BETA THALASSEMIA TRAIT IN TURKEY AND THE MIDDLE EAST: A META-ANALYSIS OF PREVALENCE

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ABSTRACT

Introduction*:Beta thalassemia (β thal) is a genetic blood disorder, which is endemic in especially Mediterranean countries. Hemoglobinopathy Control Programs are conducted in endemic areas, in order to reduce the number of risky newborns with thalassemia. The study's aim was to present the results of a Meta-analysis of the prevalence of beta thalassemia trait (β thal trait) in Turkey and the Middle East Islamic countries since 2000.*

Materials and methods*: This study is a meta-analysis of prevalence. A meta-analysis was conducted on results of studies about the prevalence of β thal trait from Turkey's provinces and from the other Middle East Islamic countries. Meta-analysis of prevalence was studied with MetaXL. Random effects model was used to evaluate heterogeneity. Prevalence was presented with low and high Confidence Interval 95% (LCI and HCI), and weight (%). Pooled prevalence, I-squared and Cochran's Q (homogeneity test), and Chi-square p were presented.*

Results*: Pooled prevalence was 2.6%. In Turkey, provinces from the Mediterranean and Aegean region have high prevalence of β thal trait, generally. Pakistan has a high prevalence of β thal trait, conversely, Iran national data reported a low prevalence of β thal trait.*

Conclusion*: Meta-analysis including in Turkey and the Middle East Islamic countries show a prevalence of β thal trait between 0.2% to 7.9%. Iran's national data presented the lowest prevalence of β thal trait. Geographical features were considered as the main cause of heterogeneity. Premarital screening programs should be conducted in endemic countries.*

Keywords*: β thal trait, prevalence, meta-analysis.*

DOI: 10.19193/0393-6384_2018_6_265

Received *January 30, 2018;* ***Accepted*** *March 20, 2018*

Introduction

Carrier screening programs aim to identify asymptomatic carriers of recessive conditions so that they can be counseled and understand their reproductive risks and options. Hemoglobinopathy Control Programs are an important part of premarital health screenings. Worldwide, almost 70.000 infants are born with beta thalassemia (β thal) each year and 270 million people are carriers of hemoglobinopathies. Beta thal is most commonly present among populations in all Mediterranean countries, as well as in Southeast Asia, India, Africa, Central America and the Middle East.

There are three clinical forms as follows:

1) Thalassemia minor,

2) Thalassemia major,

3) Thalassemia Intermedia. Thalassemia minor is called as thalassemia carrier or thalassemia trait. If there is a healthy gene in the bearers that makes the faulty gene function, the symptom of the disease does not occur or not emerge severe symptoms[1,2].

Turkey Hemoglobinopathy Control Program has been initiated in 33 provinces, which are endemic areas for hemoglobinopathy, in 2003 by the Ministry of Health. Whereupon, 32% of all couples in 2003, and 78% of all couples in 2012 were screened. The percentage of screened couples increased to 86.0% in 2013. Thus, the mapping of Turkey's β thal was established. Beta thal is an endemic disease also in Turkey.

According to the screening results of the Turkish National Hemoglobinopathy Council

(2006), the average prevalence of β thal trait was 4.3% in Turkey. While the number of newborn with thalassemias and hemoglobinopathies was 272 in 2002, it had dropped to 25 in 2010[3, 4]. The aim of the study was to present the results of Meta-analysis of the prevalence of β thal trait in Izmir and the other provinces of Turkey and the other Middle East Islamic countries since 2000.

Materials and methods

Search Strategy

Searches were conducted in Google Scholar and Pubmed in September 2017. Both database's text world fields were searched terms as follows: β thal trait (or and other synonymous terms as β thal carrier), Prevalence, Premarital screening, with the boolean "AND". In Google Scholar, the search was made in English and Turkish. Date restrictions were applied. All literature between 2000 to 2017 has been screened. Manual searching was not performed.

Inclusion criteria

• Being a cross-sectional/prevalence study,
• Being a study which was defined β thal trait definition as "The mean corpuscular volume (MCV) is lower than 80 μm3 (fL)/red cell and the hemoglobin A2 level is more than 3.5%",
• Being a study which was done from Turkey or Middle East Islamic countries,
• Being a study which was presented results representing at least one province,
• Being a premarital screening study,
• Being a study which was realized among married couples,
• Being a study which was published in 2000 and later.

