European Review for Medical and Pharmacological Sciences 2022; 26: 8247-8255

Skeletal and dental manifestations of Glucose-6-phosphate dehydrogenase deficiency, thalassemia, and sickle cell anemia patients in Saudi Arabia

F. ALASSAD, O.H. ALKADHI

Preventive Dentistry Department, College of Dentistry, Riyadh Elm University, Riyadh, Saudi Arabia

Abstract. – OBJECTIVE: Glucose-6-phosphate dehydrogenase (G6PD) deficiency, Thalassemia (THL), and Sickle cell anemia (SCA) are the most common inherited hematologic diseases globally. It is important to understand the skeletal and dental manifestations in orthodontic treatment. This study aimed at assessing and comparing skeletal and dental manifestations of G6PD deficiency, THL, and SCA patients with healthy controls in Saudi Arabia.

SUBJECTS AND METHODS: This is a retrospective study of G6PD deficient, THL, and SCA patients' cephalometric records in Saudi Arabia. This study included 136 subjects (G6PD=34, THL=34, SCA=34, and healthy control=34), aged between 18-32 years. 17 skeletal, dental, and soft tissue cephalometric measurements obtained from the G6PD, THL, and SCA were compared to control measurements using ANOVA and Tukey's HSD post-hoc test.

RESULTS: Intra-class correlation ranged between (ICC: 0.971-0.996), indicating excellent reliability of measurements. A statistically significant difference in skeletal, dental, and soft tissue measurements between each condition and controls was observed, except for Wits, PP-MP, Y-axis, UI-SN, NLA, and LI-E line in SCA, FMA, ANS-Me, UI-SN, and LI-A Pog in G6PD and Wits, Y-axis, UI-SN, UI-NA, LI-MP, LI-Apog and UI-E line in THL group ($p>0.05$).

CONCLUSIONS: SCA and THL patients showed class II skeletal patterns, while class III skeletal relationship was evident in patients with G6PD deficiency.

Key Words:
Cephalometry, Dental, Thalassemia, G6PD, Sickle cell anemia, Skeletal, Soft tissue.

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, Thalassemia (THL), and sickle cell anemia (SCA) are the most common inherited hematologic diseases globally. These conditions accompany several dental and skeletal manifestations, such as maxillary incisor proclination and skeletal class II malocclusion, subsequent to the maxillary protrusion in THL and impacted and abnormal mandible growth in patients with both THL and SCA. These deformities may affect the patient's appearance and orthodontic treatment options[1-3].

G6PD deficiency is the most common enzymatic disorder of red blood cells, affecting 400 million people worldwide. It is a group of X-linked, hereditary genetic disorders caused by mutations in the G6PD gene. These mutations result in protein variants with decreased levels of enzyme activities and are correlated with a wide range of biochemical and clinical phenotypes[4]. In people with G6PD deficiency, the red blood cells (RBC) do not make enough G6PD, or what is produced cannot function properly. Without enough G6PD to protect RBCs, they can be damaged or destroyed. Hemolytic anemia occurs when the bone marrow fails to compensate for this destruction by increasing its RBC production[5]. This disorder is especially prevalent in certain parts of Africa, Europe, the Middle East, Southeast Asia, the Pacific Islands, and the Mediterranean[6]. The Mediterranean mutation is one of the most prevalent mutations, producing G6PD deficiency in Egyptian favism children[7].

THL is a genetic disorder that remains a public health challenge in many countries worldwide, with a high prevalence, especially in the Mediterranean, Middle East, and South-East Asia[8]. THL, described in 1927 by Cooley et al[9] presents the thickening of the cranial bones. THL patients usually present with skeletal class II malocclusion due to maxillary prognathism[10]. However, it has been found that THL patients may suffer from growth retardation of the mandible and increased vertical growth[11,12].

Corresponding Author: O.H. Alkadhi, MD; e-mail: omaralkadhi2@gmail.com

In SCA, red blood cells (RBCs) are destroyed with a characteristic sickled appearance under the microscope. It is a class of chronic, recessively inherited red blood diseases characterized by abnormal hemoglobin[13]. SCA is a significant global health problem affecting about 400,000 infants yearly[14]. Over time, SCA produces various musculoskeletal abnormalities. Familiarity with the imaging features of SCA is essential for diagnosing and managing complications. Ischemia and infarction are common complications that may have long-term effects on the growth of bone; these conditions have characteristic radiographic appearances. Infection may be more difficult to identify[15]. International researchers have found that the SCA condition is connected with class II skeletal characteristics. This class II pattern is mainly due to mandibular retrusion and clockwise rotation (posterior rotation) rather than the maxillary protrusion[1,3,16,17].

Many previously published studies[18-20] addressed the facial features of SCA and THL patients individually, but none explored or contrasted this with G6PD deficiency. Since no previous studies have focused on the skeletal and dental manifestations of G6PD patients and none have compared the skeletal and dental manifestations of these three conditions, it is necessary to gain a greater understanding of the skeletal and dental manifestations of G6PD deficiency, THL, and SCA patients and compare them with healthy control subjects. Therefore, recognizing these diseases' craniofacial and dental manifestations is essential since it strongly influences proper orthodontic management. Hence, this study aimed at assessing and comparing the skeletal and dental manifestations of G6PD deficiency, THL, and SCA patients with healthy controls in Saudi Arabia.

