Review Article *Iran J Ped Hematol Oncol. 2016, Vol 6.No 3, 261-276*

Prevalence of Hypothyroidism, Hypoparathyroidism and the Frequency of Regular Chelation Therapy in Patients with Thalassemia Major in Iran: A Systematic Review and Meta-analysis study

Milad Azami MD[1], Naser Parizad MD[2], Kourosh Sayehmiri MD[3*]

1. Student Research Committee, Ilam University of Medical Sciences, Ilam, Iran
2. Nursing and midwifery faculty, Urmia University of Medical Sciences, Urmia, Iran
3. Department of Biostatistics, Psychosocial Injuries Research Center, Ilam University of Medical Sciences، Ilam, Iran
*Corresponding author: Kourosh Sayehmiri, MD. Department of Biostatistics, Psychosocial Injuries Research Center, Ilam University of Medical Sciences, Ilam, Iran E-mail: Sayehmiri@razi.tums.ac.ir

Received: 18 May 2016 **Accepted:** 28 July 2016

Abstract

The present study aimed to determine the prevalence of hypothyroidism, hypoparathyroidism and the frequency of regular chelation therapy in patients with thalassemia major in Iran. Searching process was performed by two independent researchers using a valid keywords in the national and international database, including: Magiran, Iranmedex, SID, Medlib, Scopus, PubMed, Science Direct, Cochrane, Web of Science, Springer, Wiley Online Library and google scholar search engine. All studies were searched until 2016 with no time limit. All articles met inclusion criteria were evaluated and the data were analyzed by using SATA Software Ver.11.1. Twenty seven studies about hypothyroidism (sample size of 4851, the mean age of 16.36±5.5) and 19 studies related to hypoparathyroidism (sample size of 3219, the mean age of 17.44±6.5) were examined. The prevalence of hypothyroidism was calculated 5.7% (95% CI: 6.8-4.7) in patients with thalassemia major in Iran (P=0.000; I2 index=93.9%). The prevalence of overt and subclinical hypothyroidism was estimated 3.1% (95% CI: 1-4.7) and 6.7% (95% CI: 3.3-10), respectively. The prevalence of hypoparathyroidism was calculated 10% (95% CI: 7-12) in patients with thalassemia major in Iran. In reviewing 5 studies, the frequency of regular chelation therapy was estimated 54.6% (95% CI: 28-81.2) in these patients. The prevalence of hypothyroidism and hypoparathyroidism is high in patients with thalassemia major in Iran. Thus, new planning and supervising seem to be essential to minimize endocrine complications in these patients. There is no connection between serum ferritin level and developing hypoparathyroidism. A high percent of Iranian patients with thalassemia major perform the chelation therapy irregularly. It's been recommended to adopt the necessary measures such as educating and enhancing awareness of the patients about its complications.

Keywords: Chelation Therapy, Hypoparathyroidism, Hypothyroidism, Meta-analysis, Thalassemia Major

Introduction

Thalassemia syndrome is a hereditary hemoglobinopathies that is transmitted to a person as a consequence of mutation in genes that are responsible for producing the alpha or beta-globin chains. If the genes for beta chains are mutated, it will lead to beta thalassemia. If both beta genes are defective, the person has thalassemia major and severe anemia (1-2). This disease is prevalent in Mediterranean regions, some parts of north and west Africa, the Middle East, the Indian Peninsula, the Far East and Southeast Asia. Above-mentioned areas are known to "the thalassemia belt". Beta thalassemia major is the most common hemoglobinopathies in Iran. Studies show that around 20000 patients and about 2-3 million (4% of the population) are carriers of the disease in Iran. The distribution of the disease is not the same in different parts of the country. On the margins of the Caspian Sea in the north and the Persian Gulf and Oman Sea in the south is more common than other areas.

The results show up to 10 percent of the population carry the gene for thalassemia in the provinces of Khuzestan, Bushehr, Hormozgan, Sistan and Baluchestan, Kerman, Gilan, Mazandaran and even in the central provinces such as Isfahan and Fars (3-4).

The red blood cells have an abnormal life and are destroyed at a faster rate in these patients (5). The symptoms start with anemia, and associated with changing appearance, bone abnormalities, weakness and growth retardations (6). Treatment includes regular monthly blood transfusion that reduces acute symptoms. But receiving blood cause many complications such as infections, alloimmunization and excess iron deposition in various organs that can cause liver failure, heart disease, diabetes mellitus, hypothyroidism, hypoparathyroidism and hypogonadism (7-10). To prevent these complications, chelation therapy is used to remove excess iron. But, endocrine disorders can be still observed (11). The complications of patients with thalassemia major may be caused by inappropriate chelation therapy in the developing countries (8). Some studies suggest that the possible causes of the high prevalence of endocrine complications in patients who receive chelation therapy is an irregular and improper treatment. This has been reported differently in similar studies in Iran.

Hypothyroidism

Hypothyroidism is a clinical syndrome caused by lack of thyroid hormones. It is usually primary (Thyroid failure), but may be secondary (failures of the pituitary gland or the hypothalamus) or because of the resistance of thyroid hormone cell surface receptor. Iron deposition in the thyroid gland declines its ability to produce hormones in patients with thalassemia major and develops the primary hypothyroidism (12-13). Studies have shown that early diagnosis and treatment of hypothyroidism in patients with thalassemia major reduce cardiac dysfunction and increase quality of life (14). Primary hypothyroidism is characterized by elevated TSH and low T4, while low levels of TSH and T4 indicate secondary (central) hypothyroidism (15).

Hypoparathyroidism

Parathyroid hormone (parathormone) is a polypeptide hormone secrets by chief cells of the parathyroid glands. Hypocalcemia stimulates the release of parathyroid hormone. Four parathyroid glands are located in the posterior part of the thyroid gland. They are responsible for regulating of the serum calcium level. Parathyroid hormone plays a role in maintaining extracellular calcium through a direct effect on the kidneys and bones as well as an indirect effect on the small intestine. The falling parathyroid hormone in the blood causes the blood calcium and calcitonin to drop. Since, parathyroid hormone along with vitamin D regulate the body calcium level, so its deficiency lead to hypocalcemia symptoms, including pain and muscle cramps, numbness, tingling, seizures, Carpopedal spasms, Trousseau and Chvostek signs (16-18).

Systematic review and metaanalysis study seems essential to combine all relevant evidences and provide an an overall estimation to present a full picture of the problem (19-20). So far, various studies have been conducted on the prevalence of hypothyroidism and hypoparathyroidism in patients with thalassemia major in Iran. The results show the prevalence of these disorders has been reported differently (21-49). Thus, the present study aimed to determine the prevalence of hypothyroidism, hypoparathyroidism and the frequency of regular chelation therapy in patients with thalassemia major in Iran.

Material and Methods

Meta-analysis is a statistical technique that extracts and analyzes data from several studies to provide a reliable estimate for the effectiveness of some interventions or

observations in medicine (50). In a meta-analysis, collecting data from several studies leads to a larger sample size. Therefore, the range of variation and probability decreases. This improves the statistical results and making this method more reliable (50-51).
The present study was performed based on the PRISMA check list for meta-analysis studies (51). To prevent the bias, search process, study selection, quality assessment and data extraction conducted by two researchers independently.

