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Review Article

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Dental and Skeletal Manifestation of Sickle-Cell Anaemia and Thalassemia in Saudi Arabia; A Systematic Review

Ajwa Nancy[1]*, Alzahir Sukinah[2], Alawamy Maram[2], Alkhalifah Sara[2], Alsumur Hiba[2], AlMarhoun Manar[2]

[1]Department of Preventive Dentistry, Orthodontic Division, College of Dentistry, Riyadh Elm University, Riyadh, KSA.
[2]College of Dentistry, Riyadh Elm University, Riyadh, KSA.

***Email:** Nancy.ajwa@riyadh.edu.sa*

ABSTRACT

Patients with Sickle Cell Disease (SDC) suffer from many systematic manifestations such as muscular imbalance, absence of labial scaling, and changes in the osseous skull base. Thalassemia patients are characterized by many systematic manifestations such as skeletal deformities. The study aimed to systematically assess the literature about the relationship between dental and skeletal manifestations of SCD and Thalassemia among Saudi subjects. Following preferred reporting items for systematic reviews (PRISMA), 5 databases were searched for related articles. Data were collected following certain keywords. Studies in humans, English language, from 2000 to 2020, among growers, were included.
145 articles were selected. Duplicates were excluded leading to 138 articles. Upon screening titles and abstracts, 80 articles were selected. 55 articles were chosen and only 3 high-level evidence papers met the criteria for the qualitative synthesis. Thalassemia and SCD patients had a greater prevalence of severe malocclusion and they require an earlier orthodontic intervention compared to norm-occlusive subjects. The commonly found dental manifestations among Thalassemia and SCD are Class II skeletal malocclusion, with a maxillary protrusion, constricted arches, and incisal crowding.

Key words: *Skeletal malocclusion, Thalassemia, Sickle-Cell anemia, Dental malocclusion, Children*

INTRODUCTION

Sickle cell disease (SCD) is a genetically transmitted disease characterized by mutation of hemoglobin chain [1-3]. The genetic distortion is a result of valine replacement for glutamic acid in the 6th position of the β chain in hemoglobin. Consequently, SCD patients will suffer from chronic hemolytic anemia and vaso-occlusive episodes with restriction of blood supply to multiple tissues in the body [1, 2]. There are different forms of SCD. The principal genotypes include sickle cell-β-thalassemia (Hb S-β0- thalassemia (βsβ0), and Hb S-β+-thalassemia (βsβ+). The most common type is homozygous sickle cell anemia (βsβ+). Whereas (βsβs) is the less frequent type in Saudi Arabia [2].
In SCD, red blood cells morphology is altered from the biconcave discoid shape into sickled shape due to low oxygen concentration in the cell. As a result, hemoglobin S chain (Hb-SS) molecules are deoxygenated. Moreover, the plasticity of RBCs is reduced due to the hydrophobic interaction of valine in the beta chain. Consequently, Blood becomes viscous in nature instead of liquid. In addition, the life span of sickling red blood cells will reduce from 120 to almost 20 days [4, 5].

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Accordingly, SCD will have a great impact on patients systematically. One of the main systematic manifestations of SCD is malocclusion. The main factors contributing are muscular imbalance, absence of labial sealing and changes in the osseous skull base which simultaneously will increase the demand for an orthodontic intervention [6].

Furthermore, the musculoskeletal features of SCD patients directly affect the craniofacial complex and influence the dental classification or occlusion. The main features are delayed puberty/growth in children and small growth patterns in adults, as well frontal bone eminence and protruded anterior labial division. Moreover, there will be an increased overjet and deep overbite [7].

Radiographically, some features are often verified such as the decrease in bone radiodensities for both maxilla and mandible. Also, the formation of a coarse trabecular pattern is noticed radiographically, which can be described as "ladder-shaped" [8, 9].

On the other hand, Thalassemia is one of the most common monogenic autosomal diseases universally. It is characterized by the deterioration of α or β globin chains production [10-12]. Accordingly, there are two types of thalassemia: α and β. Furthermore, there will be a further subdivision of the main two types into 3 groups: heterozygous, homozygous, and compound heterozygous [13].