Subjects and Methods

This retrospective study was registered at the Research Centre at Riyadh Elm University, Riyadh, Saudi Arabia, and approved by the institutional review board (FPGRP/2020/492/267/278). It was performed at the Division of Orthodontics in different governmental and private hospitals in different regions (Central, North, South, East, and West) of Saudi Arabia between September 2020 and June 2021.

Sampling

The study sample used a convenient sampling of G6PD deficient, Thalassemia, sickle cell anemic patients, and controls. Lateral cephalometric radiographs of study participants were collected from hospitals in different regions (Central, North, South, East, and West) in the Kingdom of Saudi Arabia.

Sample Size and Grouping

The sample size was calculated using previously reported means and standard deviations of Sella-Gonion of two groups: the thalassemia group (Mean=66.35, SD=5.38) and the control group (Mean=71.05, SD=9.34) (Amini et al[12]). Alpha level was set at 0.05, power (1-Beta) = 0.8, and the effect size was found to be 0.616662. The sample size was determined using G*Power software (Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany) to be 34 individuals per group.

Each patient was matched with a normal control based on chronological age and sex. Both the sample and the control group were of the same ethnic origin since all of them were native-born Saudis. All 136 lateral cephalograms were taken from previous records under standardized conditions with the teeth in occlusion and lips in a relaxed position.

Eligibility criteria

Inclusion criteria

- Male and female adult Saudi citizens with the age range of 18-32 years;
- Absence of any craniofacial syndrome;
- No history of orthodontic or orthopedic treatment;
- No history of permanent tooth extractions;
- Diagnosed with G6PD deficiency or Thalassemia or SCA.

The control group had a class I skeletal relationship, no history of orthodontic treatment, nor present with any craniofacial anomalies.

Exclusion criteria

- Non-Saudi residents;
- Presence of any craniofacial syndrome;
- History of orthodontic or orthopedic treatment;
- History of permanent tooth extractions;
- Control group with Class II and Class III skeletal relationship;
- Poor quality cephalograms.

Measurements

Tracing of the lateral cephalometric radiographs for 17 linear and angular cephalometric parameters defining craniofacial morphology was carried out. Nine skeletal (SNA, SNB, ANB, Wits, PP-MP, FMA,

Table I. The description of cephalometric variables utilized in this study.

Variable	Landmark	Description
Skeletal	SNA	Sella-Nasion-point A
	SNB	Sella-Nasion-point B
	ANB	ANB angle
	Wits	Wits appraisal
	PP-MP	palatal plane to mandibular plane angle
	FMA	Frankford horizontal to a mandibular plane angle
	Y-axis	Sella-Gnathion to Frankfort horizontal
	ANS-Me	Lower anterior facial height
	ANS-Me/N-Me	Lower to total facial height
Dental	UI-PP	Upper incisors to palatal plane angle
	UI-SN	Upper incisors to Sella Nasion
	UI-NA	Upper incisors to Nasion-A point
	LI-MP	Lower incisors to mandibular plane
	LI-A Pog	Lower incisors to A pogonion
Soft tissue	Cotg-Sn-Ls	NLA Nasolabial line
	UI-E line	Upper incisors to aesthetic line
	LI-E line	Lower incisors to aesthetic line

Y-axis, ANS-Me, ANS-Me/N-Me), five dentoalveolar (UI-PP, UI-SN, UI-NA, LI-MP, LI-A Pog), and three soft-tissue (Cotg-Sn-Ls, UI-E line, LI-E line). Tracing was performed using Quick Ceph Studio software 5.0.2 (San Diego, CA, USA). Cephalometric variables and their description are shown in Table I.

Intra and Inter-Examiner Reliability

Intra-examiner consistency was determined by tracing 20 cephalometric radiographs for 17 landmarks then retracing the same radiographs one week later by the same examiner. The two readings for each landmark were recorded and compared using the intraclass correlation coefficient. Similarly, inter-examiner reliability was determined by comparing the examiner's tracing to that of an orthodontic specialist having more than eight years of experience.

Statistical Analysis

Descriptive statistics of frequency distribution, mean, standard deviation (SD), and the difference between means for each group were calculated across the study variables. The mean values of the normally distributed cephalometric variables were compared among G6PD, SCA, THL, and control groups using ANOVA (Analysis of variance) with Tukey's post-hoc tests. All Statistical tests were performed using the Statistical Package for Social Science (SPSS, IBM Corp., Version 20, Armonk, NY, USA). The level of significance for all the statistical tests was kept at $p<0.05$.

Results

One-hundred and thirty-six (n=136) lateral cephalometric radiographs of the participants who met the eligibility criteria were included in this study and divided into four groups: G6PD deficiency (n=34), thalassemia (n=34), SCA (n=34), and control (n=34) groups. The demographic data of the study participants are shown in Table II.

Intra-class correlation ranged between (ICC: 0.971-0.996), indicating excellent reliability between the initial measurements and after two weeks, as shown in Table III.

Table II. Descriptive statistics showing age and gender distribution.

Conditions	Male n (%)	Female n (%)	Total	Age Mean (SD)
G6PD deficiency	20 (58.8)	14 (41.2)	34	23.50 (3.25)
SCA	21 (61.8)	13 (38.2%)	34	24.41 (4.36)
Thalassemia	12 (35.3)	22 (64.7%)	34	23.64 (4.35)
Control	19 (55.9)	15 (44.1%)	34	23.0 (4.26)

Table III. Intra-examiner reliability tests for each variable using inter-class correlation coefficient.