Data Sources

The present study was conducted by reviewing the articles and theses until 2016. No time limit is considered in the study. To investigate the findings, searching process was conducted by two independent researchers using a valid keywords in the national and international database, including: Magiran, Iranmedex, SID, Medlib, Scopus, PubMed, Science Direct, Cochrane, Web of Science, Springer, Wiley Online Library and also google scholar search engine. To maximize the comprehensiveness of searching, the general Persian and English keywords including: haemoglobinopathy, Prevalence, Complications, Endocrine, Hypothyroidism, Thyroid Disorders, Hypoparathyroidism, Endocrine Disorders, Ferritin, Hemosiderosis, Iron Overload, Chelation Therapy, Thalassemia Major, Deferral, desferrioxamine and Iran were used. MeSh keywords and word combination (using "AND" or "OR") was used in an electronic English database. The list of references in the related articles was reviewed to obtain more studies.

Inclusion and Exclusion Criteria

Inclusion criteria include the studies that investigated the prevalence of hypothyroidism, hypoparathyroidism and chelation therapy in patients with thalassemia major. Exclusion criteria include the studies: 1- with non-random sample size 2- unrelated to the topic 3- with inadequate data 4- that diagnosis isn't based on clinical and laboratory findings.

Definition

Hypothyroidism was diagnosed by clinical examination and thyroid function tests (TFT) and hypoparathyroidism diagnosis was determined based on clinical examination and laboratory results such as low calcium level, elevated serum phosphate, low parathyroid hormone level and the disproportion of parathyroid hormone level with the serum calcium level (6). The experience shows that after 10-20 blood transfusions or when the ferritin level reached more than 1000mg. Desferal 30-40 mg/kg per day during 8-12 hours for 5 days a week needs to be injected subcutaneously by mechanical pumps (15).

Quality assessment

Two researchers evaluated the selected articles independently by using the STROBE statement (52). The authors utilized a simple method for rating. Two points were given for each part of the Checklist. Then, the given points of the articles were compared by two researchers. Accordingly, the studies were divided into three categories: 1-Low quality with less than 16 points; 2- Medium quality with 16-29.5 points; 3- High quality with 30-44 points. The studies which obtained the minimum points were selected for the meta-analysis. Articles that received the minimum quality evaluation score (16 was considered minimum score) were entered into meta-analysis.

Data extraction

Data extraction was conducted by two researchers independently, and using an extraction form (the author's name, year of publication, the number of participants, the overall prevalence rate, the prevalence by sex), to minimize bias and error in collecting data. If some information was not clear or missing in the articles and need to be clarified, required questions

were asked from the author by e-mail. Extracted data were compared by two researchers. If there was any conflict in extracting data, it was discussed by a third researcher to come to an agreement by re-evaluating and comparing the results.

Statistical analysis

Since, the prevalence of hypoparathyroidism and sample size were extracted in every study, binomial distribution was used to calculate the variance of each study. Cochran test and I2 index were used to assess the heterogeneity of the studies. The heterogeneity of this study was 88% and placed among the studies with high heterogeneity (I2 index less than 25% = low heterogeneity; between 25%-75% = moderate heterogeneity; more than 75% = high heterogeneity). The random effects model was used in the meta-analysis, due to the heterogeneity of the studies and significant heterogeneity index (53-54). Mean weight is used for combining the prevalence of different studies; weight was given to each study inversely proportional to its variance. The Meta - regression model was used to investigate the relationship between the prevalence of hypoparathyroidism and the year of study. Data were analyzed using SATA software ver. 11.1. A significance level was considered less than 0.05. There's no need to measure publication bias and funnel plot, because all analyzed data were about the prevalence rate and checklist parameters considered carefully in the quality control process for selecting qualified studies.

Results

In this systematic review, 620 articles were identified. After reviewing titles, 340 articles were excluded due to duplication. The full text of 280 relevant articles was reviewed and 231 articles excluded: unrelated to the topic (127), unrelated to the patients with thalassemia (53), not about Iranian patients (13), no data about hypothyroidism, hypoparathyroidism and chelation therapy, (45) Review studies (4), Non-random sample (2), and poor quality (2). Figure 1 shows the flowchart for selecting the studies.

Finally, 27 studies about hypothyroidism (sample size of 4851 and the mean age 16.36±5.5 years old) and 19 studies related to hypoparathyroidism (sample size of 3219 and the mean age 17.44±6.5 years old) were investigated (Table I).

In this study, the prevalence of hypothyroidism was calculated 5.7% (95% CI [Confidence Interval]: 6.8 to 4.7) in patients with thalassemia major in Iran (P=0.000; I2 index=93.9%). The high I2 index represents significant heterogeneity among the studies. The lowest prevalence of hypothyroidism is related to Mostafavi study in Shiraz in 2003 (0%) and the highest prevalence is related to Najafipour study in Tabriz in 2006 (26.7%). The lowest and highest prevalence of hypothyroidism in the conducted studies by geographical regions was associated with East (0%) and North of Iran (15%), respectively (Figure 2).

The prevalence of hypothyroidism by sex had been investigated in 4 studies, and estimated 13.1% (95% CI, 5 to 21.3) in males and 10.2% (95% CI, 0.7 to 21.2) in females (Table II).

The prevalence of overt and subclinical hypothyroidism was estimated 3.1% (95% CI: 1 to 4.7) and 6.7% (95% CI, 3.3 to 10), respectively (Table III).

The prevalence of hypoparathyroidism was calculated 10% (95% CI: 7 to 12) in patients with thalassemia major in Iran. The lowest prevalence was in the study of Arjmandi Rafsanjani in Tehran in 2004 (1.2%) and the highest prevalence was related to the Zandi study in Ahwaz in 2003 (27.1%) (Figure3).

Due to the heterogeneity of the studies, the prevalence of hypoparathyroidism was investigated in every region of Iran. Its prevalence was 14% in the west, 18% in the east, 10% in the north, 12% in the

south and 7% in the center of Iran. (Figure 4)

No significant relationship was found between the prevalence of hypoparathyroidism and sex (P>0.05). The prevalence was estimated 14% (95% CI: 8 to 20) in women and 9% (95% CI: 5 to 13) in men. (Table II)

Four studies were evaluated the relationship between serum ferritin level and hypoparathyroidism in patients with thalassemia major. Our estimate of the standardized mean difference in serum ferritin was 1 ng/ml (95% CI: 27 to 24) in the case and control groups. Because the confidence interval crossed the zero line, the difference was not statistically significant. (Figure 5)

The Meta-regression model was used to investigate the relationship between hypothyroidism and hypoparathyroidism based on the year of study. P-value was estimated 0.874 and 0.433 respectively, and the relationship was not statistically significant. (Table III)

By reviewing 5 studies (sample size of 492 and I2 index=97.8%), the frequency of chelation therapy was estimated 99.6% (95% CI: 99.1 to 100), but the frequency of regular chelation therapy was estimated 54.6% (95% CI: 28 to 81.2) in patients with thalassemia major in Iran.

