ORAL MANIFESTATIONS AND DENTOFACIAL ANOMALIES IN BETA THALASSAEMIA MAJOR CHILDREN IN DUBAI (UAE)

A CASE CONTROL STUDY 2015

By

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ABSTRACT

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Aims:

The purpose of this study was to identify special oral and dentofacial manifestations peculiar to beta thalassaemia major children in Dubai, United Arab Emirates (UAE).

Materials and Methods:

A total of 38 Emirati children with beta thalassaemia major (mean age =10.18 ± 3.19) and 76 healthy Emirati children (mean age = 10.79 ± 3.54) were recruited from Dubai Genetic & Thalassaemia Centre, along with public schools in Dubai. A dental examination including caries assessment using dmft/DMFT indices, oral hygiene assessment using the Simplified Oral Hygiene Index, an assessment of occlusal anomalies, dentofacial abnormalities and soft tissue abnormalities was conducted.

Results:

There was a clear and statistically significant difference in caries experience amongst thalassaemia children compared to the healthy controls with DMFT (2.73 ± 0.22 vs 0.21 ± 0.56, p-value = 0.017). The Met Need Index (MNI) and the Restorative Index (RI) were calculated from the mean dmft/DMFT of the studied sample. Children in the thalassaemia group received
less treatment than their controls in all age groups; however, this was not shown to be statistically significant. Calculus Index (CI) was found to be significantly higher among children with beta thalassaemia (0.27 ± 0.43) compared with healthy controls (0.09 ± 0.32) p-value 0.002. Conversely, the proportion of gingivitis was found to be significantly lower among children with thalassaemia compared with that of the healthy controls 44.7% and 69.7% respectively (p-value = 0.009). On the other hand, beta thalassaemia subjects had a higher proportion of class II Molar Angle Malocclusion (40%) compared to the healthy controls class II (25%). Children with thalassaemia had significantly higher proportion of retained primary teeth compared with healthy controls (18.4% vs. 0%, p-value = 0.001). It was observed that gingival pigmentation in children with thalassaemia was significantly higher compared with healthy controls (23.7% vs 0%, p-value = 0.001).

**Conclusions:**

The findings of this study concluded that children with thalassaemia in Dubai had higher caries rate compared to healthy children. Other oral and dentofacial anomalies were observed in the group. There is a need to implement awareness programs to alert patients’ parents and caretakers of the need to provide better care.
DEDICATION

This thesis is dedicated to my husband and my daughters

For their endless love, support and encouragement
DECLARATION

I declare that all the content of the thesis is my own work. There is no conflict of interest with any other entity or organization.

Name: Shaikha Al Raeesi

Signature:
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Sometimes it is difficult to find words to show one’s sincere thanks to those who contributed to one’s professional success and completion of tasks. I would like to record my indebtedness to all those who have contributed in one way or another to the development of this thesis and helping it come to light.

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List of Abbreviations

CEJ = Cemento-enamel junction
DHCC = Dubai Health Care City
DHA = Dubai Health Authority
D = Decayed
F = Filled
GCP = Good Clinical Practice
Hb = Haemoglobin
Hb Bart’s = Haemoglobin Bart’s
HbF = Fetal haemoglobin
HbA = Adult haemoglobin
HIV = Human Immunodeficiency Virus
JE = Junctional epithelium
M = Missing
MNI = Met Need Index
NICE = National Institute for Clinical Excellence
OHI-S = Oral Hygiene Index Score
RBCs = Red Blood Cells
RI = Restorative Index
TH = Thalassaemia
UAE = United Arab Emirates
WHO = World Health Organization
1. Introduction

Haemoglobinopathies are the most common autosomal recessive inherited diseases in humans with an estimated 240 million carriers worldwide. Thalassaemia is one of the most common haemoglobinopathies as well as the most widely distributed genetic disorder.¹

The term Thalassaemia derives from the Greek word “thalassa” meaning sea and “haemia” meaning blood, and was first used by Wipple and Bradford in 1932.²

Thalassaemia refers to a group of inherited haematologic disorders caused by defects in the synthesis of one or more polypeptide chains of haemoglobin. Haemoglobin consists of an iron-containing haeme ring and four globin chains: two of each alphas and non-alphas. The composition of these four-globin chains determines the haemoglobin type. Fetal haemoglobin (HbF) has two alpha and two gamma chains (alpha2 gamma2), while Adult haemoglobin A (HbA) has two alpha and two beta chains (alpha2 beta2). The transition from gamma globin synthesis (HbF) to beta globin synthesis (HbA) begins before birth; by approximately six months of age, healthy infants will have mostly transitioned to HbA.³

Thalassaemia is divided into two major groups; alpha thalassaemia, which is caused by, reduced or absent synthesis of alpha globin protein chains, and beta thalassaemia which is caused by reduced, or absent synthesis of beta globin protein chains. Imbalances of globin chains cause haemolysis and impaired erythropoiesis. The alpha type affects the foetus and is noted at birth where beta thalassaemia major (Cooley’s anaemia) is the most severe form of congenital haemolytic anaemia. It results from the abnormal synthesis of the beta-chain haemoglobin, which usually begins to manifest as early as 4-6 months of infancy, during the switch from HbF to HbA.⁴
Thalassaemia is classified as homozygous, heterozygous, or compound heterozygous based on both genetic and clinical entities. The heterozygous form of the disease (thalassaemia minor) is mild and generally asymptomatic; the only manifestation of the disease being hypochromic microcytic anaemia. The homozygous form of thalassaemia, beta thalassaemia major, exhibits the most severe clinical symptoms and includes marked orofacial deformities.\(^5\)

Beta thalassaemia is considered to be a major public health issue, as well as being a life threatening condition characterized by severe anaemia, hepatosplenomegaly, growth retardation, endocrine dysfunction, cardiac failure and skeletal changes.\(^6\) The hypertrophy and expansion of erythroid marrow is reflected at the skeletal level, and especially in the facial bone.

Approximately 5 % of the world’s population was found to have a globin variant, with only 1.7 % having an alpha or beta thalassaemia trait.\(^7\) Thalassaemia affects both men and women equally, and occurs in approximately 4.4 of every 10,000 live births.\(^3\)

Thalassaemia major patients may suffer from anaemia as a complication in early childhood. Multiple blood transfusions can prolong lives to the age of 15-25 years old and improve growth.\(^8\) However, death may occur due to cardiac complications of iron overload as a result of these transfusions.

The common orofacial features among thalassaemic patients include frontal bossing, skeletal changes due to bony overgrowth (with characteristic appearances known as chipmunk facies), upper lip retraction, protrusion of pre maxilla bone associated with alveolar enlargement that causes malocclusion in the dentition with the clinical appearance of protrusion, flaring, spacing of anterior teeth and anterior open bite. The oral mucosa appears pale or a lemon yellow colour
due to deposition of bilirubin pigmentation and anaemia. Sometimes the gingival colour tends to be dark, caused by high ferritin level in the blood.\textsuperscript{9,10}

Dental caries and orofacial changes in thalassaemia major patients are reported by several investigators, finding that dental caries was significantly higher in thalassaemic patients as compared to healthy controls due to the difficulty thalassaemic patients face in following oral hygiene instructions.\textsuperscript{11}

Many studies show the highest rates of prevalence of beta thalassaemia are in the Mediterranean region, the Middle East, the Indian subcontinent and Far East Asia, with prevalence rate of around 15–20% in Greece, Turkey, Cyprus, and southern Italy.\textsuperscript{12} However, because of population migration thalassaemia has spread to continental Europe, the North and South Americas, as well as Australia.\textsuperscript{4}

The United Arab Emirates (UAE), like many countries in the region, has a large population of individuals suffering from beta thalassaemia. Due to the number of homozygous mutations has a direct correlation with the degree of consanguinity. In the UAE, more than 50% of all marriages are between relatives and more than half of these are between first cousins.\textsuperscript{13} Currently, there are no studies from the UAE indicating the prevalence of beta thalassaemia. Further, few studies have been conducted to study the prevalence of dental caries and other oro-facial conditions in thalassaemia patients in this region; there has been no study conducted in the UAE in this field.
1.1 Literature Review

1.1.1 Definition

The thalassaemia syndromes are a heterogeneous group of inherited conditions characterized by either a partial or complete suppression in the production of normal haemoglobin as a result of defective synthesis of one or more of the globins chains.\(^\text{14}\)

Haemoglobin disorders are thought to have originated in countries where malaria was endemic. The malaria parasite causes a serious infectious disease in humans by attacking red blood cells (RBCs). These RBCs can undergo genetic modifications in their DNA, in order to prevent the parasite’s survival and multiplication. This can cause illness or death in the infected individual. This mutation led to what we know today as the beta thalassaemia carrier status.\(^\text{15}\)

In addition, the disease shows an anomaly of RBCs which manifest as an autosomal recessive hereditary trait. This affects the alleles of one or more of the globin genes, located on either chromosome 11 or chromosome 16. This trait was accidentally observed in the heterozygous group (thalassaemia minor), the mild form of the disease. However in the severe from of the disease, homozygous group (thalassaemia major),\(^\text{14}\) it is observed that the red blood cells have a shortened life span, and contain fetal haemoglobin.\(^\text{16}\) The term “thalassaemia intermedia” is used to describe the disorder with manifestations of the train which are milder than the major form but more severe than the minor form.\(^\text{17}\)