One of the most common systematic manifestations is skeletal deformities due to the elevation of iron levels in the blood. Additionally, there will be an overgrowth in the bone marrow and thinning of the cortical bone. Also, one of the most prominent effects is on the skull base [10, 14]. Interestingly, thalassemia patients have facial features that are similar to Mongolian facial characteristics such as saddle depression of the nose and prominence of the zygomatic arch, but the most distinguishable skeletal feature is prognathic maxilla [10, 14, 15].

According to Caffey and baker [16, 17] thalassemia patients were described as rodent face. The most characteristic oral manifestations were flared anterior maxillary teeth with an increased overjet and decreased overbite [18, 19]. According to the previously reported features, they are presented as class II malocclusion [10, 14]. In conclusion, the craniofacial changes associated with Thalassemia require orthodontic interference. In other words, dental malocclusion can develop due to the alteration of craniofacial bone structure.

Lastly, Both SCD and Thalassemia are anonymous diseases, which have little attention in the litterateur of Saudi Arabia. One of the main reasons establishing the current review is to bring more awareness toward this topic. Therefore, the purpose of the current review is to systematically assess the literature about the relationship between dental and skeletal manifestations of SCD and Thalassemia among Saudi subjects.

MATERIALS AND METHODS

Search strategy and data sources

This systematic review was conducted among Saudi growing subjects. After obtaining the ethical approval from the IRB committee of Riyadh Elm University (REU) #RC/IRB/2018/1379. 5 databases were searched for related articles "Saudi Digital Library (SDL), Google Scholar, Science Direct, PubMed, and Cochrane Library". According to PubMed and Cochrane Library, the search sequence of MeSH and terms were (Skeletal malocclusion and Thalassemia/Sickle-Cell Anemia children), (Sickle-Cell Anemia children/Dental malocclusion among Thalassemia). The review was performed to address the question: "Is there any relationship between blood disease (Sickle cell – thalassemia) and skeletal/dental malocclusion when compared to medically fit growing subjects?".

The data collection process followed the PRISMA [20] statement: Identification, screening, eligibility, and inclusion **(Figure 1)**. The article selection criteria were as follows **(Table 1)**.

Table 1. Eligibility criteria

Inclusion Criteria	Exclusion Criteria
English language.	Unpublished/under progress researches checked through the ClinicalTrials.gov
Publication year between 2000-2020.	Studies wit h low evidence but not limited to studies with questionnaires, case series, case reports, books, and review articles.
The study sample size must be at least 15 growing patients among both genders.	Studies performed on patients with genetic syndromes and/or severe facial malformations.
Studies done among humans who had no history of Trauma nor orthodontic treatment.	Studies investigated medical conditions rather than Thalassemia OR Sickle-Cell diseases.

Studies done among humans who had Thalassemia or Sickle cell diseases only	Studies evaluated the skeletal and/or dental manifestation using other methodology rather than lateral cephalometric radiographs.
Studies covered the assessment of skeletal and/or dental malocclusion among selected medical conditions.	Presence of any situation that mismatches one inclusion criterion or more.

RESULTS AND DISCUSSION

Following PRISMA [20] statement **(Figure 1)**, 145 published articles were identified as relevant to the topic in Saudi Arabia. Duplicates were removed and articles were screened initially by title and abstract resulting in 138 papers. 80 articles were excluded due to the incompatibility with the criteria. Accordingly, the full text of articles was read and only 58 of them met the criteria. Following the qualitative synthesis, 55 articles were eliminated due to the following reasons: studies with a sample age group of more than 19, studies performed in patients with more than a medical condition, studies performed outside Saudi Arabia, studies evaluated a combination of conditions (sickle cell and thalassemia with other conditions). Ultimately, three articles met all the eligibility criteria. A summary of the most valuable information from the selected papers is described **(Table 2)**.

Table 2. Summary of the findings of Included the included studies summary of findings.