Table I: A summary of articles included in the study

Author Name	Place	Year	Sample size	Mean age (Mean±SD)	Prevalence of Subclinical hypothyroidism (%)	Prevalence of overt hypothyroidism (%)	Prevalence of hypothyroidism (%)	Prevalence of hypoparathyroidism (%)	Frequency of Regular Iron Chelation Therapy(%)
Company (9)	Sanandaj	2006	40	12.7±5.8	15	0	15		60.6
Mehrvar (21)	Tehran	2005	379	27.1± 7			3.9		
Najafipour (22)	Tabriz	2006	65	15.6±4.4	10.7	16	26.7		67
Zandeyad (23)	Gorgan	2001	185	17.8±9			16.2		87.7
Zandian (24)	Ahvaz	2009	214		2.8	2.4	5.2	1.27	
Rostami (25)	Bushehr	2009	60	20.23±23	1.7	1.7	3.4	7.21	
Vahidi (26)	Kerman	2008	340	14.72±7.6			3.5	8.5	
Mostafavi (27)	Shiraz	2003	44	15.7±3.7			0		
Shamshirsaz (2)	Tehran	1999	220	15.2±5.1	0	7.7	7.7	7.6	
Safari (4)	Qazvin	2006	63	20.89±5			6.3	6.3	
Chahkandi (28)	Birjand	2003	31	2.5-16			0	9.12	
Hadaegh (29)	Hormozgan	2002	109	13±3.7			0		
Farahani (30)	Tehran	2006	178	17.2±8	13.5	3.4	16.9		
Kashanchi Langroodi (6)	Karaj	2010	184	19.64±7.1	19	1.6	20.6		
Razavi (31)	Hamedan	2002	56				5.3	2.14	
Ansari (32)	Shiraz	2005	806	15.34±6.8			2.4	6.9	
Karami (33)	Infectious	2007	60	19±5.7			3.3		
Rabani (5)	Tehran	2000	315					2.2	
Soheili Khah (34)	Yazd	1998	53	10.7	1.9	5.3	7.2	5.24	
Mahdavi Anari (35)	Tehran	1999	60				10	5	
Seyedi (36)	Kerman	1998	72	11.6±3.5	4.2	2.7	6.9		
Nasiri (37)	Tehran	1998	500				7.4		
Shiva (38)	Tabriz	2006	71	12.9±5.2			16.9	9.16	
Hashemi (39)	Yazd	2011	65	10.3±7.9	7.6	1.5	21.4		
Rafsanjani Arjomandi (40)	Tehran	2004	243	14±6.5			2.8	1.2	
Mozyeri (41)	Tehran	2004	158	15.1±4.8		4.4	4.4	6.7	
Bahraqi (42)	Babylon	2010	280	19.6±8.5			15.7		
Yazdi (43)	Yazd	2005	65	10.3				6	
Safari (44)	Qazvin	2012	77	21.2±4.5					
Karamifar (45)	Shiraz	2003	150					7.3	
MiriAliabad (46)	Zahedan	2013	233	23±4				18.4	
Hamidieh (47)	Qom	2007	130	16±10				14.6	
Company (48)	Sanandaj	2009	84	12.8±5.8					40.5
Azimipour (49)	Qazvin	2001	87						17.3

Table II: Estimated prevalence of hypothyroidism and hypoparathyroidism in patients with thalassemia major in Iran by sex

Variable	Sex	Number of studies	Sample size	I^2	CI	The overall prevalence (%)
Hypothyroidism	Male	4	216	69.6	5-21.3	13.1
	Female	4	358	95.2	0.7-21.2	10.2
Hypoparathyroidism	Male	6	844	70.2	5-13	9
	Female	6	870	80.8	8-20	14

Table III: Prevalence of clinical and subclinical hypothyroidism in patients with thalassemia major in Iran

Variable	Number of studies	Sample size	I^2	CI	The overall prevalence (%)
Clinical Hypothyroidism	11	1309	81.9	1-4.7	3.1
Subclinical Hypothyroidism	10	1151	91.2	3.3-10	6.7

Table IV: Meta-regression of hypothyroidism and hypoparathyroidism in patients with thalassemia major in Iran by year

Variable	Year	Diagram Motion	P-Value
Hypothyroidism	1998-2011	Ascending	0.176
Hypoparathyroidism	1998-2013	Ascending	0.433