Landmark	Correlation coefficient	p
SAN	0.985	<0.001
SNB	0.979	<0.001
ANB	0.989	<0.001
Wits	0.996	<0.001
PP-MP	0.992	<0.001
FMA	0.995	<0.001
Y-Axis	0.986	<0.001
ANS-Me	0.984	<0.001
LAFH	0.971	<0.001
UI-MP	0.989	<0.001
UI-SN	0.984	<0.001
UI-NA	0.991	<0.001
LI-MP	0.996	<0.001
LI-Apog	0.991	<0.001
NLA	0.992	<0.001
UI-E line	0.993	<0.001
LI-E line	0.995	<0.001

When the mean and standard deviation values of cephalometric variables were compared among different conditions (control, SCA, THL, and G6PD), statistically significant differences were observed, except for UI-SN, as shown in Table IV. There were significant differences between the SCA group and the control group for SNA, SNB, ANB, FMA, ANS-Me, ANS-Me/N-Me, UI-PP, UI-NA, LI-MP, LI-A Pog, and UI-E line ($p<0.05$). However, no significant differences in Wits, PP-MP, the Y-axis, UI-SN, NLA, and the LI-E line were observed between the SCA group and the control group ($p>0.05$). Likewise, SNA, SNB, ANB, Wits, PP-MP, Y-axis, ANS-Me/N-Me, UI-PP, UI-NA, LI-MP, NLA, UI-E line, and LI-E-line significantly differed between the control group and G6PD deficiency group ($p<0.05$). On the contrary, no significant differences were identified between FMA, ANS-Me, UI-SN, and LI-A Pog ($p>0.05$). Similarly, the THL group differed significantly from the control group concerning SNA, SNB, ANB, PP-MP, FMA, ANS-Me, ANS-Me/N-Me, UI-PP, NLA, and LI-E-line ($p<0.05$). While Wits, Y-axis, UI-SN, UI-NA, LI-MP, LI-Apog, and UI-E line all showed no significant difference ($p>0.05$). A Comparison of skeletal, dental, and soft tissue measurements between control and each condition using ANOVA and Tukey's HSD post-hoc test is shown in Table IV.

SCA and THL groups have similar class II skeletal patterns due to retruded mandible and vertical basal configuration with increased lower facial height and proclined upper incisors to palatal plane angle. However, it differed around the position of the upper incisors to NA. In SCA pa-

Table IV. Comparison of skeletal, dental, and soft tissue measurements among different groups.

Variables	Control A	SCA B	THL C	G6PD D	p*	The significant mean difference between groups (Pairwise comparisons using Tukey's test)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
SNA	80.9 (1.5)	83.1 (2.1)	82.2 (0.48)	78.0 (0.21)	<0.001	A *vs.* B; A *vs.* C; A *vs.* D; B *vs.* D; C *vs.* D
SNB	78.5 (1.36)	74.6 (1.53)	75.1 (1.47)	82.2 (2.19)	<0.001	A *vs.* B; A *vs.* C; A *vs.* D; B *vs.* D; C *vs.* D
ANB	3.98 (0.87)	6.45 (1.00)	6.17 (0.97)	-1.85 (0.76)	<0.001	A *vs.* B; A *vs.* C; A *vs.* D; B *vs.* D; C *vs.* D
Wits	0.56 (1.78)	0.36 (2.59)	-0.13 (2.51)	-3.39 (0.79)	<0.001	A *vs.* C; A *vs.* D; B *vs.* D; C *vs.* D
PP-MP	25.36 (2.32)	26.98 (4.42)	31.69 (3.43)	23.00 (1.13)	<0.001	A *vs.* C; A *vs.* D; B *vs.* C; B *vs.* D; C *vs.* D
FMA	26.70 (3.85)	29.57 (4.34)	28.97 (3.05)	24.83 (1.43)	<0.001	A *vs.* B; A *vs.* C; B *vs.* D; C *vs.* D
Y-axis	63.53 (4.62)	62.38 (3.45)	62.62 (4.07)	58.98 (0.82)	<0.001	A *vs.* D; B *vs.* D; C *vs.* D
ANS-Me	63.56 (3.43)	67.89 (2.19)	66.76 (3.24)	62.56 (1.07)	<0.001	A *vs.* B; A *vs.* C; B *vs.* D; C *vs.* D
ANS-Me/N-Me	55.97 (2.01)	60.38 (3.35)	58.56 (0.37)	54.42 (0.99)	<0.001	A *vs.* B; A *vs.* C; A *vs.* D; B *vs.* C; B *vs.* D; C *vs.* D
UI-PP	111.76 (5.61)	116.81 (4.39)	115.00 (3.72)	116.12 (4.42)	<0.001	A *vs.* B; A *vs.* C; A *vs.* D; C *vs.* D
UI-SN	106.44 (6.41)	107.53 (4.82)	107.89 (3.23)	106.99 (2.53)	0.571	-
UI-NA	5.51 (2.17)	8.00 (2.74)	6.07 (1.36)	10.77 (0.85)	<0.001	A *vs.* B; A *vs.* D; B *vs.* C; B *vs.* D; C *vs.* D
LI-MP	3.58 (3.41)	9.16 (2.95)	5.45 (4.06)	-2.20 (1.86)	<0.001	A *vs.* B; A *vs.* D; B *vs.* C; B *vs.* D; C *vs.* D
LI-A Pog	1.71 (3.22)	4.49 (3.79)	3.57 (3.29)	2.19 (1.58)	0.001	A *vs.* B; A *vs.* C; B *vs.* C; B *vs.* D
NLA	100.56 (6.83)	101.77 (8.07)	107.47 (7.58)	95.55 (8.63)	<0.001	A *vs.* C; A *vs.* D; B *vs.* C; B *vs.* D; C *vs.* D
UI-E line	-2.02 (1.47)	-0.90 (1.89)	-1.10 (1.68)	-3.91 (0.99)	<0.001	A *vs.* B; A *vs.* D; B *vs.* D; C *vs.* D
LI-E line	-2.81 (2.13)	-2.96 (1.79)	-1.25 (4.03)	2.59 (0.64)	<0.001	A *vs.* B; B *vs.* C; B *vs.* D; C *vs.* D