Author	Year	Sample size	Comparison	Location	Assessment method	Study design	Outcome	Conclusion	Commonest features
Ahmad B. [21]	2018	112 SCD patients – 124 age-matched vs non-SCD controls Age group: 12-18 years old	Compare between SCD vs control group	Dammam	Cephalometric radiographic examination. -Clinical examination: calibration of an experienced orthodontic examiner using DAI.	Comparative cross-sectional	SCD patients: Sever malocclusion detected 37%. -Non-SCD controls: 26.6%.	Malocclusion is more prevalent among adolescents with SCD and where there is greater demand for orthodontic intervention rather than control	Crossbite 67%
Maha H.[22]	February 2018	82 children (41 SCD – 41 Control group) Age group: 2-13 years old	Compare between SCD vs control group	Abha and Khamis mushait	Clinical examination: Maxillary deformities.	Comparative cross-sectional	-Both SCD patients and control subjects had 24.4% malocclusion. -Normal occlusion 75.6% for both groups.	In comparison between SCD and control group, no significant difference was noted in dental diseases and treatment needs.	Dental Malocclusion 24.4%
Mohammed M. [23]	January 2020	36 Beta-Thalassemia patients (23 Males – 13 Females) Mean age: 18 years old	NA	Jazan	Clinical examination: " Skeletal examination including overgrowth of the upper jaw, prominent malar eminence, frontal bossing, as well as upper incisors exposure assessment"	Non-Comparative cross-sectional	There is a deference of upper teeth exposure detected between male and female thalassemia patients: Male (84.2%), Female (37.5%).	The most common feature among βTM patients was Exposure of the upper teeth followed by maxillary hypertrophy. Other features were less frequent, including the prominence of the malar eminence, frontal bossing, and a depressed nasal bridge.	Exposure of the upper teeth 59.4%

NA= Not Applicable., SCD= Sickle Cell Disease, DAI = Dental aesthetic index, βTM = beta thalassemia major

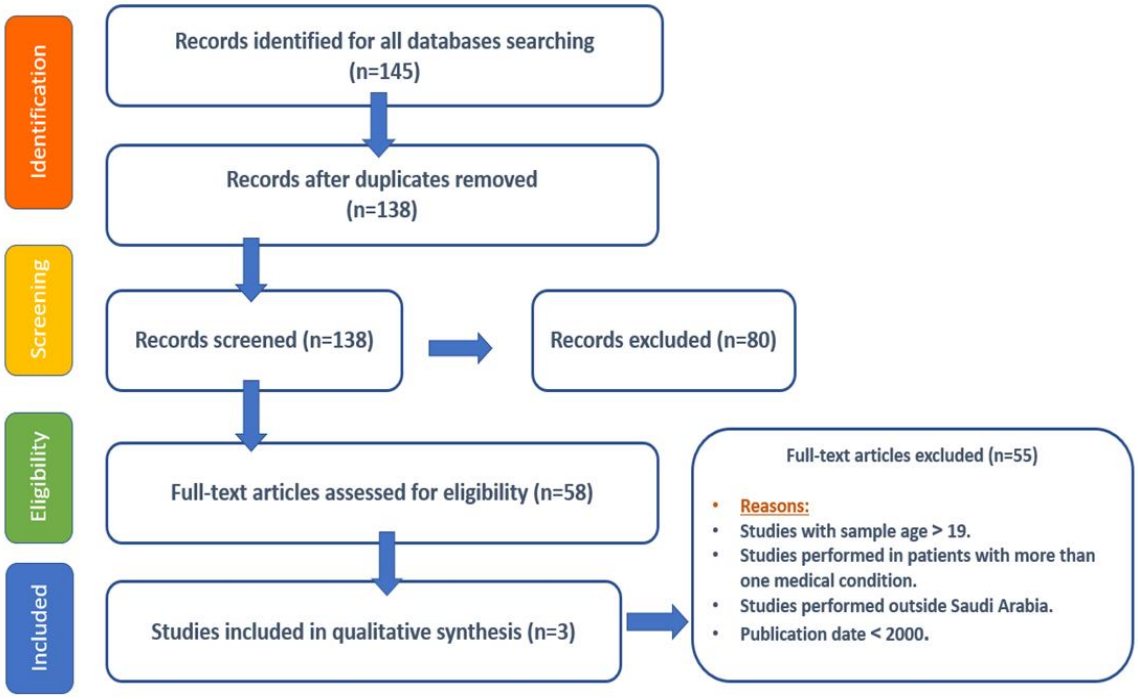

Figure 1. PRISMA flow diagram showing the strategy of literature search

Quality synthesis

Quality assessment of the included articles was reported for risk of bias by one independent reviewer (NA) using the Cochrane quality assessment tool [24]. Sampling bias was reported by assessing and evaluating the sample selection, performance, detection of outcomes, attrition, and reporting. The overall assessment was given to a range of low-moderate risk of bias for all eight articles. The main methodological points of the quality assessment are summarized in **Table 3**.