Thalassaemia is considered a haemoglobinopathy. Haemoglobinopathies are a group of disorders, which result from an inherited abnormality of globin production, and are classified in two subdivisions; thalassaemia, and sickle cell anaemia. Thalassaemia consists of an inherited defect in the rate of synthesis of one or more of the globin chain, which results in imbalanced
globin chain production, ineffective erythropoiesis, haemolysis and variable degrees of anaemia. Sickle cell anaemia results from an inherited structural alteration in one of the globin chains. Sickle cell anaemia results from an inherited structural alteration in one of the globin chains. \(^\text{[17]}\)

Thalassaemia has different types which will be discussed in the classifications; the most common type in the Middle East region is the beta thalassaemia. \(^\text{[18]}\)

1.1.2 Definition of beta thalassaemia syndrome

Beta thalassaemia disorders are a group of hereditary blood disorders characterized by reduced or absent synthesis in beta globin chains. This results in reduced haemoglobin (Hb) in RBCs, decreased RBC production, and anaemia. Most thalassaemia is inherited as a recessive trait. \(^\text{[19]}\)

1.1.3 History

Thomas Cooley and Lee first recognized the clinically severe form of anaemia that was associated with splenomegaly and bone change in 1925. \(^\text{[17]}\)

Wipple and Bradford first used the term Thalassaemia in 1932, derived from the Greek words “thalassa” meaning sea, and “haemia” meaning blood. In 1940, the genetic characteristics of the disease were fully understood. \(^\text{[17]}\)

1.1.4 Epidemiology

Most studies demonstrate that the rate of prevalence of beta thalassaemia major are disseminated, with high incidence (2.5% - 25%), in the Mediterranean basin, the Middle East, along with the tropical and subtropical regions of Africa, the Asian subcontinent, and Southeast Asia. The milder form of the disease is the most commonly observed, \(^\text{[20]}\) with the highest prevalence rate of around 15–20% in Greece, Turkey, Cyprus, and southern Italy. \(^\text{[21]}\) However, due to extensive migration of the high gene occurrence population, thalassaemia has spread to Continental
Europe, North and South America and Australia.\(^4\) It has been estimated that carriers of beta thalassaemia comprise about 1.5\% of the international population (between 80 to 90 million), with about 60,000 symptomatic individuals born each year. The great majority of these symptomatic individuals are in the developing world; the total incidence of symptomatic individuals annually is estimated at 1 in 100,000, and 1 in 10,000 in the European Union. However, accurate data on carrier rates among many populations is lacking, especially in regions of the world it is anticipated this would be the case.\(^{22}\)

According to the Thalassaemia International Federation 2014, approximately 7\% of the global population are carriers for haemoglobin disorders. Each year, between 300,000 and 500,000 children are born with severe haemoglobin disorders. Only around 200,000 patients with thalassaemia major are presently alive and registered as receiving regular treatment around the world.\(^{23}\)

The United Arab Emirates, like other countries in the region, has a large number of beta thalassaemia patients. Presently, there have been no studies in the UAE reporting the prevalence of beta thalassaemia major; however, the Dubai Genetic & Thalassaemia Centre is dedicated to managing this condition by providing chronic disease management for thalassaemic patients at internationally recognised standards. About 420 patients with various haematological disorders receive regular treatment and blood transfusions at the centre. According to their statistics in 2008 around 46\% of these patient are from UAE nationals
1.1.5 Classification of thalassaemia syndrome

Genetic classification

This disorder is generally inherited as alleles of one or more of the globin genes – located on either chromosome 11 (for beta, gamma and delta) or on chromosome 16 (for alpha chain) – are either reduced or completely absent. These deformities can result in two types of thalassaemia.\textsuperscript{24}

*Alpha Thalassaemia*

Alpha thalassaemia is the result of deficient or absent alpha globin chain production, leading to an increase in the amount of beta globin chains. Alpha globin chain production is controlled by two genes on each chromosome 16.

Alpha thalassaemia has four forms:

I. **Silent carrier alpha thalassaemia:**
   A condition characterized by a single gene deletion, resulting in the asymptomatic alpha thalassaemia condition, with normal hematologic findings.

II. **Alpha thalassaemia trait (mild):**
   A condition characterized by a two-gene deletion, with microcytosis and, usually, no anaemia.

III. **Haemoglobin H disease (alpha thalassaemia intermedia):**
   The three alpha genes are deleted, resulting in significant production of haemoglobin H (HbH), containing four beta chains (beta4), and causes significant manifestations such as anaemia, haemolysis, and splenomegaly.

IV. **Alpha thalassaemia major with Hb Bart’s:**
The deletion of four alpha genes results in the significant production of haemoglobin Bart’s (Hb Bart’s) contains four gamma chains (gamma4). This produces a serious condition resulting in fatal hydropsfetalis.\textsuperscript{3}

**Beta Thalassaemia**

Beta thalassaemia is caused by a deficiency or absence of beta globin chain production, resulting in an excess of alpha chains. Beta globin synthesis is controlled by one gene on each chromosome 11. The severity of beta thalassaemia is dependent, to some extent, on the kind of beta thalassaemic genes that an affected individual has inherited.\textsuperscript{3}

Beta thalassaemia is the most common type of thalassaemia that occurs in the Middle East region. For this reason, we will limit our review and study to this type of thalassaemia.

I. **Beta thalassaemia minor (trait)**

Is a symptomatic condition resulting from a single gene defect; manifests as microcytosis of RBCs and mild anaemia. This condition can be detected by a routine laboratory blood evaluation.

II. **Beta thalassaemia major (cooley’s anaemia)**

The synthesis through both genes is severely reduced or absent, and results in severe anaemia, a potentially life-threatening condition. The symptoms begin to develop by six months of age due to the presence of HbF at birth.

III. **Beta thalassaemia intermedia**

The two genes are defective, resulting in a mild to moderate decrease in the synthesis of beta globin. This condition does not require any blood transfusion.
Clinical classification of beta thalassaemia

Beta thalassaemia syndromes are classified into three clinical groups:

I. **Severe thalassaemia (major).**

Clinical manifestations of thalassaemia major occur between 6 and 24 months of life. Affected infants fail to thrive and become progressively pale due to a low level in haemoglobin that generally reach 6 g/dl or lower. The entirety of clinical features will be discussed in detail in the clinical features section.

II. **Thalassaemia intermedia**

Thalassaemia intermedia presents later in life than thalassaemia major, and presents with milder anaemia with haemoglobin levels of 7 g/dl. It is associated with mild jaundice and hepatosplenomegaly. Iron overload is constantly exhibited by increased plasma ferritin levels. Normally patients with thalassaemia intermedia do not require blood transfusions, except when they develop infections, which precipitate further anaemia. The life span of these patients is generally short.

III. **Asymptomatic thalassaemia (minor).**

In this type of thalassaemia, the carriers are usually clinically asymptomatic. The haemoglobin levels are either normal, or near to normal, with no jaundice or hepatosplenomegaly present.

The most common challenge encountered by asymptomatic thalassaemia patients is to receive a "thalassaemia" diagnosis without clear clarification and proper examination from the clinician. This will often result in panic in the patient.
1.1.6 Aetiopathogenesis

Beta thalassaemia is caused by any of the more than 200-point mutations in functionally important regions of the beta globin gene. There are several methods to detect the defective gene which include ARMS or dot blot analysis; the more recent analysis is direct DNA sequence analysis. The beta globin gene mutations result in the reduction or absence of the production of beta globin chains. However, the deletion of the beta globin gene is rare.

1.1.7 Pathophysiology and Haemoglobinopathies

The production of all types of blood cells occurs in the bone marrow, as a result of differentiation from primitive stem cells. This is a self-regulating process, with normal target distribution of cell types, and maintenance of steady-state production balanced with natural senescence and removal from the system.

The pluripotent stem cell matures into two common precursor lines; lymphopoietic and haematopoietic. The lymphopoietic cell becomes either B-cell or T-cell. The haematopoietic common precursor cell becomes committed to megakaryocytic cells that mature to platelets, erythroid cells that mature to erythrocytes, or the myelomonocytic cell lines.

The hematopoietic system can respond to demands placed on it by triggers – such as infection, immune challenges, haemorrhage, or hypoxia – by altering the production and distribution of the cell types.

Haemoglobin comprises of haeme (the iron–containing portion of haemoglobin) and globin (amino acid chains that form a protein). Normal haemoglobin types include two types of adult haemoglobin A: HbA1 about 95 – 98% (contain two alpha chains and two beta chains), and HbA2 about 2 – 3 % (contain two alphas and two delta chains). The other type is fetal
haemoglobin (HbF) which contains two alpha and two gamma chains. HbF is the first haemoglobin produced by the foetus during gestation, the production of which falls to a low level shortly after birth. Haemoglobinopathies occur when point mutations or deletions in the globin genes cause changes in the amino acids which make up the globin protein, resulting in an abnormal form of haemoglobin.¹⁰

**Pathophysiology of major beta thalassaemia**

All the pathophysiologic features of thalassaemia can be related to a primary imbalance of globin-chain production, thus making the thalassaemia fundamentally different from all other genetic and acquired disorders.¹⁰

The depression amount of (beta+) or absence of (beta0) beta globin chains production results in a relative excess of unbound alpha globin chains that precipitate, and lead to premature RBC precursors death and accelerate the apoptosis process. The latter process leads to ineffective erythropoiesis, severe microcytic hypochromic anaemia, bone marrow expansion, skeletal deformities and increased gastrointestinal iron absorption.²⁶ The nature of the mutation of the beta globin gene, located on chromosome 11, determines the degree of globin chain reduction.¹⁹

**1.1.8 General Manifestation of beta thalassaemia major**

*Clinical Manifestations*

*Anaemia*

The onset of the severe form of the Cooley’s anaemia is seen in the first two years of life and is characterized by severe hypochromia and microcytosis. The child becomes symptomatic when
the haemoglobin level drops to 3 to 4 g per decilitre, with signs of a yellowish pallor of skin or jaundice, general weakness, fatigue, malaise, and lethargy.\textsuperscript{27}

\textit{Massive Erythropoiesis and bone disease}

Bone resorption, extramedullary haemopoiesis and bone marrow expansion occur as a result of severe infectious erythropoiesis as a consequence of anaemia. A radiographic image can show extramedullary haematopoietic masses around the ribs and at paravertebral sites, though no symptoms are present. On the other hand, such masses in the skull may lead to convulsion, and if present in the spinal canal may lead to paraplegia.