Exclusion criteria

• Prospective studies,
• Retrospective studies,
• Case-control studies,
• Methodological studies,
• Intervention studies,
• Case reports,
• Editorials,
• Reviews,
• Thesis,
• Congress posters,
• Being a study which was done among population outside married couples,
• Being a study which was not done premarital screening,
• Neither Turkey nor Middle East Islamic countries' studies.

Flow Diagram

In our study, total 931 records were screened through database searching (Google Scholar and Pubmed). Duplication was 58 records, and 837 of the remaining 873 records were not appropriate and therefore excluded. According exclusion criteria; 6 prospective studies, 6 retrospective studies, 6 intervention studies, 6 congress poster, 2 methodological studies, 2 case reports, 1 editorial letter, 1 thesis, 107 review or chapter of book, 130 non-Turkey or non-Middle East studies, 135 no premarital screening studies, and 435 not a β thal trait prevalence studies were excluded (a total of 837).

For the meta-analysis, 16 studies from Turkey and 20 studies from Middle East Islamic countries (total 36 studies) were included[2-37].

The same province/country studies were numbered among themselves (e.g. Iran1, Iran2, and Iran3).

The flow chart was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[38], and PRISMA Flow Diagram is presented in Figure 1.

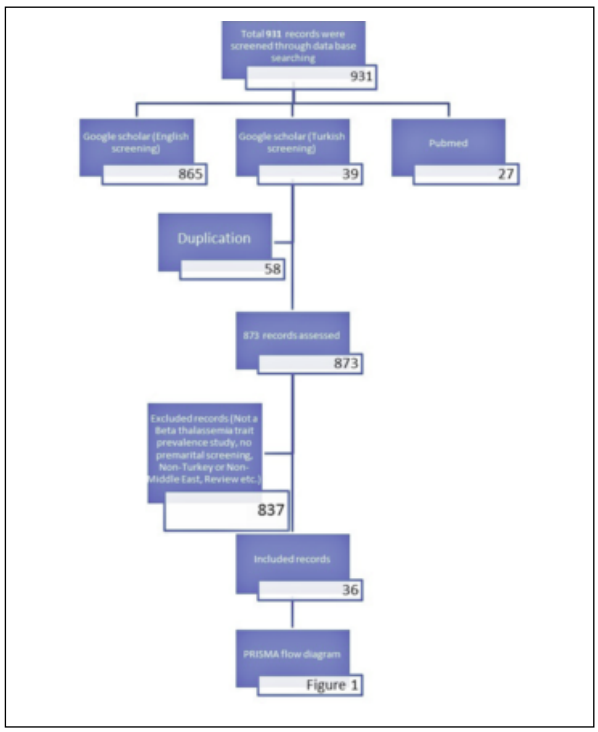

Figure 1: PRISMA Flow Diagram

Outcome measures

The main outcomes of interest for this meta-analysis were to compare the prevalence of β thal trait.

Data extraction

An author (M.T.) independently reviewed the studies. The data were extracted using a standardized data extraction form. Descriptive characteristics of the included studies are presented in Table 1. Any disagreements were resolved by discussion and consulting with other authors (E.T. and A.B.B).

