35-6.

11. Rund, D. and Rachmilewitz, E. (2005). Medical progress in b-Thalassemia. N Engl J Med 353: 1135–46.

12. Salih, K.M. and Al-mosawy, W.F. (2013). Evaluation some consequences of thalassemia major in splenectomized and non-splenectomized Iraqi patients. Int J Pharm Pharm Sci, 5 (Suppl 4): 385-8

13. Borgna-Pignatti, C.; Rugolotto, S.; De Stefano, P.; Zhao, H.; Cappellini, M.D. and Del Vecchio, G.C. (2004) Survival and complications in patients with thalassemia major treated with transfusion and desferrioxamine, Haematologica, 89(10): 1187-93.

14. Kattamis, C.; Liakopoulou, T. and Kattamis, A. (1990). Growth and development in children with thalassemia major. Act Paediatr Scand Suppl 1: 111-7.

15. Asadi-Pooya, A.A. and Karamifar, H. (2004). Body mass index in children with beta-thalassemia major. Turk J Haematol. 21(4): 177-80.

16. Morsy, M.M.; Alnajjar, A.A.; Almuzainy, I.S.; Alhawsawi, Z.M.; Alserafi, M.H. and Ahmed, AA. (2008). splenectomized versus non- splenectomized patients with thalassemia major (Ecocardiographic comparision). Saudi Med J. 29(9):1310-4.

17. Tavazzi, D.; Duca, L.; Graziadei, G.; Comino, A.; Fiorelli, G. and Cappellini, M.D. (2001). Membrane-bound iron contributes to oxidative damage of beta-thalassaemia intermedia erythrocytes. Br J Haematol. 112:48–50.

18. Eldor, A. and Rachmilewitz, E.A. (2002). The hypercoagulable state in thalassemia. Blood 99:36–43.
19. Cappellini, M.D.; Motta, I.; Musallam, K.M. and Taher, A.T. (2010). Redefining thalassemia as a hypercoagulable state. AnnN YAcad Sci 1202:231–6.
20. Belhoul, K.M.; Bakir, M.L.; Saned, M.S.; Kadhim, A.M.; Musallam, K.M. and Taher, A.T. (2012). Serum ferritin levels and endocrinopathy in medically treated patients with β thalassemia major. Ann Hematol 91:1107-14.
21. Gamberini, M.R.; De Sanctis, V. and Gilli, G. (2008). Hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism: incidence and prevalence related to iron overload and chelation therapy in patients with thalassaemia major followed from 1980 to 2007 in the Ferrara Centre. Pediatr Endocrinol Rev 6(Suppl 1):158–69.
22. Jaruratanasirikul, S.; Chareonmuang, R.; Wongcharnchailert, M.; Laosombat, V.; Sangsupavanich, P. and Leetanaporn, K. (2008). Prevalence of impaired glucose metabolism in beta-thalassemic children receiving hypertransfusions with a suboptimal dosage of iron chelating therapy. Eur J Pediatr 167:873–6.
23. Skordis, N.; Michaelidou, M.; Savva, SC.; Ioannou, Y.; Rousounides, A.; Kleanthous, M.; et. al. (2006). The impact of genotype on endocrine complications in thalassaemia major. Eur J Haematol 77:150–6.
24. Brewer, C.J.; Coates, T.D. and Wood, JC. (2009). Spleen R2 and R2* in iron-overloaded patients with 422 sickle cell disease and thalassemia major. J Magn Reson Imaging 29: 357-64.
25. Burtis, C.A. and Ashwood, E.A. (2008). TIETZ Textbook Of Clinical Chemistry. 6th ed. WB Saunders, Philadelphia. pp 766-79.

مقارنة فحوصات وظيفة الغدة الدرقية بين مرضى الثلاسيميا الكبرى نوع بيتا ممن استؤصلت لهم طحالاتهم مع من لم تستأصل لهم

وسن أياد حديد[1] ، يسرى احمد حسين الحيالي[2] ، احمد يحيى دلال باشي[1]

[1]قسم الكيمياء الحياتية ، كلية الطب ، جامعة الموصل ، الموصل، العراق

[2]قسم طب الأطفال ، كلية طب نينوى ، جامعة نينوى ، الموصل ، العراق

الملخص

الهدف من هذه الدراسة هو لتقييم و اجراء مقارنة فحوصات وظيفة الغدة الدرقية و مستويات الفريتين في مصل الدم بين مرضى الثلاسيميا الكبرى نوع بيتا ممن استؤصلت لهم طحالاتهم مع من لم تستأصل لهم. اجريت هذه الدراسة في مركز الثلاسيميا في مستشفى ابن الاثير التعليمي في محافظة نينوى حيث، شملت الدراسة 50 شخصا من مرضى الثلاسيميا الكبرى نوع بيتا و 25 شخصا سليما كمجموعة ضابطة. قسم المرضى الى مجموعتين مجموعة من المرضى ممن قد تم استئصال الطحال لديهم ومجموعة من المرضى ممن لم يستأصل لهم الطحال (25 مريض لكل مجموعة). تم اخذ التاريخ الطبي و عينات الدم واجريت الفحوصات المختبرية الخاصة بوظيفة الغدة الدرقية ومصل الفريتين وتم قياس مؤشر كتلة الجسم لكل المشاركين.

وجد مؤشر كتلة الجسم وال FT4 منخفض بشكل معنوي, بينما وجد الفريتين, وال TSH لمصل الدم كان مرتفع بشكل معنوي في مرضى الثلاسيميا (حيث كان قد شخص 10% منهم مصابين بكسل في الغدة الدرقية) مقارنة بالأشخاص السليمين. لم يكن هناك اي اختلاف معنوي في مجموعة المرضى الذين استؤصل منها الطحال عن مجموعة المرضى بدون استئصال الطحال في الفحوصات المختبرية ماعدا وجود علاقة معنوية طردية بين مصل الفرتين وال TSH وعلاقة معنوية عكسية بين مصل الفريتين وال T4 في مجموعة المرضى الذين استؤصل منها الطحال حيث وجد 16% منهم لديهم كسل في الغدة الدرقية. عند مقارنة مجموعة المرضى الذين استؤصل منها الطحال مع المجموعة الضابطة، وجدنا ارتفاع معنوي في مصل الفريتين وال TSH وانخفاض معنوي في ال FT4, بينما عند مقارنة مجموعة المرضى الذين بدون استئصال الطحال مع المجموعة الضابطة، لم يلاحظ اي فرق معنوي ما عدا الارتفاع في فريتين مصل الدم. نستنتج من هذه الدراسة ان هنالك عدد من الفروقات المعنوية لفحوصات وظيفة الغدة الدرقية بين مرضى الثلاسيميا الكبرى نوع بيتا وبين مجموعة السيطرة بينما لا يوجد فروقات معنوية في معدلات جميع الفحوصات التي تم دراستها بين مرضى الثلاسيميا ممن استؤصل لهم طحالاتهم مع من لم تستأصل لهم. كما وجد فرق معنوي طردي للعلاقة بين الفريتين وال TSH في مصل الدم والعلاقة المعنوية العكسية للفريتين وال T4 في مصل الدم لدى مجموعة المرضى المستأصل طحالاتهم مما ادّى الى كسل الغدة الدرقية لديهم.