Osteoporosis and pathological fractures are significant signs of bone marrow expansion, erosion, thinning of the cortex, and decreased bone density.\textsuperscript{24} One study reports that osteoporosis occurs in 51\% of persons older than 12 years with thalassaemia major.\textsuperscript{28}

\textit{Growth endocrine function}

The most noticeable defect in endocrine function is the absence, or impairment, of secondary sexual development in thalassaemic patients (hypogonadism). Diabetes mellitus often occurs in untreated adult patients. Hypoparathyroidism and associated with bone resorption can both be treated by blood transfusion. Thyroid function is rarely disturbed.\textsuperscript{26} Reduced to normal growth hormone secretion is reported. However, many patients with beta thalassaemia have been shown to have low levels of somatomedin, a factor produced by the liver in response to growth hormone which stimulates cartilage growth.\textsuperscript{29}

\textit{Iron overload}

Nearly every cell of the human body contains iron, a vital trace element which is required for the production of haemoglobin present in red blood cells (RBCs) and myoglobin, along with playing
an important role in the production of other significant proteins involved in DNA production, as well as in cell division. The normal total iron content of the adult human body is 4.5 g. Beta thalassaemia major patients have an increased accumulation of iron in blood due to multiple blood transfusions, and the breakdown of alpha chains. It was approximated that one unit of transfused RBCs contains around 250 mg of iron, despite the fact that the body cannot excrete more than 1 mg of iron per day. Any iron which exceeds the iron binding capacity of transferrin appears in the plasma as non-transferrin bound iron, which is highly toxic to tissues and has the ability to damage the developmental organs such as the heart, spleen, liver, and may result in skin pigmentation, poor appetite and weight loss. Providing chelation therapy to thalassaemic patients helps in preventing these complications; when this treatment is given in intensive combination therapy, it may reverse the complications of iron overload.

Heart

Cardiac failure, arrhythmias, myocarditis, pericarditis, and myocardial infarction are the lead complications in thalassaemia patient which may result in death, with the primary cause being iron deposition in the heart.

Liver and hepatitis infection

Liver disease is becoming a more relevant cause of death in patients with beta thalassaemia major. Liver disease in these patients can manifest as hepatomegaly, decreased albumen concentrations, Hepatitis B and C, liver cirrhosis, and hepatocellular carcinoma. These complications are largely a result of iron overload and inadequate chelating therapy. Splenomegaly and hepatomegaly may lead to protrusion of the abdomen.
**Infections**

Severe thalassaemic patients are more vulnerable to viral, bacterial and fungal infections. Accordingly, it is believed that these infections are a leading cause of death. These infections range from minor infections such as upper respiratory tract infections and diarrhoea, to more severe infections such as pneumonia and septicaemia.\(^{24}\)

In these cases, massive splenomegaly is a cause of major distress. Hypersplenism can cause thrombocytopenia and abnormal bleeding in thalassaemic children; however, patients who undergo therapeutic splenectomy have a very high chance of developing bacteraemia and post-splenectomy sepsis that is caused by Gram-negative bacteria.

Fungal infections by Pythium organisms can lead to arterial occlusion and gangrene of the legs. Investigations have not yet been able to pinpoint the key mechanisms of the infection in thalassaemic disorders. In addition, infections in thalassaemia do not appear to be related to defective lymphocytes, but might have a relationship to iron overload and severe anaemia.\(^{35}\)

**Osteoporosis**

Osteoporosis often arises in patients with thalassaemia, reflected by marrow expansion, endocrine deficiencies, iron toxicity, and the potential toxicity of chelators. Cortical thinning and subclinical fractures, as well as problematic clinical fractures may occur; the latter with minimal trauma. A hypercoagulable state, which increases the possibility for thromboembolism, has also been described in patients with thalassaemia secondary to platelet activation, red cell membrane damage and endothelial cell activation.\(^{36}\)
**Dento-facial Manifestations**

The most common craniofacial deformity in the thalassaemic patient is Class II skeletal base relationship with short mandible, a reduced posterior facial height, and an increased anterior facial proportion.\[^{10}\] In addition, it has been reported in the literature that the severity of the disease is closely related to the degree of cephalofacial deformities—which include prominent frontal and parietal bones, sunken nose bridge, protruding zygomas and mongoloid slanting eyes, enlargement of maxilla and obliteration of maxillary sinus due to bony expansion, with depression of the bridge of the nose– are the major facial discrepancies in thalassaemic patients resulting in the characteristic facial appearance called “Chipmunk face”.\[^{9,37}\]

In addition, the dental arch morphology in thalassaemic patients differs from that of the unaffected population; this may include a narrower maxilla and a smaller incisor width for maxillary and mandibular arches.\[^{38}\] The overdevelopment of the maxilla results in increased overjet, spacing, and protrusion of upper anterior teeth, as well as severe over bite and open bite.\[^{39}\] It was also found that the dental development in beta thalassaemic children is delayed by a mean of 1.01 years compared with normal children; this delay is consistent with significant general growth retardation in this group.\[^{10}\]

**Radiographic features**

The radiographic features in beta thalassaemia major patients were extensively studied using intra oral periapical views of the posterior region, lateral cephalometric and panoramic radiographs.\[^{40}\]

Skull: Thickening of the calvarium of the skull is mostly observed in the frontal region.\[^{41}\] One of the most significant radiographic indicators of beta thalassaemia is “hair on end appearance”.

\[^{10}\]
This radiographic appearance is due to the extreme thickening of diploe; the inner and the outer plates become poorly defined and the trabeculae between the plates become elongated, producing a bristle–like appearance on the surface of the skull.9

Teeth and jaws: short and spike–shape roots may be observed with the most frequency in the mandibular first molars and central incisors, taurodontism and thin lamina dura. The maxilla radiographs demonstrate sharply demarcated intermaxillary sutures, prominent anterior maxilla and small maxillary sinuses.42 In the jaws, there is generalized rarefaction of the alveolar bone, thinning of cortical bone, and a “chicken-wire” appearance of enlarged marrow spaces and coarse trabeculation,43 as well as faint inferior alveolar canal, and thin cortex of mandible.44

1.1.9 General Management of beta thalassaemia major

Management strategies for beta thalassaemia major patients emphasise prolonging life expectancy, as well as using blood transfusion and chelation therapy to improve the control of anaemia, suppression of erythropoiesis, and inhibition of gastrointestinal iron absorption.

Blood transfusion therapy

The decision to begin blood transfusion in patients with confirmed diagnoses of thalassaemia should be based on the presence of severe anaemia, which impairs the growth and development (Hb < 7 g/dl for more than two weeks, excluding other causative factors including infections). In addition, in patients with Hb > 7 g/dl, other factors should be measured including facial changes, poor growth, evidence of bony expansion, and splenomegaly. Patients starting at the age of six months may be in need of blood transfusions.19
Different transfusion regimens have been followed over time, but the most widely accepted regime aims at a pre-transfusion Hb level of 9 to 10 g/dl, and a post-transfusion level of 13 to 14 g/dl. This approach prevents growth impairment, organ dysfunctions, and bone deformities. This helps in improving normal quality of life and activity.\textsuperscript{3}

The frequency of these transfusions is generally every two to four weeks. Shorter intervals may promote reduction in blood requirement, but are contrary to an acceptable quality of life.

The frequency of blood transfusion depends on numerous factors including weight of the patient, the target increase in Hb level, and haematocrit of blood unit. The capacity of transfused RBC should not exceed 15 to 20 ml/kg/day, infused at a maximum rate of 5 ml/kg/hour, in order to avoid a fast increase in blood volume. The most adverse effect associated with blood transfusion is iron overload.\textsuperscript{45}

\textit{Chelation}

Transfusion-dependent patients develop iron overload as there is no physiologic mechanism, which may eliminate excess iron resulting from multiple transfusions; consequently, there is a need for treatment with an iron chelator starting between five and eight years of age.\textsuperscript{46} Currently there are three iron chelators are available for use as either mono therapy or combination.

- Deferoxamine–Iron chelation was introduced with parentral Deferoxamine, and binds iron with a1:1 ratio. It is not orally absorbed and has a very short half-life, as such; the most common form of administration is through slow subcutaneous infusion via small portable pumps. Dosage is 20-60mg/kg bw/infusion 5-7 days a week, depending on the degree of iron load.
• Deferiprone– Introduced in 1999, orally administered Deferiprone binds iron at a 3:1 ratio. The approved dose is 75-99 mg/kg bw/24hrs, usually 8 hours apart. It is particularly effective in removing iron from the heart.