Reference No	Published Date	Study period	Country	Province	Sample size (N)	Number for beta thalassemia trait (n)
2	2009	From July 2005 to the end of December 2008	Turkey	Kocaeli	88.888	791
3	2013	From January 2011 to March 2012	Turkey	İzmir	38.554	1.912
4	2000	From October 1995 to August 1999	Turkey	Denizli1	19.804	514
5	2001	From 1994 to 1999	Turkey	Denizli2	14.200	311
6	2006	From February 1999 to February 2004	Turkey	Mersin	79.000	1.611
7	2007	2004	Turkey	Konya	72.918	1.465
8	2010	From 2007 to 2009	Turkey	Kahramanmaras	48.126	1.010
9	2012	From January 2009 to March 2010	Turkey	Kayseri	10.261	175
10	2012	-	Turkey	Adiyaman	1.616	31
11	2014	From January 2011 to March 2014	Turkey	Sanliurfa	75.924	1.853
12	2014	From January 2013 to November 2013	Turkey	Adana, Kadirli	1.994	98
13	2016	From 2008 to 2010	Turkey	Kutahya	14.815	744
14	2016	From January 2006 to October 2012	Turkey	Hatay1	70.226	4.214
15	2010	From 2004 to 2009	Turkey	Hatay2	175.660	13.921
16	2016	From January 2008 to June 2012	Turkey	Canakkale	8.904	125
17	2008	From May 2005 to February	Turkey	Erzurum	1610	11
18	2004	From 1998 to 2002	Iran1	National data	2.700.000	12.150
19	2007	From 1995 to 2005	Iran2	Southern Iran	1.038.371	4.154
20	2013	From 2010 to 2011	Iran3	Quchan	1.000	35
21	2013	From 1992 to 2010	Iran4	Isfahan, central part of Iran	703.082	1317
22	2013	From 1997 to 2010	Iran5	Isfahan	616.457	1.194
23	2006	From February 2004 to November 2004	Saudi Arabia1	Al-Hassa	8.918	303
24	2007	From February 2004 to October 2006	Saudi Arabia2	Al-Qassim	38.153	63
25	2007	From February 2004 to January 2005	Saudi Arabia3	National data	488.315	15.724
26	2011	From 2004 to 2009	Saudi Arabia4	National data	1.572.140	28.235
27	2017	From February 2012 to November 2012	Saudi Arabia5	Hafar Al Batin	620	32
28	2010	2010	Iraq1	Dohuk	1.182	44
29	2003	From 1 August 2000 until the end of	Iraq2	Basra, Southern Iraq	1064	49
30	2013	From 1 January 2008 to 30 December 2012	Iraq3	Sulaimaniyah, Northeastern Iraq	108.264	4.309
31		From 23rd September 2006 to the 14th January 2007.	Iraq4	Sulaimani	1.472	61
32	2013	From January 2007 and December 2010	United Arab Emirates1	Dubai	6.420	293
33	2016	From January 2008 to March 2015	United Arab Emirates2	Ras Al Khaimah	17.826	513
34	2014	2010	Pakistan1	Sindh	256	17
35	2012	From 2006 to 2010	Pakistan2	Islamabad, Rawalpindi	2.101	85
36	2007	From April 2003 to May 2005	Palestine	Gaza	21825	562
37		From 1st April to15th May 2006	Bahrain	National data	1.070	30

Table 1: Descriptive characteristics of the included studies.

Meta-analytic methods

Meta-analysis of the prevalence of β thal trait was studied with MetaXL software in Microsoft Excel for Windows. Random effects model was used to evaluate heterogeneity. Prevalence was presented with Low Confidence Interval (LCI) 95% and High Confidence Interval (HCI) of 95%, and weight (%). Pooled prevalence, I-squared and Cochran's Q (homogeneity test), and Chi-square p were presented in Meta-analysis results. For Cochran's Q, $p<0.1$ value refers to heterogeneity. For I-squared the heterogeneity was defined as follows; 0% to 40% as low, 30% to 60% as middle, 50% to 90% as enough, and 75% to 100% as high.

Results

In our study, prevalence of β thal trait in Turkey varies between 0.7% in Erzurum[17] and 7.9% in Hatay2[15].

For the Middle East Islamic countries (except for Turkey), prevalence of β thal trait was changing between 0.2% in Iran5[22] and 6.6% in Pakistan1[34].

Results of the meta-analysis of prevalence of β thal trait in random effects model are presented in Table 2.