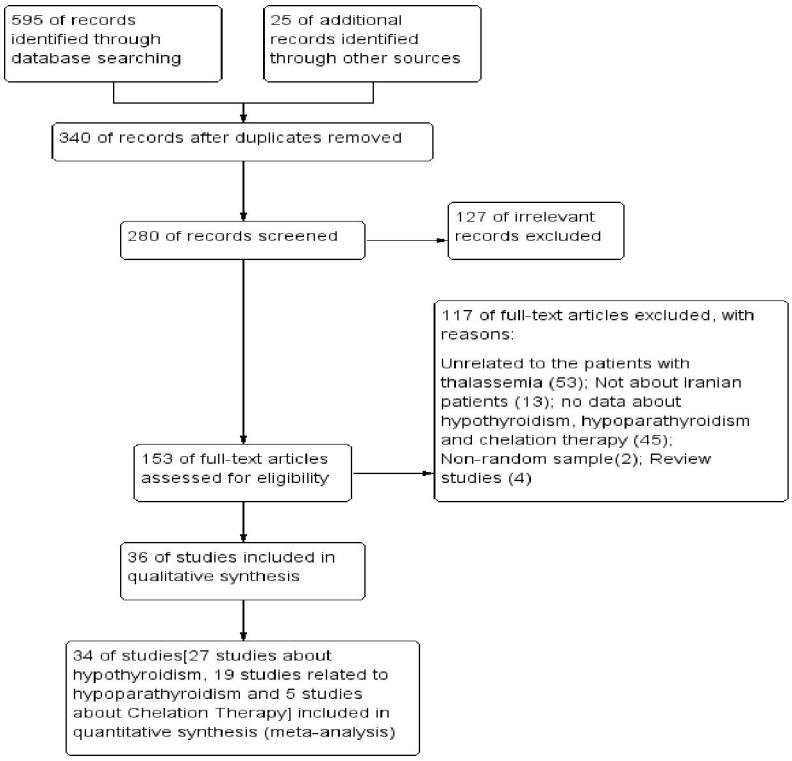

Figure1. Study Flowchart

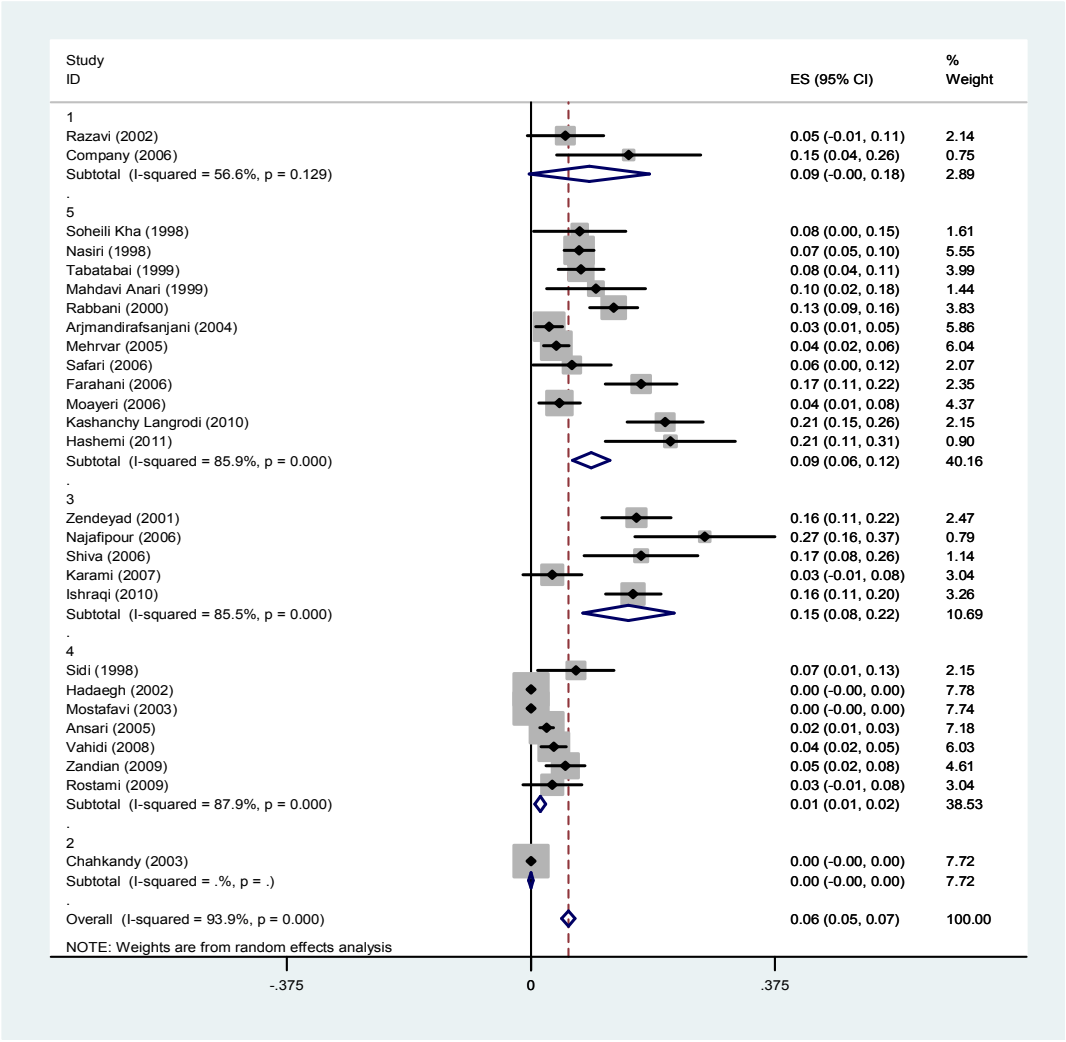

Figure 2. The prevalence of hypothyroidism in patients with thalassemia major in Iran by Geographic regions based on a random effects model, point estimate and segment length show percentage rate and 95%confidence interval in each study, respectively. Lozenge-shaped mark shows the prevalence of hypoparathyroidism for all the studies (1. West, 2. East, 3. North, 4. South, 5. Center).

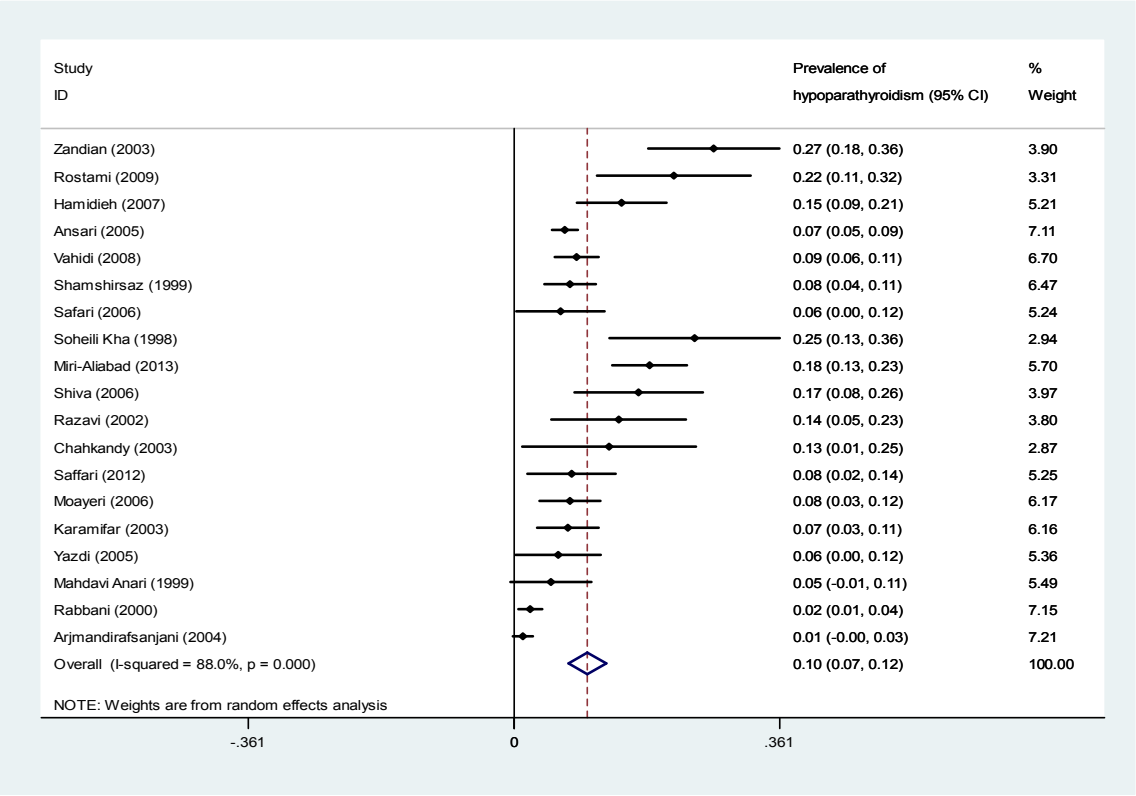

Figure3. The prevalence of hypoparathyroidism in patients with thalassemia major based on a random effects model, point estimate and segment length show percentage rate and 95%confidence interval in each study, respectively. Lozenge-shaped mark shows the prevalence of hypoparathyroidism for all the studies.