• Deferasirox– This oral chelator was introduced in 2006 binds to iron at a 2:1 ratio. Due to its relatively long half-life, it may be administered in a once daily dose, at a range between 10-40 mg/kg.47

_Bone marrow transplantation_

Bone marrow transplant is considered an excellent curative therapy in thalassaemic patients during childhood. The first successful bone marrow transplant for a thalassaemia major patient was performed in 1982 (Thomas _et al_, 1982); currently over 1500 transplants have been performed worldwide.48 Haematopoietic stem cell transplantation, too, generally results in an excellent outcome in low-risk persons with no presence of liver fibrosis or hepatomegaly, and patients in regular chelating therapy.26

1.1.10 Dental caries in beta thalassaemia major patient

_Dental Caries_

Dental caries is defined as a progressive, irreversible, microbial disease affecting the hard parts of the tooth, which is exposed to the oral environment. This disease results in the demineralisation of the inorganic constituents, and dissolution of the organic constituents, thereby leading to cavity formation.49
Dental caries is the most prevalent chronic disease affecting the human race. Once it occurs, its manifestation persists throughout life even if the lesion is treated. There exists practically no geographic area in the world whose inhabitants do not exhibit some evidence of dental caries. It affects persons of both sexes and all races. The development usually begins soon after the teeth erupt into the oral cavity. Dental caries is a multifactorial disease in which there is interplay of three principal factors: the host, microflora, and substrate. In addition, time is considered the fourth factor which influences dental caries.\textsuperscript{50,51}

Dental caries is affected by factors within the host, which may be related to the structure of dental enamel, immunologic response to cariogenic bacteria, and the composition of saliva. The factors of saliva that have been proven to be associated with increased risk of dental caries include salivary flow rate, buffer capacity and pH, oral clearance rate, immunoglobulin, and innate non-immunoglobulin factors.\textsuperscript{52}

The immunological basis of dental caries includes salivary IgA antibodies, serum antibodies and cell-mediated immune responses.

Salivary Immunoglobulin A: The formation of salivary IgAs in the saliva correlate with the colonisation of bacteria in the oral cavity. In most children over three years of age, salivary IgAs to Streptococcus mutans can be detected, and length of exposure increases their amount.\textsuperscript{53}

Reduced salivary flow rate and the concomitant reduction of oral defence systems may cause severe caries and mucosal inflammations. Dental caries is probably the most common consequence of hypo-salivation. Carious lesions develop rapidly, and on tooth surfaces, which are usually not susceptible to caries. Several studies have established a strong association of chronologically low salivary rate (less than 0.8-1.0 ml/min stimulated whole saliva) and increased risk of caries prevalence or incidence. Such an alteration in the flow rate is considered
pathologic and occurs in a number of medical conditions that lead to salivary gland dysfunction.52

The immunoglobulins, IgG, IgM, IgA, and secretary IgA (sIgA), form the basis of the specific salivary defence against oral microbial flora, including Streptococcus mutans. The most abundant Ig in saliva, as in all other human secretions, is IgA, which is produced by plasma cells located in the salivary glands. Two IgA subclasses are present in saliva: IgA1 forms the major component of Igs, although the relative amount of IgA2 is higher in saliva than in other secretions. Salivary Igs bind to the salivary pellicle and are also found in dental plaque. In the oral activity, Igs act by neutralizing various microbial virulence factors, limiting microbial adherence, and agglutinating the bacteria, as well as preventing the penetration of foreign antigens in the mucosa.54

Indices used for measuring dental caries

According to National Institute of Dental Research for Epidemiologic Studies of Oral Diseases, implementing indices helps to improve the understanding of the disease process and improve the examiner’s consistency in, and reproducibility of the studies, most especially in descriptive population surveys.

Permanent/primary teeth index(DMFT/dmft)

Decayed-Missing-Filled Index (DMFt) which was introduced by Klein, Palmer and Knutson in 1938, has been modified by World Health Organisation (WHO) and includes:

- DMF teeth index (DMFT), which measures the prevalence of dental caries/Teeth.
- DMF surfaces index (DMFS), which measures the severity of dental caries.
There are limitations to DMF indices, which can be seen as invalid scoring in older adults, or in children (dmf) as the index can overestimate caries record by factors other than dental caries.

Dental caries in beta thalassaemia major

Studies have shown that patients with thalassaemia have a higher rate of dental decay than the normal population. This may be because patients have difficulty accessing regular dental care, or may be reluctant to attend if they feel the dentist does not understand their condition. However, patients may also be more concerned with potentially serious medical complications of thalassaemia, leading to a neglect in oral hygiene. In addition, the median saliva concentrations of phosphorous and IgA are significantly lower in such patients which makes them more prone to dental caries. Al-Wahadni, et al. report in their study that a higher risk of dental caries was found in the thalassaemic group compared to normal groups. On the other hand, Scutellari et al. found similar incidence of dental caries in beta thalassaemic patients and normal controls. Lower concentrations of immunoglobulin A (IgA) in saliva of thalassaemic patients have been claimed to be related to higher rates of dental caries.

Another study conducted reported the prevalence and distribution of dental caries in thalassaemia major patients. DMFt index was used to examined dental caries and found that the prevalence of dental caries in thalassaemia major patients was higher when compared with a normal Jordanian sample.
1.1.11 Periodontal and soft tissue conditions related to beta thalassaemia major

A healthy periodontium

In children with healthy gingival and periodontal conditions, the gingival margin is several millimetres coronal to the cemento-enamel junction (CEJ). The gingival sulcus may possibly be 0.5-3 mm deep on a fully erupted tooth. In teenagers with a healthy periodontium the alveolar crest is situated between 0.4 - 1.9 mm apical to the CEJ.58

Classification of periodontitis in children and young adult

There are numerous forms of periodontal disease, which can affect children and adolescents; based on the 1999 International Workshop for the Classification of Periodontal Diseases and Conditions (Armitage, 1999; Clerehugh et al 2004) these include:

- Gingival diseases (plaque-induced and non-plaque-induced)
- Chronic periodontitis (localized and generalized)
- Aggressive periodontitis (localized and generalized)
- Periodontitis as a manifestation of systemic diseases
- Necrotising periodontal diseases
- Abscesses of the periodontium
- Periodontitis associated with endodontic lesions
- Developmental or acquired deformities and conditions59

Gingivitis is an inflammation of the gingivae, which is plaque-induced, recognised by erythema and oedema, bleeding on brushing, or probing and perhaps detachment of the gingivae from the teeth.60
The main features of periodontitis are the loss of attachment of the periodontal connective tissues to cementum, apical migration of the junctional epithelium (JE) beyond the cemento-enamel junction, transformation of the JE to pocket epithelium (often thin and ulcerated), and alveolar bone loss.\textsuperscript{60}

*Periodontitis in beta thalassaemia major*

Little data is available on the association of periodontal disease in beta thalassaemia major patients.\textsuperscript{55}

A study\textsuperscript{41} was conducted to assess the prevalence of periodontal disease, orofacial changes and craniofacial abnormalities in patients with thalassaemia major. The sample consisted of 54 patients; and a similar number of unaffected individuals matched by age and sex served as a control. The results conclude that poor oral hygiene and gingivitis were observed in thalassaemic patient compared to control group.

Another was conducted to know of any association between an increased severity of periodontal disease in thalassaemic patients. 16 thalassaemic major patients and 63 healthy controls were examined for plaque deposits, gingivitis and periodontitis. The study concluded that thalassaemia major was not associated with increased prevalence of gingivitis or periodontitis.\textsuperscript{55}

A new study conducted in Italy\textsuperscript{61} assesses the prevalence of periodontal disease, orofacial changes and craniofacial abnormalities in patients with thalassaemia major. Clinical and radiographic examinations were carried out. The sample consisted of 100 patients affected by beta thalassaemia major and 98 patients with beta thalassaemia intermedia; each sample was compared to the respective control groups of healthy individuals. Patients were examined for plaque deposits, gingivitis, periodontitis using Silness and Löe plaque index and Löe and Silness
gingival index. The results showed a significant increased level of periodontal attachment loss in older patients with beta thalassaemia.

1.1.12 Dental managements and considerations of thalassaemia patients

Dentists should be attentive to the complications of thalassaemia to ensure safe dental management to these patients. All dental treatments planned should be in liaison with the haematologist. Dental appointments should be kept as short as possible, to avoid fatiguing of the patient. Further, all dental procedures should be performed after the patient has received blood transfusion.62

Patients with beta thalassaemia should always be asked specifically about a history of splenectomy. A patient who has had splenectomy is at risk of massive infection following bacteraemia due to an immune defect. Antibiotic prophylaxis prior to dental treatment should be considered for those patients.63

Patients with thalassaemia are at an increased risk of viral infection such hepatitis B, C and HIV carriage; as such, all members of the dental team should be aware of this condition and take appropriate precautions during dental treatment of the patient.63

Most children with thalassaemia may be treated regularly, using local analgesia, supplemented with inhalation sedation if necessary. The use of general anaesthesia should be avoided because of the difficulties caused by low Hb levels and cardiac insufficiency, and enlargement of the maxilla caused by bone marrow expansion, which may cause difficulties in intubation for induction of general anaesthesia.63
Oral complications are common in the thalassaemic patient, however, painful swelling of the parotid gland and xerostomia caused by iron deposition in the serous cells and a sore or burning tongue related to the foliate deficiency, in particular, may occur. \textsuperscript{63}
1.2 Aims

The primary aim of this study was to identify special oral manifestations peculiar to beta thalassaemia major children in Dubai, UAE. There is little information on the oral health status and prevalence of dental caries among beta thalassaemia major children in Dubai, UAE. This data is important in order to develop interventions, which may improve the oral health of this group of special needs children. Therefore, the secondary aim of this study was the use of the collected data to suggest intervention plans to Dubai Health Authority, in order to improve the oral health of this group of special needs children.