Reference No	Province / Country	Prevalence of beta thalassemia trait (%)	LCI95%	HCI95%	Weight (Random) (%)
TURKEY					
2	Kocaeli	0.9	0.8	0.10	2.838
3	Izmir	5.0	4.7	5.2	2.835
4	Denizli1	2.6	2.4	2.8	2.831
5	Denizli2	2.2	2.0	2.4	2.827
6	Mersin	2.1	2.0	2.2	2.838
7	Konya	1.7	1.5	2.0	2.822
8	Kahramanmaras	2.1	2.0	2.2	2.836
9	Kayseri	1.7	1.5	2.0	2.822
10	Adiyaman	1.9	1.3	2.6	2.726
11	Sanliurfa	2.4	2.3	2.6	2.838
12	Adana, Kadirli	4.9	4.0	5.9	2.747
13	Kutahya	5.0	4.7	5.4	2.828
14	**Hatay1**	**6.0**	**5.8**	**6.2**	**2.838**
15	**Hatay2**	**7.9**	**7.8**	**8.1**	**2.839**
16	Canakkale	1.4	1.2	1.7	2.819
17	Erzurum	0.7	0.3	1.2	2.726
MIDDLE EAST ISLAMIC COUNTRIES					
18	Iran1	0.4	0.4	0.5	2.840
19	Iran2	0.4	0.4	0.4	2.840
20	Iran3	3.5	2.4	4.7	2.661
21	Iran4	0.2	0.2	0.2	2.840
22	Iran5	0.2	0.2	0.2	2.840
23	Saudi Arabia1	3.4	3.0	3.8	2.819
24	Saudi Arabia2	0.2	0.1	0.2	2.815
25	Saudi Arabia3	3.2	3.2	3.3	2.840
26	Saudi Arabia4	1.8	1.8	1.8	2.840
27	Saudi Arabia5	5.2	3.5	7.1	2.561
28	Iraq1	3.7	2.7	4.9	2.687
29	Iraq2	4.6	3.4	6.0	2.671
30	Iraq3	4.0	3.9	4.1	2.839
31	Iraq4	4.1	3.2	5.2	2.716
32	United Arab Emirates1	4.6	4.1	5.1	2.811
33	United Arab Emirates2	2.9	2.6	3.1	2.830
34	**Pakistan1**	**6.6**	**3.9**	**10.1**	**2.248**
35	Pakistan2	4.0	3.2	4.9	2.752
36	Palestine	2.6	2.4	2.8	2.832
37	Bahrain	2.8	1.9	3.9	2.672
Pooled		**2.6**	**2.0**	**3.2**	100.0
Statistics					
I-Squared		99.964	99.963	99.965	
Cochran's Q		97008.596			
Chi², p		<0.001			
Tau^2		0.015			

Table 2: Results of meta-analysis of prevalence of β thal trait in random effects model.

Pooled prevalence of β thal trait was found as 2.6% (95% CI: 2.0% - 3.2%). Distribution of prevalence for all studies has shown heterogeneity. I-squared was calculated as 99.964%. Cochran's Q was 97008.596 ($p<0.01$).

For Turkey studies, pooled prevalence of β thal trait was found as 2.7% (95% CI: 1.7% - 4.0%).

For other Islamic countries except for Turkey, pooled prevalence of β thal trait was found as 2.4% (95% CI: 1.8% - 3.4%).

Forest plot is presented in Figure 2.

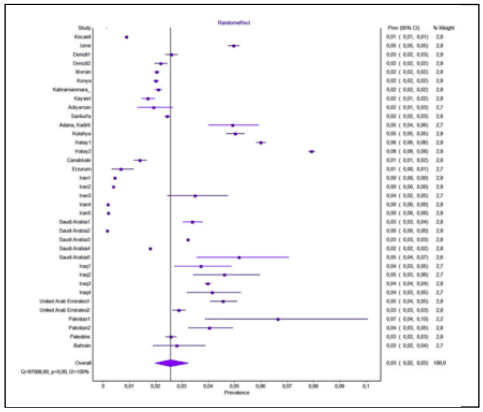

Figure 2:Forest Plot

Discussion

In Turkey, Canatan[39] presents a summary of studies on thalassemia and hemoglobinopathies. Beta thal studies in Turkey began in the 1940s. Preventive health services for thalassemias, such as premarital screening programs, have been presenting in Turkey by the Ministry of Health, the Turkish National Hemoglobinopathy Council and the Thalassemia Federation of Turkey since 2000. Hemoglobinopathy Prevention Program was started in endemic provinces on May 8, 2003. From 16 different cities in the Marmara, Aegean and Mediterranean region between 1995 and 2000, a total of 380,000 healthy subjects were screened. The 16 endemic cities are Adana, Antakya, Antalya, Aydin, Bursa, Denizli, Diyarbakir, Edirne, Isparta, Istanbul, Izmir, Kahramanmaras, Kirklareli, Mersin, Mugla, and Urfa. Average prevalence of β thal trait was 4.3%. The highest prevalence of β thal was reported in the West Mediterranean and in the East Mediterranean, with a frequency of 13.1%.