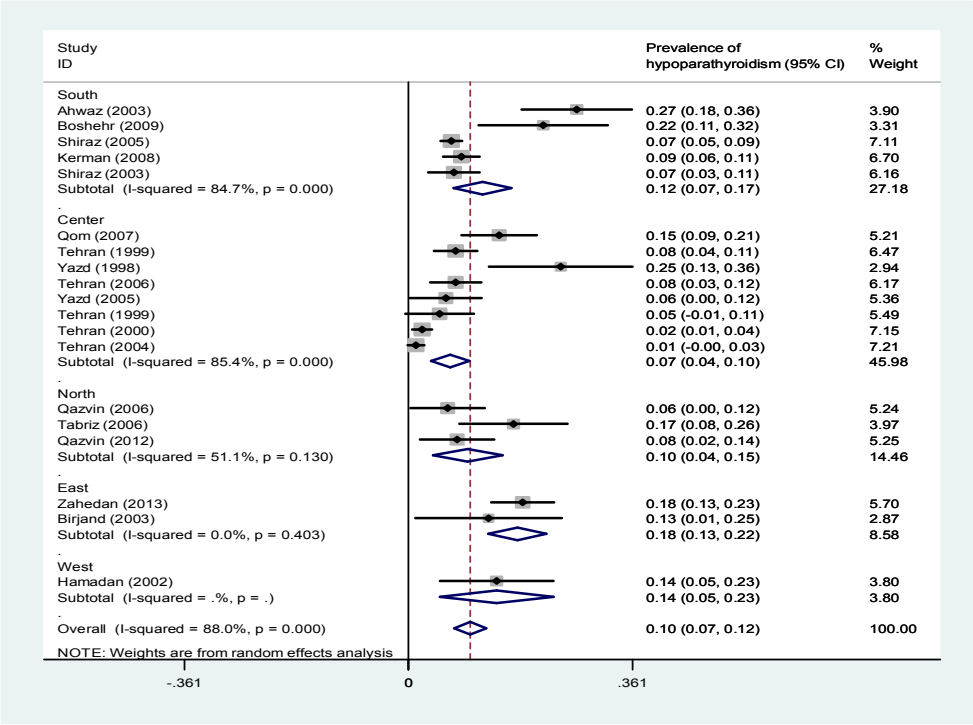

Figure4. The prevalence of hypoparathyroidism in patients with thalassemia major in Iran by Geographic regions based on a random effects model, point estimate and segment length show percentage rate and 95%confidence interval in each study, respectively. Lozenge-shaped mark shows the prevalence of hypoparathyroidism for all the studies.

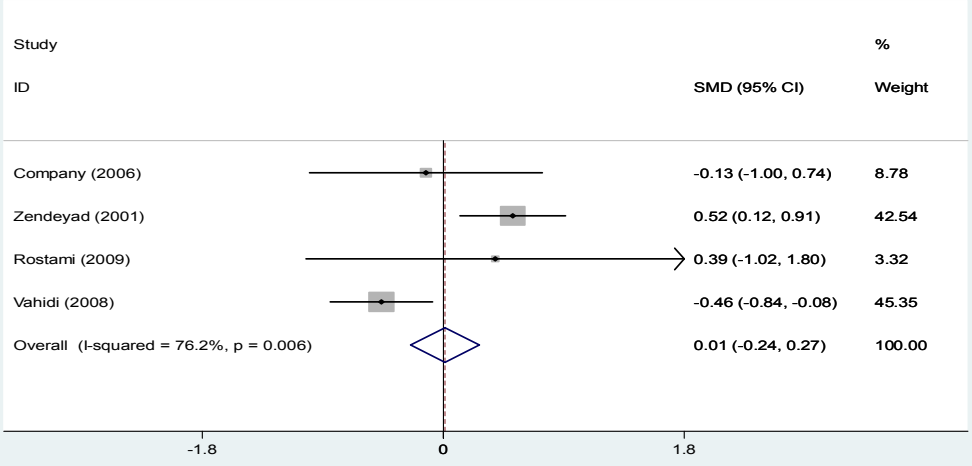

Figure5. The relationship between serum ferritin and hypoparathyroidism based on a random effects model, point estimate and segment length shows the standardized difference and 95% confidence interval in each study, repectively.

Discussions:

This study is the first systematic review and meta-analysis about the prevalence of hypothyroidism, hypoparathyroidism and the frequency of regular chelation therapy in patients with thalassemia major in Iran. In this study, the prevalence of hypothyroidism, hypoparathyroidism was studied by geographic regions, sex and year of study in patients with thalassemia major.

The overall prevalence of hypothyroidism and hypoparathyroidism was calculated at 5.7% and 10%, respectively in these patients. Review studies have been conducted on other endocrine disorders, and the prevalence of impaired glucose tolerance, diabetes and hypogonadism has been reported at 9.6%, 9.5% and 42.3%, respectively in the patients with thalassemia major in Iran (55-57). The pathogenesis of endocrine disorders has been mentioned iron overload due to frequent blood transfusions in these patients. Therefore, using iron-chelation therapy has been suggested widely (55-57).

In this study, the prevalence of hypothyroidism in patients with thalassemia major in Iran is consistent with scientific resource statistics that it has been reported between 5-7% (58). In some of the studies entered into the analysis, T4 and TSH cutoff point has been mentioned variously for the diagnosis of hypothyroidism. This may cause confusion in the results reported in this study which should be taken into consideration. The prevalence of hypothyroidism has been reported differently in patients with thalassemia major in other studies, including: Toumba (5.9%), Belhoul (6.5%), Kurtoglu (12.8%), Kidson-Gerber (16%), Zervas (16.5%) and Gamberini (31%) (59-64). The prevalence of hypoparathyroidism has been also represented diversely in patients with thalassemia major in other countries, including Saudi Arabia (20 to 11.1%), the United Arabic Emirates (10.5%), Turkey (2.8%), Oman (10.1%) and Italy (3.6%) (65-68). The difference in the prevalence of endocrine disorders in patients with thalassemia in different countries can result from a genetic susceptibility to the toxic effects of iron accumulation in endocrine tissue. It can also cause by a difference in the follow-up and treatment of these patients regarding quality of blood transfusion, how to treat with Desefral (regular or irregular), starting time and dose of Desefral administration (62, 69-70).

Iron toxicity may cause overt hypoparathyroidism in 3-4% of patients with thalassemia, while recent reports show that pre-clinical hypoparathyroidism occurs in close to 100% of thalassemic patients with iron toxicity (70). The best strategy to reduce endocrine complications in patients with thalassemia major seems to be a regular administration of deferoxamine and coordinate the age of starting chelation therapy and blood transfusion (56-57).

In this study, the prevalence of subclinical hypothyroidism (6.7%) was more than overt hypothyroidism (3.1%), which indicates annual follow-up of these patients for thyroid function tests and appropriate therapeutic measures to prevent converting subclinical to overt hypothyroidism, is important.

On the other hand, hypoparathyroidism can also be asymptomatic (24). Considering the high prevalence of the disease, it seems essential to evaluate the patients with thalassemia major for hypoparathyroidism once every six months especially from the age of 10.