2. Materials and Methods

2.1 Study Design, Location and Population
A quantitative case control study design was conducted to compare oral health characteristics of beta thalassaemia major children and healthy control in Dubai. A summary of the flowchart of study methodology is presented in Figure (1).

The study group consisted of beta thalassaemia major children in Dubai Genetic & Thalassaemia Centre, Dubai, United Arab Emirates. The controls were healthy children from government schools that were located in the same demographic region in Dubai. The controls were matched to the thalassaemia group in age, sex and dentition. The calculation of the sample size is explained in the below section.

### 2.1.1 Sample Size

The sample size calculation was based on Cochran Equation and the main research objectives. The calculation was dependent on the proportion of dental caries among beta thalassaemia patients from previous studies in comparable communities in the region. The data used in this study was published by Dr. Faiez et al.\textsuperscript{64}

\[
N = \left( \frac{Z_{\alpha/2}\sqrt{2p(1-p)} + Z_{1-\beta}\sqrt{p_1(1-p_1)p_2(1-p_2)}}{(p_1 - p_2)^2} \right)^2
\]

Where \(p\) (\(p_1+p_2/2\)), \(p_1\) and \(p_2\) is the proportion of caries among thalassaemic and non-thalassaemic group.

With a power of 90% and with assumption of unequal size in the two groups, the sample size was calculated for the comparative case control study design, in order to compare the manifestations of oral health conditions into two groups: thalassaemic and non-thalassaemic.
Using the study, it was concluded that the proportion of caries in the first group of 22.7%, and 4.84 % in the second group – as a reference, our sample calculation yielded a minimum of 35 thalassaemic patients required. For the purpose of keeping the power at 90%, it was proposed the number of the control be doubled.65

2.1.2 Sampling Technique

1. Thalassaemia group:

For this group, a census-sampling technique was used. According to the inclusion criteria of the study, all the local major beta thalassaemia patients who were on regular blood transfusions and attending the Dubai Genetic & Thalassaemia Centre were examined. This study was carried out from the 1st to the 15th of June 2015. An approval letter was obtained from the University Students Research Evaluation Committee of Dubai Health Authority, Dubai, UAE to access Dubai Genetic & Thalassaemia Centre, Dubai. (Appendix I).

2. Control group:

For this group, a stratified random sampling technique was used. This was done by random selection of every third student from the aforementioned schools. With regard to the age, for each thalassaemia age group a matching grade in the school were chosen that had similar age ranges. Similarly, the number of females and males was matched between thalassaemia group and the control within the age groups.

2.1.3 Participating Schools
An approval letter was obtained from the Ministry of Health in Dubai to access the control group in the public schools in Dubai (Appendix II). The following schools agreed to participate in the study:

- Jumeirah Model Girls School
- Zayed Bin Sultan School for Boys

### 2.2 Inclusion and Exclusion Criteria

#### 2.2.1 Inclusion Criteria

1. Thalassaemia Group:
   - Thalassaemia patients aged 4 to 18 were invited to participate;
   - UAE nationals were eligible to participate;
   - All children previously diagnosed with beta thalassaemia major according to the medical records;
   - Consent was obtained from parents or legal guardians for both thalassaemia and control groups (Appendices III & IV).

2. Control Group:
   - All participants in the control group were medically fit;
   - The healthy group was selected from school children and matched with thalassaemia patients by age, gender, and geographic location;
   - UAE nationals were eligible to participate
   - Approval to access the centres and schools was obtained from the headmasters.
2.2.2 Exclusion Criteria

- Children suffering from other diseases known to influence dental caries or the severity of periodontal disease such as Down’s syndrome and diabetes;
- Any other transfusion dependent disorders such as haemophilia.

2.3 Data Collection

Data was collected using standard form (Appendix V) through dental examination. Two principal investigators conducted the examination and an assistant recorded the findings in the data sheet. Initially the data sheet was identifiable by the child’s name. Once the data sheet was checked for completeness, the sheets were coded. The data was destroyed upon withdrawal of any subject(s) from the study.

The investigator confirmed that for any data used for future research, an approval will be obtained from the Research Ethics Review Committee (Appendix VI).

2.3.1 Examiners Calibration

A pilot study was conducted before initiating data collection. The two examiners were trained and calibrated to use the basic WHO Oral Health survey methods by Dr. Mawlood Kowash Associate Professor in Hamdan Bin Mohamed College of Dental Medicine, who was also calibrated for all the indices used in this research. Intra-examiner and inter-examiner reliability was calculated using Kappa statistics prior to beginning data collection. The results were as follow:

- Intra Kappa: There was matching between before and after reading (X (1, P=0.317)).
- Inter Kappa (Mc Nemar’s test): There was matching between the two examiners’ reading (Kappa= 0.029, P=0.606).

2.3.2 Dental Examination

The dental examination was performed on a portable dental chair at the centre/school nurse’s room. One student at a time was examined using sterile gloves, artificial light, disposable mouth mirror and a WHO ball ended dental probe.\textsuperscript{67} The probe was only used to remove debris and not to probe any fissures.\textsuperscript{66} The data sheet used in the study is presented in appendix V. The purpose of the study was explained to the subjects and their legal guardians and consent was obtained (appendix III & IV).

2.3.3 Cross Infection Control

National Institute for Clinical Excellence (NICE) guidelines were followed for cross infection measures during the examinations:\textsuperscript{68}

- Hands were decontaminated immediately before and after examining each patient. This was done by using alcohol hand rubs or hand washing;
- Alcohol hand rubs were used preferably, while liquid soap and water were used if the hands were visibly soiled with bodily fluids;
- Gloves were used as single-use items for each candidate, since there was contact with oral mucosal surfaces and saliva. Gloves were worn immediately before patient contact and removed after completing the examination;
- Alternative to natural rubber latex gloves were available for use with patients with a history of latex allergy;
- All instruments were disposable. The gloves were discarded immediately by the examiner into waste disposable bags, and the sharp instruments were placed in the sharp container.

### 2.3.4 Indices

The following indices were used:

1. **Caries Index: dmft/DMFT**
   
   This index was used to examine the dentition status of the child. Both primary and permanent teeth were examined and given a specific code as in d, D (decayed), m, M (missing) and f, F (filled). The WHO criteria was followed to correctly record findings. Met Need Index (MNI), an indication of treatment received by an individual is determined using the ratio of the mean missing (m, M) plus filled (f, F) teeth to mean decayed, missing and filled teeth (dmf, DMF) that is M+F/DMF (m+f/dmf). While Restorative Index (RI) –which reflects the restorative care of those who have suffered the disease- is measured by the ratio of filled (f,F) to filled plus decayed teeth (F+D), (f+d) percent that is F/F+D (f/f+d) percent as described by Jackson.

2. **Simplified Oral Hygiene Index of Greene and Vermillion**
   
   This index is a combination of debris index (i.e. plaque and calculus). Six Index teeth are examined (buccal and lingual surfaces of each tooth) and scored according to specific criteria from 0 to 3. The scores range from zero, which is absence of debris, to 3, which is debris covering more than two thirds of the examined tooth surface. This index was used for permanent dentition. However, for primary dentition a separate record was noted, where the presence of gingivitis, calculus, and debris were marked as present or absent.

3. **Angle Molar Malocclusion classification and primary molar terminal plane relationship**
This was used to record the various molar relationships in each individual. For permanent dentition, the classification is based on where the buccal groove of the mandibular first molar contacts the mesiobuccal cusp of the maxillary first molar: on the cusp (Class I, normal occlusion); distal to the cusp (Class II); or mesial to the cusp (Class III).21 Primary molars are classified as flush terminal plane, distal step, or mesial step, according to the relationship of the distal surfaces of the primary second molars to each other. 72

4. Dentofacial anomalies and oral soft tissue lesions examination

Soft tissue conditions and developmental defects of the tooth structure were evaluated clinically by looking at the following conditions known to be present in thalassaemic patients: atrophy of tongue papillae, median rhomboid glossitis, gingival pigmentation, geographic tongue, fissure tongue, irritation fibroma, angular cheilitis, gingival hyperplasia, supernumerary teeth, enamel defects, retained primary teeth, hypoplastic teeth and peg shaped lateral incisors.
Approval to conduct the study was obtained from the following Authorities in Dubai:
- Research Ethics Review Committee in Dubai Healthcare City.
- The University Students Research Evaluation Committee of DHA.
- Ministry of Health

Study Aim: to study the oral health in Thalassaemia children compared to a control group in Dubai, UAE
Study Design: case-control study

Study population
- Power sample: 35
- Dubai Genetic & Thalassaemia centre, Dubai
- 50 Consent sheets were sent to the parents/guardians of all thalassaemia
- A total 40 consent sheet were signed by parents and agreed to participate

38 Thalassaemia children were examined
2 Thalassaemia children were uncooperative and were excluded

Control
- Power sample: 70
- 2 schools participated
- Every 3rd student was given a consent to be signed by his parents/guardians
- A total of 150 consent sheets were sent to parents
- A total of 76 consent sheets were signed by parents and agreed to participate

76 healthy children were examined and were all cooperative

Figure (1): Flowchart of the study methodology summary
2.4 Statistical Analysis

The collected data was transferred to computer spreadsheets and analysed using computerized Statistical Package for Social Sciences (SPSS, version 20, Chicago, SPSS Inc). Descriptive statistics were performed for general descriptions of the data. Chi-square and Exact Fisher test were performed to examine differences between categorical data, and t-test was performed to compare continuous variables. In all the above tests, a P-value < 0.05 was considered significant in all statistical analysis.