Our study result, pooled prevalence of β thal trait was found as 2.7% for Turkey's studies. Our outcome was lower than in the Hemoglobinopathy Prevention Program. A reason for this result is because we added the results of less endemic cities, such as Erzurum[17], and Kocaeli[2] to meta-analysis. However, high prevalence is reported from Hatay (East Mediterranean), Izmir, and Kutahya (Aegean Region) as expected. Hatay2[15], Hatay1[14], Kutahya[13], and Izmir[3] have a prevalence of β thal trait as 7.9%, 6.0%, 5.0, and 5.0%, respectively. The distribution of β thal is broadly consistent with that of malarial infection.

In Turkey, the distribution of β thal alleles displays a decreasing gradient of mutational heterogeneity from East to West Anatolia. Additionally, Eastern Anatolia is not an environment conducive to the proper development of the malarial parasite, and this region's altitudes higher than 5000 meters[40]. This information may explain the lowest prevalence value of Erzurum that a city of the Eastern region.

According to the findings of this study, other Middle East countries have a lower prevalence of β thal trait than Turkey (2.4% vs 2.7%). We could not find any study of countries with high prevalence, such as Cyprus[1] since 2000. This event can affect our prevalence comparison results between countries.

It should also be stated that in recent years, prevalence studies are more frequent in Islamic countries in the Middle East. In countries such as Cyprus, Greece, and Italy, molecular basis and prenatal studies seem to have replaced the β thal trait prevalence studies. There are also other reasons for this. Namely: Cyprus started a program in 1973, and successfully decreased the number of affected births from 51 to 0 annually between 1974 and 2002. Similar programs were implemented in Italy and Greece[41].

In addition to studies from Turkey, we observed that some studies of prevalence of β thal trait were held in Saudi Arabia, Iraq, United Arab Emirates, Pakistan, and Iran, since 2000. Thus, we considered the situation of Islamic countries in the Middle East. When we investigated other Islamic countries except for Turkey, we observed low prevalence results in four of Iran's five studies[18, 19, 21, 22]. A high prevalence was reported from Quchana city in Khorasan Razavi region of Iran[20]. As a general conclusion, low prevalence values have been reached in Iran as a result of the premarital screening program. Five studies from Saudi Arabia were included[23, 27].

Three studies reported high[23, 25, 27], two studies[24, 26] low prevalence of β thal trait, when compared with pooled prevalence. Heterogeneity is observed. Four studies from Iraq were added in meta-analysis in the study. High prevalence of β thal trait in Iraq has been reported[28, 29, 30, 31]. Emirates, Palestine and Bahrein studies are compatible with the pooled prevalence[32, 33, 36, 37]. The highest prevalence value of this study was reported by Pakistan[34]. As a general conclusion, Pakistan[34, 35], and Iraq[28, 29, 30, 31] have a higher prevalence of β thal trait values according to their premarital screening results.

In this paragraph, we will focus on the reasons for the low prevalence values for β thal trait in Iran, and the high prevalence values in Iraq, and Pakistan. Saffi & Howard[41] investigated premarital screening and genetic counseling programs for β thal in the Middle East. How did Iran succeed in β thal control program? Iran started premarital screening and genetic counseling in 1997. Carrier couples found at risk of having β thal affected children were included in the programs. With the prenatal diagnosis programs, reforms in abortion-related laws were implemented in 2003. Islamic clergies declared a fatwa permitting the abortion of homozygote β thal fetuses up to 16 weeks of gesta-

tional age. Iran's successful β thal reduction placed the Iranian program as a benchmark for other national programs[41].