The highest prevalence of hypothyroidism and hypoparathyroidism is related to north (15%) and east (18%) of Iran, respectively. Perhaps the most likely reason for the high prevalence of hypoparathyroidism in the east of Iran might be because of small sample size in this region.

Endocrine complications occur more in the second decade of the life in patients with

thalassemia major (68). In this study, the mean age of patients with thalassemia major for both disorders were over 15 years old, and more patients were over 10 years of age. The prevalence of these disorders was different in the studies. For example, the highest prevalence of hypothyroidism was in Najafipour (26.7%), Hashemi (21.4%) and Langeroodi (20.6%) studies (22, 39, 6) and the lowest prevalence had been reported in Chahkandi (0%) and Mostafavi (0%) studies (27-28). Although, the prevalence of hypothyroidism has been reported differently, but the mean age of the participants had no significant differences in these studies. Reduction in the prevalence of hypothyroidism to the 0% could indicate appropriate treatment such as receiving regular deferoxamine and starting chelation therapy and blood transfusion, together at the same age in patients.

Ansari's study (32) in Shiraz is the most comprehensive study in terms of sample size (806 participants) and studied regions in Iran in 2005. The prevalence of hypothyroidism and hypoparathyroidism has been reported 2.5 and 7 percent. And the results are consistent with this study.

Based on the four investigated studies, the prevalence of hypothyroidism in males (13%) was higher than females (10%) and prevalence of hypoparathyroidism in the girls was higher than boys; Since the confidence intervals overlap, the relationship is not statistically significant ($p>0.05$). The prevalence of hypothyroidism by sex has been reported variously in different studies (65-68). But the prevalence of hypoparathyroidism has been reported in higher (2 times and even 4 times) in males than females in some of the studies (60-62, 65-68).

The random effect model was used to investigate the relationship between mean serum ferritin and hypoparathyroidism in patients with thalassemia major and no significant relationship found statistically. Other studies conducted in this regard had different results. This relationship was not significant in Mula-Abed's study (67) but it was reported significantly in Gamberini study (59).

Meta-regression was used to investigate the relationship between the prevalence of hypothyroidism, hypoparathyroidism and the year of the study in patients with thalassemia major in Iran. It showed a growing trend from 1998 to 2001, but no significant relationship was found statistically ($p=0.433$). Considering the high overall prevalence of hypothyroidism, hypoparathyroidism and the growing prevalence of these disorders, screening for early diagnosis of endocrine disorders seems essential in these patients.

In this study, chelation therapy was performed in almost all patients with thalassemia major in Iran (99.6%), but only around 54.6% of patients had chelation therapy on a regular basis. A potential cause for irregular treatment could be depression in these patients because the incidence of depression in patients with thalassemia major is twice or several times more than the normal people (71). Complications of iron deposition in various organs, including the heart, endocrine and liver are high in Iran; despite of having chelation therapy (99.6%) one possible cause of the complications could be irregular chelation therapy (55-57). It should be noted that all patients with thalassemia major were using desferal for chelation therapy in the studies.

In meta-regression analysis, the frequency of regular chelation therapy in patients had no significant relationship with the year of the study ($p=0.702$). The frequency of regular chelation therapy has been constant during the investigated years (2000-2010). The frequency of regular chelation therapy was invariable in patients with thalassemia major in Iran during 10 years. But, the frequency of irregular chelation therapy is higher in these patients (46%). This may indicate a lack of attention and follow-up by authorities and patients about the

related issues and problems. Today, raising awareness and holding educational courses for patients and the parent seems to be necessary.

Study limitation

1- Inability of national databases for searching the combined keywords. So, we were unable to search keywords in combination.

2- Since, desferal doses, the intervals between blood transfusion and the amount of blood transfused were not mentioned in most studies, we were unable to determine the relationship between these variables with hypothyroidism and hypoparathyroidism.

Conclusion

The prevalence of hypothyroidism and hypoparathyroidism is high in patients with thalassemia major. On the other hand, chelation therapy carries out irregularly in many Iranian patients. Therefore, New planning and supervising seem to be essential to minimize endocrine complications in patients with thalassemia major in Iran. Some of these programs include improving blood transfusion protocols, chelation therapy, and informing the parent and patients about endocrine complications caused by iron overload. These patients should be examined for endocrine glands once every six months, as suggested by the World Federation of Thalassemia.

Conflict of interest

The Authors have no conflict of interest.

Acknowledgment:

The authors would like to thank to Ilam University's Student Research Committee for funding the research project.

References

1. Benz EJ. Hemoglobinopathies disorder. In: KasperDennis L, Braunwald, Fauci, Hauser, Longo, Jameson. Harrison's Principles of internal medicine. 16th Edition, Mc Grow Hill: USA, 2005.

2. Shamshirsaz AA, Bekheirnia MR, Kamgar M, Pourzahedgilani N, Bouzari N, Habibzadeh M, et al. Metabolic and endocrinologic complications in beta-thalassemia major: a multicenter study in Tehran. BMC endocrine disorders 2003; 12; 3(1): 4.

3. Al-Gazali L, Hamamy H, Al-Arrayad S. Genetic disorders in the Arab world. Bmj 2006; 21; 333(7573):831-4.

4. Saffari F, Mahyar A, Jalilolgadr S. Endocrine and metabolic disorders in beta-thalassemiamajor patients. Caspian journal of internal medicine 2012; 3(3):466-72.

5. Rabbani A, Azar Keiwan A, Farhadi Langeroudi M, Korosdari Gh.H. Clinical evaluation of 413 Thalassemic patients. Tehran Univ Med J 2000; 58: 35-41.

6. Kashanchi Langarodi M, Abdolrahim Poorheravi H. Prevalence of diabetes, hypothyroidism and hypoparathyroidism in thalassemia patients in Shahid Bahonar Hospital, Karaj. Sci J Iran Blood Transfus Organ. 2013; 9(4); 422-428.

7. Azami M, Sayemiri K. Prevalence of Diabetes Mellitus in Iranian Patients with Thalassemia Major: A Systematic Review and Meta-Analysis. J Mazandaran Univ Med Sci 2016; 26(141):192-204.

8. Lanzkowsky P. Manual of Pediatric Hematology and Oncology; 4th ed., Philadelphia Elsevier, 2005; PP 181-90.

9. Company F, Rezaei A, Mozaffari R. Evaluation of cardiac involvement in patients with thalassemia major and thalassemia intermedia. Sci J Kurdistan Univ Med Sci 2008; 13(2): 1-9.

10. Lukens JN. The thalassemia and related disorders. In: Jonatha W, Pine Jr. Wintrobe's clinical hematology. 10th. USA. Williams and Wilkins 1999; 1405-49.