2.5 Ethical Considerations

This study was conducted in full conformity with the principles of the “Declaration of Helsinki,” Good Clinical Practice (GCP), and with the laws and regulations of the UAE/DHCC. Ethical approval was obtained from the Research Ethics Review Committee in Dubai Healthcare City (Appendix VI).
3. Results

3.1 Study Sample Characteristics

This study was conducted to evaluate the oral health status of children with Thalassaemia (TH), and compare the proportion of dental caries to that of children of the healthy group. The results of this study are expressed in the form of Tables (1-7) and graphs (Figures 2-4).

The characteristics of the 38 children with thalassaemia and 76 healthy controls are shown in Table (1). Demographic data about their gender, dentition, and age were described.

Children with thalassaemia had an average age of 10.18 (SD 3.19), where the control group had an average age of 10.79 (SD 3.54). Table (1) shows, also, the sample proportion of males was similar between children with thalassaemia, compared with healthy controls, with 13 (34.2%) and 24 (31.6%) males respectively. The proportion of females between groups with thalassaemia and healthy controls was comparable with 25(65.8%) and 52 (68.4%) females respectively. The dentition distribution was comparable between children with thalassaemia and the healthy control Table (1).

Table (1): Demographic characteristics and type of dentition among children with thalassaemia and healthy subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>Control Nr (%)</th>
<th>TH Nr (%)</th>
<th>Total Nr (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td></td>
<td>76</td>
<td>38</td>
<td>114</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>24(31.6)</td>
<td>13(34.2)</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>52(68.4)</td>
<td>25(65.8)</td>
<td>77</td>
</tr>
<tr>
<td>Dentition</td>
<td>Primary</td>
<td>6(7.9)</td>
<td>3(7.9)</td>
<td>9</td>
</tr>
</tbody>
</table>
### 3.2 Dental Caries

The overall occurrence of dental caries among children with thalassaemia was more than healthy controls at 68.4% (26/38), whereas for the healthy controls it was 48.7% (37/76).

The proportion of dental caries prevalence in the primary dentition among children with thalassaemia was 86.4% (19/22) while in the healthy control it was 68.8% (30/43). In the same context, the proportion of dental caries in the permanent dentition among children with thalassaemia was 31.4 % (11/35) while for the healthy controls was 15.7 % (11/70), as shown in Figure (2)

![Proportion of caries in thalassaemia and healthy control](image)

**Figure (2):** Proportion of caries in thalassaemia group and healthy control
Tables (2 & 3) demonstrate the caries status of the sample population. The mean numbers of the decayed component of DMFT in thalassaemia children was significantly higher than that in healthy children (2.73 ± 0.22 vs 0.21 ± 0.56, p value = 0.017). There was a clear, statistically significant, difference in the caries experience amongst the thalassaemia children compared to the healthy controls as measured by DMFT/dmft in all age groups; this is shown in Tables (2 & 3). The DMFT/dmft scores were highest among the youngest age groups in thalassaemia with mixed dentition compared to their controls.

With regard to restorative care and treatment need received in both study groups, the two parameters were represented by the Restorative Index (RI), and the Met Need index (MNI) treatment of the decayed teeth (fillings). Children in the thalassaemia group received less treatment than their controls in all age groups.

Table (2): Caries status, Restorative Index and Met Treatment Index in thalassaemia and control children (mean values in both permanent and mixed dentition):

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Thalassaemia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nr= 70</td>
<td>Nr = 35</td>
<td></td>
</tr>
<tr>
<td>DMFT index</td>
<td>0.21 ±0.56</td>
<td>1.49 ±2.67</td>
<td>0.017</td>
</tr>
<tr>
<td>Decayed</td>
<td>0.21 ±0.56</td>
<td>1.49 ±2.67</td>
<td>0.009</td>
</tr>
<tr>
<td>Missing</td>
<td>0.014 ±0.12</td>
<td>0.11 ±0.47</td>
<td>0.477</td>
</tr>
</tbody>
</table>
Table (3): Caries status in mixed dentition (A) and permanent dentition (B) in thalassaemia and control children

(A) Mixed Dentition

<table>
<thead>
<tr>
<th></th>
<th>Mixed dentition</th>
<th>Control</th>
<th>Thalassaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr</td>
<td>Nr = 38</td>
<td>Nr = 19</td>
<td></td>
</tr>
<tr>
<td>dmft index</td>
<td>0.7 ± 0.46</td>
<td>0.89 ± 0.31</td>
<td></td>
</tr>
<tr>
<td>decayed</td>
<td>1.86 ± 2.55</td>
<td>4.89 ± 4.45</td>
<td></td>
</tr>
<tr>
<td>missing</td>
<td>0.45 ± 0.77</td>
<td>0.78 ± 2.23</td>
<td></td>
</tr>
<tr>
<td>filled</td>
<td>0.27 ± 0.69</td>
<td>0±0</td>
<td></td>
</tr>
<tr>
<td>Restorative Index (RI)</td>
<td>0.14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Met Need Index (MNI)</td>
<td>0.28</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>DMFT</td>
<td>0.13 ± 0.34</td>
<td>0.21 ± 0.42</td>
<td></td>
</tr>
<tr>
<td>Decayed</td>
<td>0.18 ± 0.51</td>
<td>0.84 ± 1.68</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0±0</td>
<td>0±0</td>
<td></td>
</tr>
<tr>
<td>Filled</td>
<td>0.52 ± 0.23</td>
<td>0±0</td>
<td></td>
</tr>
<tr>
<td>Restorative Index (RI)</td>
<td>0.74</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Met Need Index (MNI)</td>
<td>0.74</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Table (3): Continued

(B) Permanent Dentition

<table>
<thead>
<tr>
<th>Permanent dentition</th>
<th>Control</th>
<th>Thalassaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr</td>
<td>Nr = 32</td>
<td>Nr = 16</td>
</tr>
<tr>
<td>DMFT index</td>
<td>0.19 ± 0.39</td>
<td>0.44 ± 0.51</td>
</tr>
<tr>
<td>Decayed</td>
<td>0.25 ± 0.62</td>
<td>2.25 ± 3.42</td>
</tr>
<tr>
<td>Missing</td>
<td>0.3 ± 0.18</td>
<td>0.25 ± 0.68</td>
</tr>
<tr>
<td>Filled</td>
<td>0.6 ± 0.25</td>
<td>0.06 ± 0.25</td>
</tr>
<tr>
<td>Restorative Index (RI)</td>
<td>0.71</td>
<td>0.03</td>
</tr>
<tr>
<td>Met Need Index (MNI)</td>
<td>0.78</td>
<td>0.12</td>
</tr>
</tbody>
</table>

3.3 Oral Hygiene Status

The oral hygiene status of the thalassaemia and healthy groups was observed and represented in Table (4) and Figure (3). Using the Oral Hygiene Index Score (OHI-S), no significant difference between children with thalassaemia compared with the healthy controls was found (1.31 ± 0.86 vs 1.4 ± 1.12). Calculus was found to be significantly higher among children with thalassaemia (0.27 ± 0.43) compared with healthy controls (0.09 ± 0.32) p-value 0.002. On the other hand, the proportion of debris was comparable in children with thalassaemia (1.02 ± 0.52) compared with the healthy controls (1.34 ± 0.99), p-value was 0.165.

The percentage of children with calculus was significantly higher among children with thalassaemia 11 (28.9%) compared with that of healthy controls 6 (7.9%) with p-value <0.004.
Conversely, the proportion of gingivitis was found to be significantly lower among children with thalassaemia compared with that of the healthy controls, at 44.7% and 69.7% respectively (p-value = 0.009).

Table (4): Oral hygiene status in thalassaemia children and control

<table>
<thead>
<tr>
<th>Index</th>
<th>Control</th>
<th>Thalassaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>SD ±</td>
</tr>
<tr>
<td>Debris-index</td>
<td>69/29</td>
<td>1.34 ± 0.99</td>
</tr>
<tr>
<td>Calculus-index</td>
<td>69/29</td>
<td>0.09 ±0.32</td>
</tr>
<tr>
<td>Oral-Hygiene-index</td>
<td>69/29</td>
<td>1.4 ±1.12</td>
</tr>
</tbody>
</table>

Figure (3): Distribution of debris, calculus, and gingivitis in children with thalassaemia and control
3.4 Occlusal Anomalies

The results of the investigation into occlusal anomalies as shown in Table (5) and Figure (4) reveal no relationship between Molar’s Angle Classifications and thalassaemia. The proportions of class (I) among children with thalassaemia and healthy controls were comparable, at 54 % and 60.2 % respectively. The proportion of class (II) was higher among children with thalassaemia at 40% compared with proportion of healthy controls class (II) at 25%. Conversely, proportion of Class III was found higher among healthy control (14.8%) compared to children with thalassaemia (3.4%) respectively.

![Molar Angle classification](image)

Figure (4): Distribution of molar Angle malocclusion classification in thalassaemia and control.