*ANOVA, A=Control group, B=Sickle Cell Anemia group (SCA), C=Thalassemia group (THL), D=G6PD group.

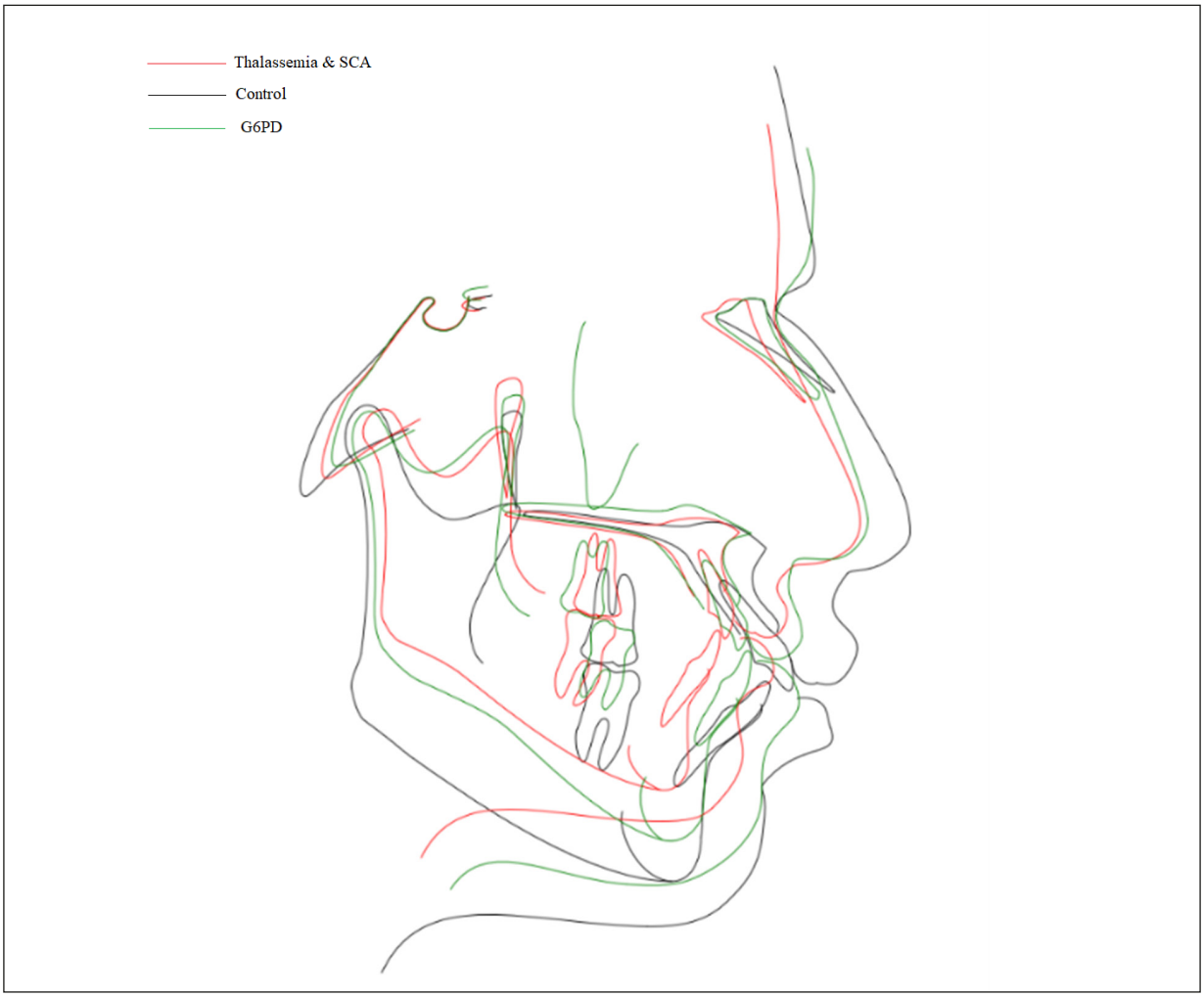

Figure 1. Superimposition of the average skeletal, dental and soft tissue tracings for study groups.

tients, the upper incisors protrude to NA and are in a normal position in THL patients. This pattern is completely different from G6PD and the control group (Figure 1).