Cousens et al.[42] mentioned public education about beta thal in Iran. Also, classes on thalassemia are conducted in high schools and are also conducted for young men in the military. Public education has also been carried out in Iran through mass media, annual public education programs, and information booklets written by the Youth Thalassaemia Group. In Iran, about half of the carrier couples identified by the premarital screening program proceeded to marry each other, and the other half separated. The separation of these high-risk couples helped to reduce the incidence of β thal[42]. On the other hand, due to the high rate of consanguineous marriages in the Iranian population (30-80 %), Iran continues to make an effort more about fighting with β thal[43]. One study from Iran, Ghotbi & Tsukatani[44] was conducted on the cost-effectiveness of the screening method. According to the study, these screening studies were not cost-effective and sometimes confusing as usually only a complete blood count (CBC) is requested and many variables in the report are evaluated without specific measures or standard criteria. In another study, it was reported that inaccessibility to service and costs not covered by insurance are barriers for screening program in various areas of Iran[41]).

In addition to this information, β thal trait prevalence is estimated to be 4%-5% in screening studies. The July 2000 census reported a population of 65.619.636. This gives us an estimated 2.620.000-3.280.000 carrier (mean 2.950.000). The prevalence of thalassemia major varies throughout Iran with the highest incidence in regions near the Caspian Sea and the Gulf. The provinces of Mazandaran, Gilan, Hormozgan, Khuzestan, Kohkiluyeh-Boyerahmad, Fars, Bushehr, Sistan-Baluchestan, Kerman, and Isfahan are the 10 provinces most afflicted. This shows that geographical features have an effect on the β thal prevalence in Iran too[44].

Hamamy & Al-Allawi[45] reported that they still saw patchy/inadequate premarital screening in many Arab countries. Saffi & Howard[41] said that Northern Iraq, with prenatal diagnosis, therapeutic abortion is allowed. Between 2008 to 2010, 91% of at-risk couples proceeded with marriage. Prenatal diagnosis was sought by 38% of those deciding to marry, and all affected pregnancies were terminated. A 5-year evaluation found that 98% of at-risk couples proceeded with marriage, with prenatal diagnosis sought by 76% and 10 of the 11 affected pregnancies terminated. The number of thalassemia-affected births in Northern Iraq decreased from 20 to 7 over 5 years, a reduction of 65%. Barriers for Iraq screening programs are reported as high consanguineous marriage rates (24-27%), distrust of test results, and high user costs for prenatal natal diagnosis, a short time between testing and marriage dates limiting cancellations and social and cultural discomfort with marriage cancellation on short notice.

Beta thal is also common in Saudi Arabia along the coastal strip of the Red Sea and in the Eastern province around Jubail, Qateef, Dammam, and Hofuf. Although β thal has been known for many years in these areas and many of its manifestations are recognized, the details of actual incidence, the natural history or clinical course of the disease from early childhood to death are unknown. This is mostly because of inadequate facilities for mass population screening, variable severity, and manifestations and complexity of the interaction of the disease process with other health-related events e.g. sickle cell disease[46]. In our study, provinces that have high prevalence of β thal trait belong to the eastern part of Saudi Arabia.

Pakistan showed a prevalence between 5–13% of β thal trait. Pakistan has a strong tradition of consanguineous marriage, and the termination of pregnancy is unacceptable for the majority of the population. According to 2013 data, treatment costs for a child with thalassemia are very high. For this reason, prevention of thalassemia in Pakistan is both desirable and challenging. In Pakistan, there is no mass level carrier detection, but the Government is currently planning to implement a law for premarital screening[34]. The reasons for the high prevalence of Pakistani studies may be those we consider.

Limitations: In this study, a detailed examination of genetic factors and sociocultural factors of countries in terms of β thal could not be included. The evaluation was based on the prevalence values, according to the meta-analysis results.

Conclusion

Meta-analysis results show that provinces from the Mediterranean and Aegean region have a higher prevalence of β thal trait in Turkey. Additionally, in Middle East countries, Pakistan has

a high prevalence of β thal trait; conversely, Iran's national data presented the lowest prevalence of β thal trait. The results of this study present heterogeneity in terms of prevalence of β thal trait. Geographical features were considered as the main cause of heterogeneity. It is recommended that premarital screening programs should be continued to be applied in countries for decreasing the prevalence of β thal trait.

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