The anterior vertical open bite and deep bite were comparable between children with thalassaemia and healthy controls. The proportions of transverse cross bite was lower among children with thalassaemia compared with healthy controls, with the number of affected
individuals as 2 (5.2%) and 21 (27.6%) respectively, while vertical deep bite was comparable between thalassaemia children and healthy controls, with zero, and a single case (1.3%), respectively. For spacing, it was found that the proportion of anterior spacing was less likely among children with thalassaemia 5(13.5%) compared with that of the healthy controls 25(32.9%) with p-value 0.02. On the other hand, the proportion of posterior spacing was comparable between children with thalassaemia and healthy controls, not exceeding 1.3% in both groups. As for crowding, the data showed that proportions of anterior and posterior crowding were comparable between the two groups.

The difference in the mean overjet value between children with thalassaemia and the healthy controls was not significantly different 4.24 (2.68) and 3.46 (1.87) respectively.

Table (5): Occlusal anomalies in thalassaemia children and control

<table>
<thead>
<tr>
<th>Anomalies</th>
<th>Control</th>
<th>Thalassaemia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertical open bite</td>
<td>7(9.2)</td>
<td>6(15.8)</td>
<td>0.229</td>
</tr>
<tr>
<td>Vertical deep bite</td>
<td>13(17.1)</td>
<td>7(18.4)</td>
<td>0.527</td>
</tr>
<tr>
<td>Transverse cross bite</td>
<td>21(27.6)</td>
<td>2(5.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Transverse scissor bite</td>
<td>1(1.3)</td>
<td>0</td>
<td>0.673</td>
</tr>
<tr>
<td>Spacing anterior</td>
<td>25(32.9)</td>
<td>5(13.5)</td>
<td>0.022</td>
</tr>
</tbody>
</table>
Spacing posterior  7(9.2)  0  0.057

Crowding
Crowding anterior  22(28.9)  7(18.9)  0.181
Crowding posterior  3(3.9)  1(2.7)  0.603

3.5 Dentofacial Anomalies

Children with thalassaemia had shown higher proportion of retained primary teeth Fig (5 & 6) compared with healthy controls with 7(18.4%) affected, compared with no cases among healthy controls. This difference was statistically significant with a p-value of 0.001. High arched plate, microdontia, and enamel defects Fig (7) were comparable among children with thalassaemia and the healthy controls, Table (6).

Table (6): Dentofacial anomalies in thalassaemia children and control

<table>
<thead>
<tr>
<th>Anomalies</th>
<th>Control</th>
<th>Thalassaemia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nr (%)</td>
<td>Nr (%)</td>
<td></td>
</tr>
<tr>
<td>High arched palate</td>
<td>26(34.2)</td>
<td>17(44.7)</td>
<td>0.187</td>
</tr>
<tr>
<td>Microdontia</td>
<td>0</td>
<td>1(2.6)</td>
<td>0.333</td>
</tr>
<tr>
<td>Retained teeth</td>
<td>0</td>
<td>7(18.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Enamel defect</td>
<td>3(3.9)</td>
<td>4(10.5)</td>
<td>0.166</td>
</tr>
</tbody>
</table>
3.6 Oral Soft Tissues

As demonstrated in Table (7), children with thalassaemia had a significantly higher proportion of gingival pigmentation with 9 (23.7 %) Fig (8) affected compared with healthy controls. The other variables in the table either had very small number, or no significant difference was shown between children with thalassaemia and the healthy controls.
Table (6): Oral soft tissues findings in thalassaemia children and control

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control</th>
<th>Thalassaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nr (%)</td>
<td>Nr (%)</td>
</tr>
<tr>
<td>Atrophy of tongue</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Median rhomboid glossitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Geographic tongue</td>
<td>0</td>
<td>2(1.8)</td>
</tr>
<tr>
<td>Fissure tongue</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Irritation fibroma</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Angular chilitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Macroglossia</td>
<td>1(1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Ulcer</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gingival pigmentation</td>
<td>0</td>
<td>9(23.7)</td>
</tr>
</tbody>
</table>

Figure (8): Gingival pigmentation
4. Discussion

Thalassaemia, one of the most common genetic disorders, often causes serious medical, social, and psychological problems. Beta thalassaemia major is a life-threatening form of the disorder, characterized by severe anaemia, hepatosplenomegaly, growth retardation, skeletal changes due to hypertrophy, and expansion of erythroid marrow spaces, susceptibility to infection, endocrine dysfunction and cardiac failure following iron deposition in the myocardium.\textsuperscript{12,73}

Current reports show a significant improvement in thalassaemia major patients’ survival rates and life expectancy since 1999. In younger patient groups, this may be attributed to improved survival following bone marrow transplantation; in older patients it is most probably the result of decreased mortality from cardiac iron overload.\textsuperscript{74} With increased life expectancy, the need for improved oral healthcare is very important to ensure a high quality of life for this patient population.

This study is an attempt to identify special oral manifestations peculiar to beta thalassaemia major children, and compare the findings with a closely matched healthy group of subjects in Dubai, UAE.

The study and the control groups were matched for age, dentition and gender. A sample size calculation was done prior to data collection to ensure a sufficient number of children were included. This may serve to strengthen the validity of the results, and make them applicable to the neighbouring cities in the UAE. A total of 38 children with thalassaemia, along with 76 controls, were examined; this exceeded the calculated sample size.
4.1 Dental Caries

The results of the present research are in agreement with previous studies on the caries risk status of thalassaemia patients. The dmft/DMFT index was used in this study according to the WHO criteria of caries diagnosis. This index is the standard in epidemiological studies and its use has allowed comparison of this study’s results with regional and international studies.

In the present study, the experience of dental caries observed in the children with thalassaemia was higher than healthy controls; 68% of cases were affected by caries, compared to 48.7% of the control patients. Similar results were documented in an earlier study by Hattab in Jordan (2001). The prevalence of dental caries in the thalassaemia patients of the present study were considerably higher (22.7%) than that reported in a normal Jordanian sample (DMFT 6.26 vs. 4.84).

The mean number of the decayed component of DMFT in thalassaemia children was significantly higher than that in healthy children (2.73 ± 0.22 vs. 0.21 ± 0.56, p value = 0.017). This shows that there was a higher level of active oral infection in these medically compromised individuals. The chronic nature of thalassaemia may explain this level of disease; affected individuals are preoccupied with their life-threatening problems, neglecting basic preventive dental care. The higher caries level can be also attributed to several factors including: poor oral hygiene, improper dietary habits, bone deformities, malocclusion, higher rate of infections and iron overload in parotid glands, dry mouth and lack of dental knowledge in these subjects. In one study it was shown that the higher dental caries experience in thalassaemia patients was associated with lower concentrations of IgA in saliva which could allow the increased microbial proliferation which could be involved in their higher caries experience.
The Met Need Index (MNI) and Restorative Index (RI) were calculated from the mean dmft/DMFT of the studied children with thalassaemia sample, which presented with lower MNI and RI compared with healthy control subjects. This shows that the restorative treatment needs of the study group were less met compared with those of the control group. The study mentioned above by Hattab, conducted in Jordan, found a very low percentage (1.4%) of restored teeth among the examined teeth of thalassaemia patients.

There was a clear and statistically significant difference in caries experience amongst thalassaemia children compared to the healthy controls as measured by DMFT/dmft in all age groups. The DMFT/dmft scores were highest among the youngest age groups in thalassaemia with mixed dentition compared to their controls. The mean dmft in the primary dentition was not statistically different in this study, due to a small sample size. Kaur et al. (2012) examined the experience of decay and periodontal status in patients with thalassaemia in India, finding that the average DMFT in the study group was 3.45 ± 4.20 and in the control group 1.82 ± 2.51; the average dmft in patient group was 2.82 ± 3.22 and in control group was 1.44 ± 1.79. In addition, a recent study conducted in Italy Pedullà et al. (2015) reported similar results to other studies, DMFT was significantly higher in patients with beta thalassaemia major.

This study was able to demonstrate that children with thalassaemia major received less dental treatment relative to the control group. Moreover, they had a higher caries rate compared to healthy children. The author suggested that many factors might have contributed to these phenomena, including cultural habits, lack of parental awareness on the importance of prevention and regular dental follow up, parental neglect, long waiting lists for dental treatment (especially in government hospitals), and lack of sufficient paediatric dental specialists often needed for the comprehensive treatment of thalassaemia patients. Further study into the aforementioned factors
and their possible contribution to the reduced oral health of thalassaemia patients is necessary to shed light on this dilemma.

4.2 Oral Hygiene Status

Oral health status of children with beta thalassaemia major was assessed using the debris–index, calculus–index and oral hygiene–index. The results of this study strongly suggest that the thalassaemia patients and healthy controls examined had slight variations in their oral hygiene. There was no significant difference in oral hygiene status between children with thalassaemia compared with the healthy controls (1.31 ± 0.86 vs. 1.4 ± 1.12). Likewise, the proportion of debris was similar among children with thalassaemia compared with healthy controls (1.02 vs. 1.34, p-value = 0.16). On the other hand, Calculus was found to be significantly higher among children with thalassaemia (0.27 ± 0.43) compared with healthy controls (0.09 ± 0.32) p-value =0.002).