G6PD deficiency group demonstrated class III skeletal pattern due to retruded maxilla, protruded mandible, proclined upper incisors to a palatal plane, protruded upper incisors to NA as well as horizontal basal configuration, and prominent lower lip to E-Line. However, this pattern is different from the SCA, THL, and control groups. All cephalometric radiographs in the control group were skeletally class I, with a normal position of the maxilla and mandible, as well as normal position and inclination of the upper and lower incisors and the normal position of the lips to E-line. The superimposition of cephalometric variables of G6PD deficiency, SCA and THL groups with normal groups is shown in Figures 2-4.

Discussion

Several dental and skeletal manifestations of patients with SCA and Thalassemia have been reported in the orthodontic literature, such as maxillary incisor proclination and skeletal class II malocclusion subsequent to the maxillary protrusion in THL and mandibular atrophy in patients with both THL and SCA. Some reports[1,2] described the orthodontic treatment of those patients, but none of them discussed or compared that with G6PD deficiency. Since these changes may affect the patient's appearance and, thereby, orthodontic treatment options, these facts should be considered to prevent complications during and after treatment[11,12].

The present study assessed and compared the skeletal and dental manifestations of G6PD deficiency, THL, and SCA in Saudi adult patients.

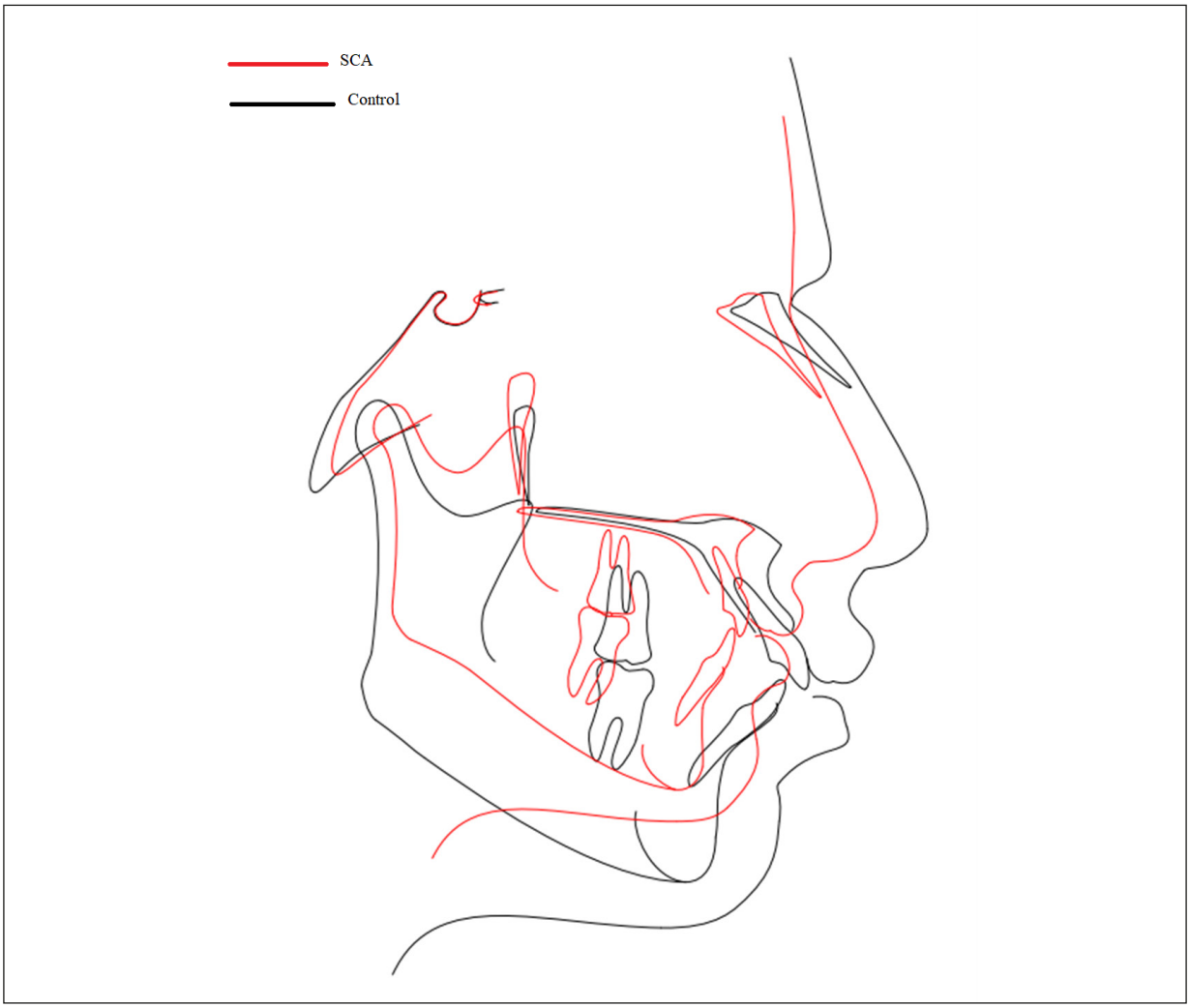

Figure 2. Superimposition of the average skeletal, dental and soft tissue tracings for SCA and contol groups.

This study finding demonstrated the class III skeletal relationship in the G6PD deficient group due to retruded maxilla and protruded mandible and horizontal basal configuration. On the other hand, class II skeletal pattern due to retruded mandible and vertical basal configuration and increased lower facial height were the main characteristic features of SCA and THL. Control group had a class I skeletal pattern with the normal position of the maxilla and mandible.