11. Alfenerio A, Motargem M, Abrishami D. About Thalassemia. Tehran, Nozhat, 2005, 46-47.

12. Sabato AR, de Sanctis V, Atti G, Capra L, Bagni B, Vullo C. Primary hypothyroidism and the low T3 syndrome

in thalassaemia major. Archives of disease in childhood 1983; 58(2): 120-7.
13. Soliman AT, Al Yafei F, Al-Naimi L, Almarri N, Sabt A, Yassin M, et al. Longitudinal study on thyroid function in patients with thalassemia major: High incidence of central hypothyroidism by 18 years. Indian journal of endocrinology and metabolism 2013; 17(6): 1090-5.
14. Michael R.Hemoglobinopathies, Chapter 462 in: Richard E, Behrman R, Kliegman R(eds). Nelson textbook of pediatrics, 18th ed. Philadelphia WB saunders, co. 2007; 2033-2037.
15. Richardson DR. The 10th International Conference on Oral Iron Chelators in the treatment of beta thalassemia and other diseases and biomed meeting. Expert Opin Investig Drugs. 2000.
16. Yavari. Epidemiology textbook of prevalent diseases in Iran. Nasher Publication Gap 2013-2014; 9(5): 1151-4.
17. Ferrara M, Matarese SM, Francese M, Borrelli B, Coppola A, Coppola L, et al. Effect of VDR polymorphisms on growth and bone mineral density in homozygous beta thalassaemia. British journal of haematology 2002; 117(2): 436-40.
18. Al-Akhras A, Badr M, El-Safy U, Kohne E, Hassan T, Abdelrahman H, et al. Impact of genotype on endocrinal complications in beta-thalassemia patients. Biomedical reports 2016; 4(6): 728-36.
19. Azami M, Khataee M, Bigam bigdeli-shamlo M, Abasalizadeh F, Abasalizadeh Sh, et al. Prevalence and Risk Factors of Hepatitis B Infection in Pregnant Women of Iran: A Systematic Review and Meta-Analysis. IJOGI 2016; 19(18): 17-30.
20. Sayehmiri K, Azami M, Nikpey S, Borji M, Sayehmiri F. Hepatitis B Vaccination Coverage in Health Personnel of Iran: A Systematic Review and Meta-Analysis Study. irje. 2015; 11 (3):1-10.
21. Mehrvar A, Azarkeivan A, saberi Nejad J, Mehran N, Faranoosh M, Vosoogh P. Prevalence of hypothyroidism and hypoparathyroidism in patients with ß thalassemia in Iran . Sci J Iran Blood Transfus Organ 2008; 5(1): 53-59.
22. Najafipour F, Sarisorkhabi R, Bahrami A, Zareizadeh M, Ghoddousi K, Aghamohamazadeh N, et al . Evaluation of Endocrine Disorders in Patients with Thalassemia Major. Iran J Endocrinol Metab 2008; 10(1): 35-43.
23. Zndehbad A, Beigom Mirbehbahani N. Assessment of the Relation between Hypothyroidism & Serum Level of Ferritin in ß Thalassemia Patients Med J Mashad Univ Med Sci 2009; 52(3): 123-128.
24. Zandian Kh, Eshagh Hossaini K, Riahi K. A study of prevalence of hypothyroidism in B-thalassemia major in Ahvaz Shafa hospital. Sci Med J Ahwaz Jundishapur Univ Med Sci 2009; 8(3): 272-290.
25. Rostami P, Hatami G, Shirkani A. Endocrine complications in patients with major β-thalassemia. ISMJ. 2011; 14(4): 240-245.
26.Vahidi A A, Parvaresh S, Torabi Nejad M, Ahmadi A, Mohammadi R. The incidence of complications in patients with beta-thalassemia major centers Kerman special diseases during the second half of 1387. J Kerman Univ Med Sci 2011; 18(3): 318-329.
27. Mostafavi H, Afkhamizadeh M, Rezvanfar M. Endocrine disorders in patients with thalassemia major. Iran J Endocrinol Metab. 2005; 7(2): 143-147.
28. Chhkndy T. Evaluation of thyroid and parathyroid function in patients with thalassemia major. J Birjand Univ Med Sci 2004; 11(2): 9-15.
29. Hadaegh F, Zaree Sh, Tohidi M, Safa O, Mahori Kh. Pituitary-thyroid axis function and metabolism of calcium and phosphorus in patients with thalassemia major Hormozgan province. Hormozgan Univ Med J. 2002; 6(2): 1-6.
30. Jalali Farahani F, Zolgaghari S, Talebian A, Azarkeivan A, Maghsudlu M, Sarmadi M, et al . Prevalence of thyroid dysfunction and relevant risk factors among thalassmia patients having referred to Iranian Blood Transfusion Organization Clinical Laboratory of Tehran. Sci J Iran Blood Transfus Organ 2009; 6(1): 59-64.

31. Razavi Z, Bazmamoun H, Sadegh Saba M. The frequency of hypoparathyroidism in patients with Beta-thalassemia in Hamadan - Iran. J Gorgan Uni Med Sci 2009; 10(4): 29-33.
32. Ansari H, Tabatabai, H. Study of factors in major beta thalassemia Complications in patients admitted to Dshahid Dastgheib hospital in Shiraz, Iran (2004-5). Sabzevar Univ Med J 2007; 14(1): 62-72.
33. Karami H, Vahid-Shahi K, Kowsarian M, Abaskhaniyan A, Parvin-nezhad N, Ehteshami S et al . Evaluation of ocular defects and its relevant factors in patients with beta thalassemia major in Sari Boo Ali Sina hospital, (2006-2008). Yafteh 2009; 10(4): 20-27.
34. Soheili Khah S, Eslami S. Endocrine disorders in Thalassemia major in Yazd Blood Bank in 1998. Journal of Shahid Sadoughi University of Medical Sciences and Health Services 2000; 8(1): 11-7.
35. Mahdavi Anari F, Ahmadian A, Haghshenas Z, Alawi Yazdi Z. Comparison of the frequency of four endocrine disorders in patients with thalassemia major referred to thalassemia clinic of Tehran Imam Khomeini Hospital in 2000. [Dissertation]. Tehran: Tehran University of Medical Sciences; 2000.
36. Seyedi J, Vahidi AA, Kashanian Moshtaghi Gh, Shahbazian N. Assessment of thyroid dysfunction in patients with thalassemia referred to number one hospital of Kerman University of Medical Sciences in 1998. [Dissertation]. Kerman: Kerman University of Medical Sciences; 1998.
37. Nasiri MR, Bastanhagh MH, Mohajer S, Khodabaneh A. Evaluation of thyroid dysfunction in patients with beta thalassemia major and related factors of patients referring to Thalassaemia Society in 1998. [Dissertation]. Tehran: Tehran University of Medical Sciences; 1998.
38. Shiva S, SariSorkhabi R. Short stature in patients with beta-thalassemia. Urmia Medical Journal. 2008; 19 (2): 125-131.
39. Hashemi A, Ordooei M, Golestan M, Akhavan Ghalibaf M, Mahmoudabadi F, Arefinia M, et al. Hypothyroidism and Serum Ferritin Level in Patients with Major ß Thalassemia. Iran J Ped Hematol Oncol 2011; 2(1): 53-56.
40. Arjmandi Rafsanjani K, Razzaghy-Azar M, Zahedi-Shoolami L, Vossough P, Modarres A, Taheri N. Bone Mineral Density in β Thalassemia Major and Intermedia, Correlation with Biochemical and Hormonal Profiles. IJBC. 2009; 1 (4):121-127.
41. Moayeri H, Oloomi Z. Prevalence of growth and puberty failure with respect to growth hormone and gonadotropins secretion in beta-thalassemia major. Arch Iran Med. 2006; 9(4): 329-34.
42. Eshraghi P, Mehrabani Tabari S, Mohseni A. An Avaluation of the Correlation between Short Stature and Endocrinopathy In Thalassemia Major Patients. J Mashad Univ Med Sci 2012; 55 (1): 7-14.
43. Saffari f, Abolfazl M. Bone mineral density in patients with Beta-Thalassemia Major in Qazvin. Journal of Isfahan Medical School. 2008; 26(89): 179-186.
44. Amanat Yazdi M, Hashemi A, Afkhami G, PourShamsi F. Evaluation relationship between endocrine disorders in B-thalassemic patients with serum ferritin levels. [Dissertation]. Yazd: Shahid Sadoughi University of Medical Sciences; 2004.
45. Karamifar H, Shahriari M, Sadjadian N. Prevalence of endocrine complications in beta-thalassaemia major in the Islamic Republic of Iran. Eastern Mediterranean health journal 2003; 9(1-2): 55-60.
46. Miri-Aliabad G, Fadaee M, Khajeh A, Naderi M. Marital Status and Fertility in Adult Iranian Patients with beta-Thalassemia Major. Indian journal of hematology & blood transfusion: an official journal of Indian Society of Hematology and Blood Transfusion 2016; 32(1): 110-3.
47. Hamidieh AA, Moradbeag B, Pasha F, Jalili M, Hadjibabaie M, Keshavarznia M.