Table 3. Criteria for reporting risk of bias using the Cochrane quality assessment tool [24]

Bias Type	Bias	Ahmad B. [21]	Maha H. [22]	Mohammed M. [23]
Selection	Random Sequence Generation	High	High	High
	Allocation Concealment	Low	High	Low
Performance	Blinding of Personnel and Participants	High	Unclear	High
Attrition	Incomplete Outcome Data	Low	Low	Low
Detection	Binding Outcome Assessors	Unclear	High	Unclear
Attrition	Incomplete Outcome Data	Low	Low	Low
Reporting	Selective Reporting	Low	Low	Low
	Overall Assessment	Moderate	Moderate	Moderate

The Bias was reported based on the following criteria: 1- Random sequence generation: selection bias due to inadequate generation of randomized sequences. 2- Allocation concealment: selection bias due to inadequate concealment of allocations before assignment. 3- Blinding of personnel and participants: performance bias due to knowledge of the allocated interventions by personnel and participants. 4- Blinding of outcome evaluation: detection bias due to knowledge of the allocated interventions by outcome assessors. 5- Incomplete outcome data: attrition bias due to handling, nature, or amount of incomplete outcome data. 6- Selective reporting: reporting bias due to selective outcome reporting.

SCD is one of the most predominant inherited blood diseases in Eastern province Saudi Arabia. Craniofacial anomalies are a characteristic feature of sickle cell patients, malocclusion, overgrowth of the midface, and facial bone depression [22]. These anomalies are a sequala of hyperplasia and bone marrow expansion, in order to

recompense for the reduced oxygen-carrying capacity in the premature red blood cells. They may have dental malocclusion as an outcome of hyperplasia and expansion of the bone marrow to cover for the short life of RBC because of disease development [21, 22].

β-thalassemia is a genetic disorder characterized by many skeletal manifestations such as exposure of upper teeth, depressed nasal bridge, maxillary hypertrophy, frontal bossing, and prominent malar bone. Significant variance was found between Maha. H *et al.* and Ahmed. B *et al.* studies in terms of malocclusion and blood disorders. According to a study carried out by Maha. H *et al.*, there was no considerable difference in malocclusion between SCD and control groups [22]. Whereas, in the study conducted by Ahmed. B *et al.*, there was a significant relation between craniofacial characteristics, malocclusion, and orthodontic treatment among Saudi SCD patients of eastern province [21]. However, in Maha's review, data were collected depending on certain landmarks: an anterior or posterior open bite, class I with anterior or posterior crossbites, rotations, Angles classification of class II and class III malocclusions [22]. Moreover, both samples had (24.4%) of malocclusion, and (75.6%) of both groups had normal occlusion [22]. Malocclusion was noticed in the majority of the selected sample, most of them were diagnosed with teeth crowding.

The etiology of malocclusion in SCD is idiopathic. Sickling leads to hypoxia, which is correlated to jaw osteonecrosis specifically in the mandible. In addition, it will give rise to hyperplasia of facial bone marrow over growth of the midface, malocclusion, and nasal bridge depression. However, scientific proof of SCD causing malocclusion was insufficient [22].

On the other hand, correlates to Ahmed's study, there was a severe malocclusion (37.5%) in SCD patients, which indicates the high demand for orthodontic intervention. Additionally, (12.5%) required compulsory orthodontic treatment due to the impairment of malocclusion. Moreover, (26.6%) of the control group had severe malocclusion and only (6.5%) had impairment in malocclusion or severe case [21]. Cephalometric analysis the main method in Ahmed's study, which gives specific information for certain skeletal landmarks. Whereas, Maha's study depended mainly on clinical examination.