The proclined upper incisors to the palatal plane and protruded upper incisors to NA are the characteristic feature dental variables in G6PD deficient group, while proclined upper incisors to the palatal plane and protruded upper incisors to NA characterize the dental features of the SCA group. Similarly, the THL group showed the dental feature of proclined upper incisors to palatal plane angle with the normal position of the upper incisors to NA, while normal position and inclination of the upper and lower incisors were observed in the control group. Soft tissue characteristics in G6PD deficient group mainly showed a prominent lower lip E-line, while in SCA and THL and control groups, a normal position of the lips to E-line was found. None of the previously published research compared the facial features of G6PD-deficient individuals to those of a control group or other conditions of SCA and THL. Therefore, this is the first research comparing facial characteristics of different conditions.

The study results showed that the individuals with SCA and THL had class II skeletal patterns, which aligns with the findings of Maia et al17 in Brazil, where a computerized cephalometric analysis revealed that 32% of the SCA patients had class

II skeletal relationships. Another study involving 45 patients with SCA exhibited class II skeletal pattern characteristics because of mandibular retrusion, unlike our study that showed proclined upper incisors to the palatal plane[1]. Contrarily, both these studies showed the absence of maxillary protrusion[1,16]. In line with our study, Helaly and Abuaffan[3] compared the malocclusion among 212 Sudanese children with SCA, aged 3-15 years, against 212 healthy children as a control group. The results revealed that class II malocclusion was most common among children with increased overjet.

Soft-tissue measurements showed a class II skeletal pattern identical to the present study's findings for THL patients. Alhaija et al[11] studied the cephalometric and facial features of beta THL patients. It was found that all THL patients had a class II skeletal base relationship, but normal length maxilla compared with the healthy control group. Another study by Amini et al[12] in Iranian children with THL. It was found that all THL patients had a class II skeletal base relationship with an average ANB angle of 8.75 with no maxillary prognathism, while the mandible of the THL patients appeared to be retruded. Dentally, incisors were found to be proclined.

Limitations

In this present study, severity and subtypes of G6PD, SCA and THL have not been taken into consideration. Despite of that, our findings matched the previously published literature that included the subtypes of this condition, especially Beta Thalassemia major. Since this study was carried out solely among Saudi adults, care should be taken when extrapolating the results to other