High Prevalence of Hypoparathyroidism in Patients with beta-Thalassemia Major. Int J Hematol Oncol Stem Cell Res 3(3); 2009: 17-20.
48. Company F, Rezaei R, Yosefi GH. Evaluation of hearing loss and otolaryngeal disorders in beta thalassemic patients treated with desferrioxamine. Sci J Kurdistan Univ Med Sci 2009; 14(3): 47-55.
49. Azimipour A, Asadi M. The prevalence of endocrine diseases in patients with thalassemia major. [Dissertation]. Qazvin: Qazvin University of Medical Sciences; 2001.
50. Spector TD, Thompson SG. The potential and limitations of meta-analysis. J Epidemiol Community Health 1991; 45: 89-92.
51. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151: 264-9.
52.Vandenbroucke JP, Elm Ev, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. PLoS Medicine 2007; 4(10): 1628.
53. Ades AE, Lu G, Higgins JP. The Interpretation of Random-Effects Meta-Analysis in Decision Models. Med Decis Making 2005; 25(6): 646-54.
54. Michael Borenstein, Larry V. Hedges, Julian P.T. Higgins, Hannah R. Rothstein. A basic introduction to fixed-effect and random-effects models for meta-analysis. Research Synthesis Methods 2010; 1(2): 97-111.
55. Azami M, Sharifi Sh, Sayehmiri K. Prevalence of Diabetes, Impaired Fasting Glucose and Impaired Glucose Tolerance in Patients with Thalassemia Major in Iran-A Meta-Analysis. Caspian Journal of Internal Medicine; 2016; In Press.
56. Sayemiri K, Tarde Z, Azami M, Milad Borji. The prevalence of hypogonadism in patients with thalassemia major in Iran – a systematic review and meta-analysis study. J Shahrekord Univ Med Sci 2016; In Press.
57. Azami M, Tardeh Z, Abangah G, Sayemiri K. The Prevalence of Impaired Glucose Tolerance in Patients with Thalassemia Major in Iran: A systematic Review and Meta-analysis. JSSU. 2016; 23(10):912-922.
58. Abolghasemi H, Eshghi P. Apprehensive thalassemia book. 2004. 1th ed. Tehran: Bagheiatallah Medical University, 2004.
59. Gamberini MR, De Sanctis V, Gilli G. 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. Pediatric endocrinology reviews: PER 2008; 6(1): 158-69.
60. Toumba M, Sergis A, Kanaris C, Skordis N. Endocrine complications in patients with Thalassaemia Major. Pediatric endocrinology reviews: PER 2007; 5(2): 642-8.
61. Belhoul KM, Bakir ML, Kadhim AM, Dewedar HE, Eldin MS, Alkhaja FA. Prevalence of iron overload complications among patients with b-thalassemia major treated at Dubai Thalassemia Centre. Ann Saudi Med 2013; 33(1): 18-21.
62. Kurtoglu AU, Kurtoglu E, Temizkan AK. Effect of iron overload on endocrinopathies in patients with beta-thalassaemia major and intermedia. Endokrynol Pol 2012; 63(4): 260-3.
63. Kidson-Gerber GL, Francis S, Lindeman R. Management and clinical outcomes of transfusion-dependent thalassaemia major in an Australian tertiary referral clinic. The Medical journal of Australia 2008; 21; 188(2): 72-5.
64. Zervas A, Katopodi A, Protonotariou A, Livadas S, Karagiorga M, Politis C, et al. Assessment of thyroid function in two hundred patients with beta-thalassemia major. Thyroid: official journal of the American Thyroid Association 2002; 12(2): 151-4.

65. Habeb AM, Al-Hawsawi ZM, Morsy MM, Al-Harbi AM, Osilan AS, Al-Magamsi MS, et al. Endocrinopathies in beta-thalassemia major. Prevalence, risk factors, and age at diagnosis in Northwest Saudi Arabia. Saudi medical journal 2013; 34(1): 67-73.
66. Aleem A, Al-Momen AK, Al-Harakati MS, Hassan A, Al-Fawaz I. Hypocalcemia due to hypoparathyroidism in beta-thalassemia major patients. Annals of Saudi medicine 2000; 20(5-6): 364-6.
67. Mula-Abed WA, Al Hashmi H, Al Muslahi M, Al Muslahi H, Al Lamki M. Prevalence of endocrinopathies in patients with Beta-thalassaemia major - a cross-sectional study in oman. Oman medical journal 2008; 23(4): 257-62.
68. Multicentre study on prevalence of endocrine complications in thalassaemia major. Italian Working Group on Endocrine Complications in Non-endocrine Diseases. Clinical endocrinology 1995; 42(6): 581-6.
69. L. Even, T. Bader and Z. Hochbeg. Diurnal Variation of Serum Calcium, Phosporus and PTH in the Diagnosis of Hypoparathyroidism. Pediatric Research (Abstract), 2001; 3:141.
70. Chern JP, Lin KH, Lu MY, Lin DT, Lin KS, Chen JD, et al. Abnormal glucose tolerance in transfusion-dependent beta-thalassemic patients. Diabetes care 2001; 24(5): 850-4.
71. Pouraboli B, Mansooreh Forouzi A, Arab M. Mental Health of Adolescents with Thalassemia Major Visiting Kerman Specific Diseases Center. Journal of Health & Development 2015; 4(1): 320-28.