The DAI showed that more than (72.4%) of SCD patients had incisal crowding than the control group with (56.7%). Also, (67.3%) of patients had overjet in comparison to (32.8%) of the control group. Simultaneously, there was a higher percentage of SCD patients with misalignment in the maxilla and the mandible comparing to the control group [21]. Moreover, there was a drastic increase in the angles of SCD patients, which was SNA (86.7°) and ANB (9.9°) whereas in the control group it was (81.5° and 2°), respectively.

According to the Lower central incisor to Frankfort horizontal (FH) plane, there was a significant decrease in SCD patient angle than in controls with a degree of (55°) and interincisal (121.5°) angles. Also, there was a significant decrease in the ratio of posterior facial height to anterior facial height in SCD patients (60.4%) than that in controls (66.8%). Furthermore, the SNB (76.8°), SN-Pog (76.4°), angle of convexity (11.4°), facial angle (81.2°) and in SCD patients were significantly lower than that in controls. Also, the nasolabial angle was significantly smaller in SCD patients (80.5°) than in control subjects (95.6°).

The outcome of the study reported that there was a higher demand for and orthodontic intervention for patients with SCD than controls. Skeletal and dental manifestation including maxillary misalignment in anterior (65.0%), overjet (67.3%), incisal crowding (72.4%) posterior crossbite, and open bite were more noticeable in diseased adolescents than control group [21, 25]. In contrast, Maha's article indicated that there was no preference between the two groups for orthodontic intervention due to the similarity in malocclusion percentage [22].

Furthermore, according to Mohammed. M *et al.*'s review, frontal bossing was observed in (14.8%) of patients with βTM and also it revealed malar bone prominence in (18.5%). The upper teeth exposure (59.4%) and maxillary hypertrophy (53.1%) were the most frequent characteristics among βTM patients, respectively. Other characteristics e.g. prominence of the frontal bossing, malar eminence, and a depressed nasal bridge were less frequent. Further analyses showed a significant difference between females and males about the upper teeth exposure [23, 25].

Moreover, study analysis conducted in Mohammed's review revealed that concerning the exposure of the upper teeth, it was a more significant feature in males than females. However, both groups had irrelatively the same other features. In addition, maxillary hypertrophy and upper teeth exposure were more prone in patients who started blood transfusion at the age of (≥1) years old than those patients who started blood transfusion (1 or <) year of age [23, 26, 27].

As a result, the high prevalence of malocclusion indicates the demand for orthodontic treatment due to systematic complications of SCD and βTM. It is recommended that these patients should be provided with frequent dental examinations and early orthodontic treatment. These measures will help accelerate the process of treatment for

malocclusion and therefore improve the quality of life of patients [21, 23, 27]. Conversely SCD patients' control group had the same demand when it came to early intervention [26, 28].

CONCLUSION

According to the high level of evidence, it was concluded that patients with hematologic disorders had a high prevalence of severe malocclusion and high demand for early orthodontic management in comparison to normal occlusive subjects. The common oral manifestations among SCD and thalassemia are incisal crowding, significantly constricted arches, maxillary protrusion, and Class II skeletal malocclusion. Gingival and dental problems are rare but mostly occur due to poor oral hygiene. The most effective method of the prevention of hemoglobinopathies is via avoiding relative marriages, antenatal and premarital diagnoses, and population screening.

Recommendation

1. Thalassemia and SCD are anonymous diseases that have little attention, therefore longitudinal studies are needed to determine the exact pattern and amount of growth from childhood to adulthood.
2. Utilization of recent technologies such as stereophotogrammetry, CBCT, and electromagnetic digitizers in future investigations is recommended to overcome the limitations of the lateral cephalograms used in the currently found studies. These technologies provide a 3D detailed analysis of the patient's facial characteristics and can be performed frequently without any additional biological burden.
3. It is also recommended that patients with SCD and Thalassemia be provided with frequent dental examinations and early orthodontic treatment. These measures will help prevent malocclusion, and thus improve the quality of life of patients.

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CONFLICT OF INTEREST : None

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