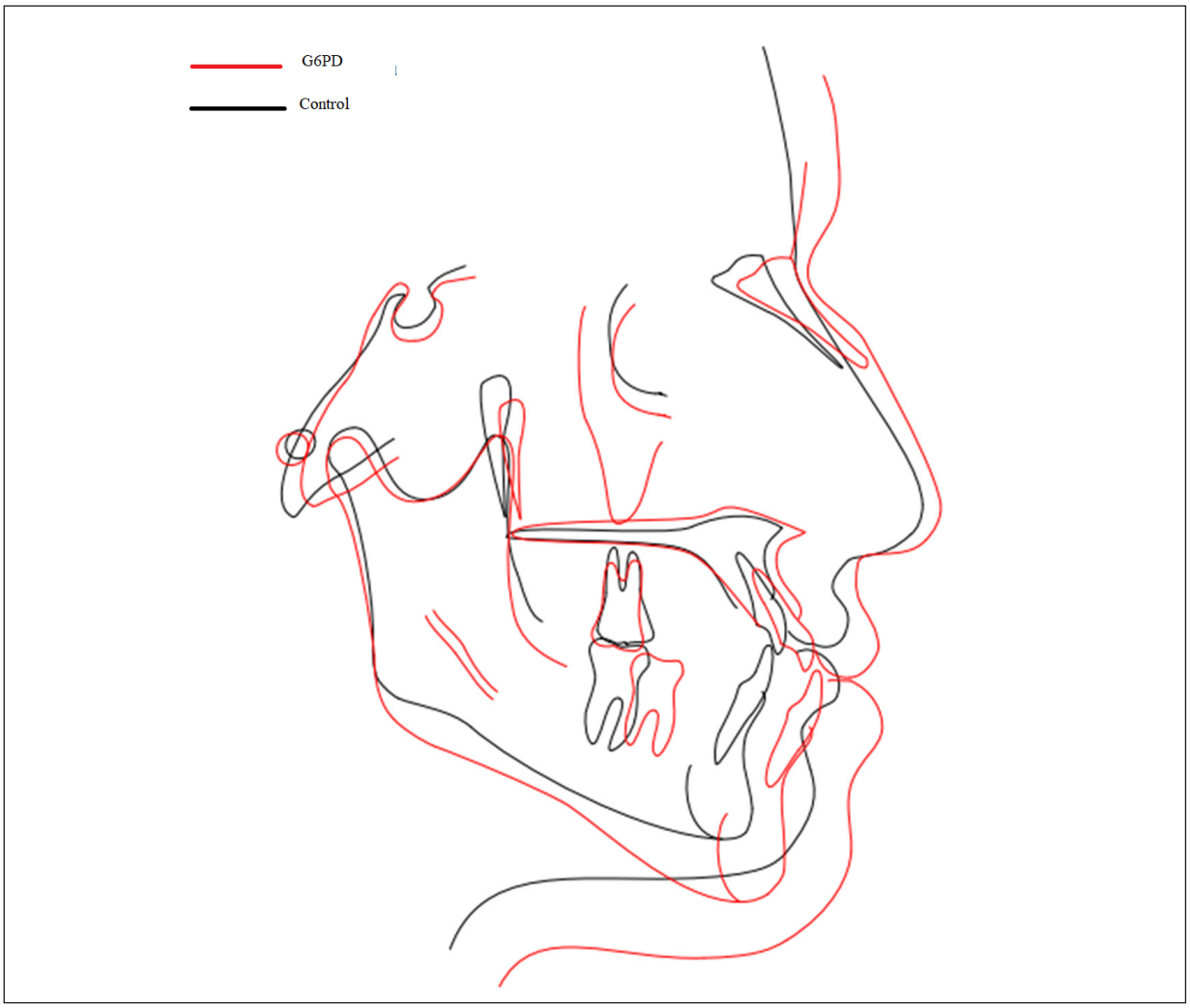

Figure 3. Superimposition of the average skeletal, dental and soft tissue tracings for G6PD and control groups.

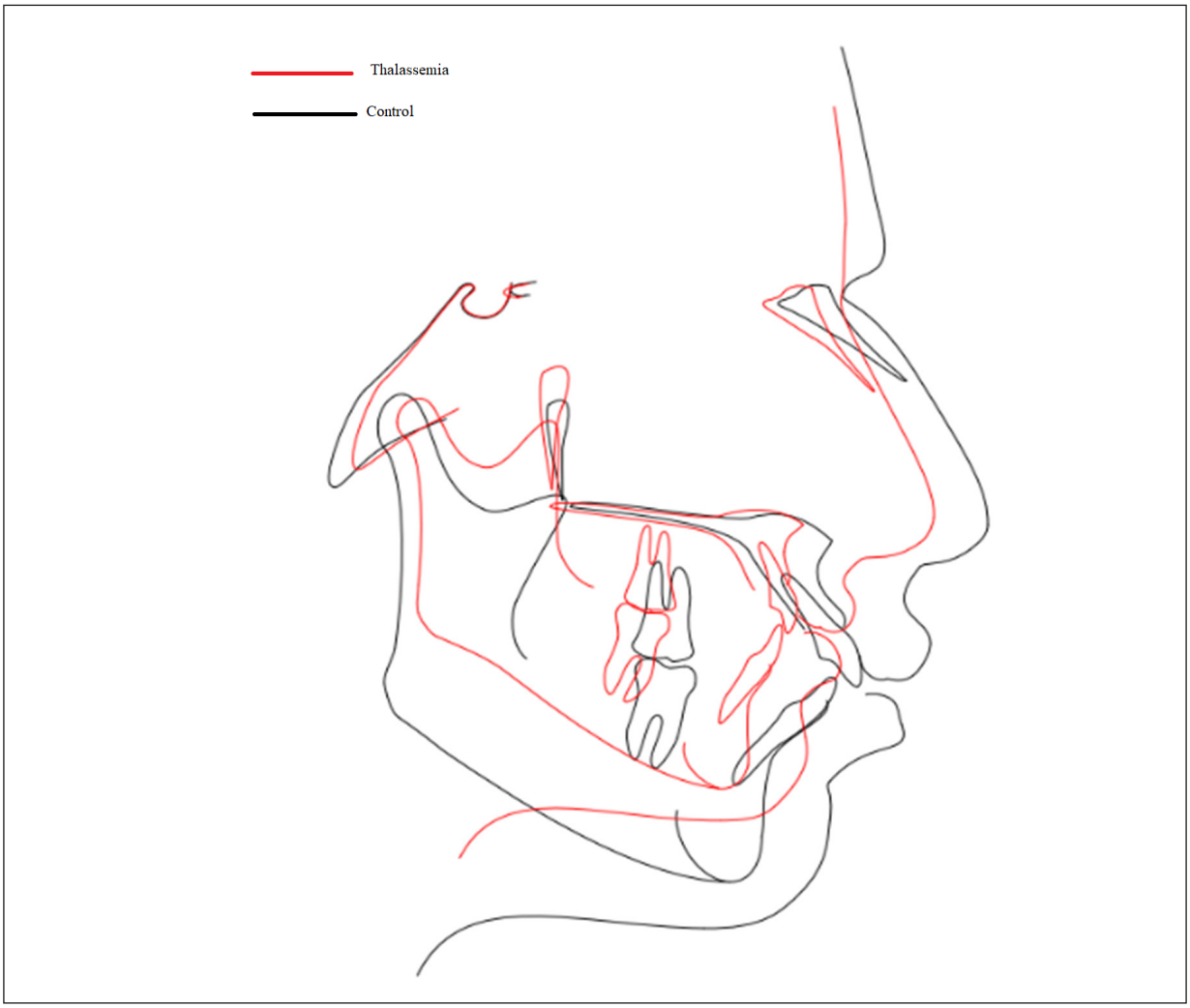

Figure 4. Superimposition of the average skeletal, dental and soft tissue tracings for Thalassemia and control groups.

populations. We recommend further similar studies from different countries taking into consideration a larger sample size and different stages of severity of the disease.

Conclusions

All THL and SCA patients had Class II skeletal base relationships compared to controls. The mandible of these patients appeared to be smaller in size and more retruded. A pronounced vertical growth direction was also evident from angular and linear measurements. The dental deviations in SCA patients were mainly seen as protruding upper incisors to NA while in normal position in THL patients. The marked convex lower face was evident from soft-tissue measurements in SCA and THL patients. While in G6PD deficiency patients, class III skeletal pattern due to retruded maxilla and protruded mandible with horizontal basal configuration and protruded upper incisors to palatal plane and proclined upper incisors to NA. Moreover, a prominent upper and lower lips were evident from soft-tissue measurements. We recommend further studies with larger sample size.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Funding
This research has not received any external funding.

Ethics Approval
The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Research and Innovation Center of Riyadh Elm University (IRB No.: FP-GRP/2020/492/267/278).

Acknowledgements
Authors would like to thank research and innovation center of Riyadh Elm University for supporting and granting this study.

Data Availability Statement
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's Contribution
Fatima AlAssad: conception and design of the study, acquisition of data, analysis, and interpretation of data, drafting the article, and final approval.
Omar H Alkadhi: conception and design of the study, analysis, and interpretation of data, drafting the article, supervision, and final approval.

References

1) Pithon MM, Palmeira LMV, Barbosa AAL, Pereira R, de Andrade ACDV, Coqueiro R da S. Craniofacial features of patients with sickle cell anemia and sickle cell trait. Angle Orthod 2014; 84: 825-829.
2) Madhok S, Madhok S. Dental considerations in Thalassemic patients. J Dent Med Sci 2014; 13: 57-62.
3) Helaly M, Abuaffan AH. Association between sickle cell disease and malocclusion among a sample of Sudanese children. Indian J Dent Educ 2016; 9: 81-87.
4) Tantular IS, Kawamoto F. Distribution of G6PD deficiency genotypes among Southeast Asian populations. Trop Med Health 2021; 49: 97.
5) Sulaiman AM, Saghir SAM, Al-Hassan FM, Yusoff NM, Zaki AH. Molecular Characterization of Glucose-6-Phosphate Dehydrogenase Deficiency in a University Community in Malaysia. Trop J Pharm Res 2013; 12: 363-367.
6) Hernández-Pérez D, Butrón-Téllez Girón C, Ruiz-Rodríguez S, Garrocho-Rangel A, Pozos-Guillén A. Dental Considerations in Children with Glucose-6-phosphate Dehydrogenase Deficiency (Favism): A Review of the Literature and Case Report. Case Rep Dent 2015; 2015: 506459.
7) Osman HG, Zahran FM, El-Sokkary AM, El-Said A, Sabry AM. Identification of Mediterranean mutation in Egyptian favism patients. Eur Rev Med Pharmacol Sci 2014; 18: 2821-2827.
8) Hashmi G, Qidwai A, Fernandez K, Seul M. Enabling routine β-thalassemia Prevention and Patient Management by scalable, combined Thalassemia and Hemochromatosis Mutation Analysis. BMC Med Genet 2020; 21: 108.
9) Cooley TB, Witwer ER, Lee P. Anemia in children: With splenomegaly and peculiar changes in the bones report of cases. Am J Dis Child 1927; 34: 347-363.
10) da Silva GB, Libório AB, Daher EDF. New insights on pathophysiology, clinical manifestations, diagnosis, and treatment of sickle cell nephropathy. Ann Hematol 2011; 90: 1371-1379.
11) Abu Alhaija ESJ, Hattab FN, al-Omari MAO. Cephalometric measurements and facial deformities in subjects with beta-thalassaemia major. Eur J Orthod 2002; 24: 9-19.
12) Amini F, Jafari A, Eslamian L, Sharifzadeh S. A cephalometric study on craniofacial morphology of Iranian children with beta-thalassemia major. Orthod Craniofac Res 2007; 10: 36-44.
13) Mediani HS, Nurhidayah I, Lusiani L, Panigoro R. Predicting factors impact to quality of life of school age Thalassemic children in Indonesia. J Adv Pharm Educ Res 2021; 11: 81-85.
14) Kambasu DM, Rujumba J, Lekuya HM, et al. Health-related quality of life of adolescents with sickle cell disease in sub-Saharan Africa: a cross-sectional study. BMC Hematol 2019; 19: 9.
15) Ejindu VC, Hine AL, Mashayekhi M, Shorvon PJ, Misra RR. Musculoskeletal manifestations of sickle cell disease. Radiogr 2007; 27: 1005-1021.
16) Licciardello V, Bertuna G, Samperi P. Craniofacial morphology in patients with sickle cell disease: a cephalometric analysis. Eur J Orthod 2007; 29: 238-242.
17) Maia NG, dos Santos LA, Coletta RD, Mendes PH, Bonan PR, Maia LB, et al. Facial features of patients with sickle cell anemia. Angle Orthod 2011; 81: 115-120.
18) Thajeel AT, Al-Taei JA. Cephalometric analysis of craniofacial deformity of thalassemic major by using computed tomography. J Baghdad Coll Dent 2013; 25: 39-43.
19) Al-Ani RA, Ghaib NH. Skeleto-dental features analysis of Iraqi Thalassemic patients aged 13-15 years (Cross sectional cephalometric study). Iraqi Orthod J 2011; 7: 19-23.
20) Shnorhokian HI, Chapman DC, Nazif MM, Zullo TG. Cephalometric study of American black children with sickle-cell disease. ASDC J Dent Child 1984; 51: 431-433.