These results are in agreement with a previous study conducted by Al-Wahadni (2002) in Jordan.55 There were no significant differences in plaque scores between thalassaemia patients and healthy control groups (P >0.05). Further study conducted in India by Kaur (2012) concluded no significant increase in the level of gingivitis or plaque accumulation was seen in beta thalassaemia patients compared to their controls.75

Other reports are in disagreement with our findings.56,79 These studies report a higher prevalence of gingivitis seen in thalassaemia patients which correlates to local factors, or the maxillofacial characteristics of thalassaemic disease. It is well known that orthodontic problems such as crowding, extreme maxillary overjet, crossbite and oral breathing are mainly implicated in gingival disease.6,80 The maxillofacial characteristics of thalassaemia patients can lead to serious gingival problems, especially in the presence of poor oral hygiene habits. These characteristics
are strictly related to the onset of transfusion therapy in thalassaemia patients. The patients with thalassaemia observed in this study underwent transfusion therapy at a very early age, thus reducing typical facial characteristics and associated problems.

4.3 Occlusal and Dentofacial Anomalies

Patients suffering from beta thalassaemia major show great clinical variability in the systemic signs and symptoms with which they present. Because of the severe anaemia they suffer in early childhood, they are more prone to bony changes, retardation in growth, splenomegaly, along with iron overload and its consequent deposition in tissues.

It has been stated that the effects of thalassaemia on bones depend on the severity of the anaemia, the patient’s age, the duration of the clinical symptoms, and the timing of both therapeutic blood transfusion and splenectomy. It has also been reported that the early initiation of regular blood transfusion therapy may diminish or prevent development of bony abnormalities in developing patients. The bone marrow hyperplasia caused by rapid red cell turnover results in changes in the bony structure in patients with beta thalassaemia major. The hyperplasia of bone marrow in the maxilla exceeds that of the mandible, which may help to explain the finding in this study in which the proportion of class (II) was higher among children with thalassaemia (40%) compared with proportion of healthy controls class (II) (25%). Conversely, the proportion of Class III was found higher among healthy control (14.8%) compared to children with thalassaemia (3.4%) respectively. Similar findings have been reported in one study where patients with beta thalassaemia major predominantly had class I occlusion (59.7%) followed by class II occlusion (23.6%).
The proportion of orofacial complications in patients with beta thalassaemia major in our study had similarities and differences with other research. Overall, there is a trend of reduction in such complications throughout the last decades, most probably due to early diagnosis, treatment, and regular follow ups. Regular and repeated blood transfusion help in preserving the appropriate haemoglobin level (at least 10 g/dl), this, coupled with iron removal may prevent deformities in the face and skull. Therefore, skull and facial deformities can be closely related to the patient's age, the intensity of anaemia, and the beginning time of treatment. Conclusively, patients receiving inadequate blood transfusions in childhood will suffer more bone expansion and deformity as a result of hyperactivity of bone marrow to compensate for the anaemia, most especially in the period of rapid development of adolescence. Early diagnosis, coupled with blood transfusions, provide the most probable explanation as to the low level of oro-facial deformities in our study group.

In this study, Children with thalassaemia had higher proportion of retained primary teeth 7 (18.9%, P value = 0.001) compared with healthy controls, which had no cases. On the other hand, high arched plate, microdontia, and enamel defects were comparable among children with thalassaemia and the healthy controls.

### 4.4 Oral Soft Tissues

The manifestation of oral soft tissues in beta thalassaemia major were documented in the present study; it was observed that the most common of these manifestations was gingival pigmentation due to iron deposition in the gingiva, which gives the characteristic brownish-black colour. Gingival pigmentation in children with thalassaemia was significantly higher compared with healthy controls (23.7% vs. 0%, P = value 0.001). The other variables were not significantly
different among children with thalassaemia and healthy controls. A study by Kataria et al.\textsuperscript{86} In India confirmed this finding, and also reported pallor colour of the gingiva and mucous membrane of the mouth due to anaemia and bilirubin produced as a result of destruction of RBC. This may be reduced by regular and repeated blood transfusion to preserve the haemoglobin amount at an appropriate level.\textsuperscript{84} Finally, the findings of this study should be interpreted with caution because of the small sample size involved. Increasing the sample size would have provided a greater probability of establishing statistical significance for the trends of occlusal, oral soft tissue, and dentofacial anomalies. Further research, using a larger sample size, is needed if these findings are to be confirmed.

4.5 Study Limitations

One limitation in this current study was that the study population was limited to Dubai city only. It would have been beneficial if children with thalassaemia from all around the UAE were able to participate, but this was unachievable due to time constraints, the number of researchers examining the children, and limitations with facilities that may accommodate a large number of participants.

The findings of this study, thus, should be interpreted with caution because of the small sample size involved. Increasing the sample size would have provided a greater probability of establishing statistical significance for the trends of occlusal, oral soft tissue and dentofacial anomalies. Further research, using a larger sample, is needed if these findings are to be confirmed.
5. Conclusions and Recommendations

5.1 Conclusions

The following conclusions can be drawn from this study:

- Children with thalassaemia in Dubai had higher caries rate compared to healthy children;
- DMFT/dmft indices were significantly higher in thalassaemia group. This could be due to poor motivation, endocrine problems, and immune deficiency.
- Children with thalassaemia had significantly more calculus and less gingivitis than healthy children;
- The study population did not show any different orofacial manifestations caused by the erythroid mass expansion compared to the control group, indicating treatment for the disease beginning at an early age;
- The proportion of class (II) Angle molar malocclusion was higher among children with thalassaemia compared with healthy controls. Conversely, the proportion of Class III Angle molar malocclusion was found to be higher among healthy controls;
- Gingival pigmentation in children with thalassaemia was significantly higher compared with healthy controls;
- Children with thalassaemia had higher proportions of retained primary teeth compared with healthy controls.

5.2 Recommendations

- Screening couples before marriage, prenatal diagnosis, and genetic counselling of the parents are of paramount importance in controlling this disorder. These practices have led
to a demonstrated significant decrease in the number of diagnosed cases of beta thalassaemia major in the UAE. The authors emphasize the importance of these practices and encourage the undertaking of better awareness and education practices with regard to this disorder among the population of the UAE.

- The risk of oral disease in thalassaemia patients remains high, and prevention against oral disease remains very important considering the higher life expectancy of these patients and the role good oral status has in an increased quality of life. A unified approach to dental care is essential, including close liaison between haematologists and paediatricians. The dentist, especially the paediatric dentist, plays a vital role in educating such patients and parents regarding the prevention of dental caries, and the importance of maintaining good oral hygiene. These patients present with several medical conditions that are of great concern to the dentist such as anaemia, splenectomy, and increased risk of viral hepatitis.

- Good knowledge about oral manifestations of thalassaemic disorders in patients, including oro-facial manifestations, is essential to the development of more suitable clinical, psychological, and social support; this may help in improve treatment outcomes in these patients.

- Further studies into the oral health status of thalassaemia patients, including all centres in the UAE, will shed clearer light on this issue.
• Oral and dental problems can be minimized through essential oral health programs, supported by local health authorities. The findings of this study should be presented to the newly restructured Federal Ministry of Health and Community Prevention. It is of paramount importance to investigate the healthcare system provided for children with thalassaemia; this includes dental appointments, dental follow-ups, and waiting lists. Focus on parental awareness programs— which stress the importance of maintaining oral health in children with thalassaemia— can provide for better care for these patients.
6. Bibliography


38. Qudeimat MA. Dental arch morphological and dimensional characteristics in Jordanian children and young adults with β-thalassaemia major. 2005;98–104.


75. Kaur N, Hiremath S. Dental Caries And Gingival Status Of 3-14 Year Old Beta Thalassemia Major Patients Attending Paediatric Opd Of Vani Vilas Hospital, Arch Oral Sci Res.


7. Appendices

Appendix I: Ethical approval from the University Students Research Evaluation Committee of Dubai Health Authority – Dubai

Appendix II: Letter of approval from the Ministry of Health – Dubai

Appendix III & IV: Study Consent sheets to be signed by parents/legal guardians

Appendix V: Data sheet

Appendix VI: Ethical approval from the Research Ethics Review Committee in Dubai Healthcare City, Dubai, UAE
Appendix I

Ethical approval from the University Students Research Evaluation Committee of Dubai Health Authority

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Dubai Scientific Research Ethics Committee (DSREC),
Dubai Health Authority

Dr. Shaikha Alraeesi

Dubai Thalassemia and Genetic Centre, Dubai

Date: 19 May 2015

Ref: DSREC-SR-05/2015_03

Subject: Approval for the research proposal: "Oral Manifestations and Dental Anomalies in Beta Thalassaemic Children in Dubai (UAE)"

Dear Dr. Shaikha,

Thank you for submitting the above mentioned research proposal to Dubai Scientific Research Ethics Committee, DHA. Dubai Scientific Research Ethics Committee has been organized and operates in accordance with the ICH/GCP guidelines.

Your request was discussed during the committee meeting held on 18 May 2015. We are pleased to advice you that the committee has granted ethical approval.

Please note that it is DSREC’s policy that the principal investigator should report to the committee of the following:

1. Anything which might warrant review of ethical approval of the project in the specified format, including:
   - any serious or unexpected adverse events and
   - unforeseen events that might affect continued ethical acceptability of the project
2. Any proposed changes to the research protocol or to the conduct of research
3. Any new information that may affect adversely the safety of the subjects
4. If the project is discontinued before the expected date of completion (reason to be specified)
5. Annual report to DSREC about the progress of the study
6. A final report of the finding on completion of the study

Please note that this approval is valid for one year from the date of this letter. It is your responsibility to ensure that an application for continuing review approval has been submitted at the required time.
The following Committee members were present at the meeting and voted for its approval:

<table>
<thead>
<tr>
<th>Name</th>
<th>Designation</th>
<th>Role in Committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Suhail Abdulla Mohammad Alrukn</td>
<td>Consultant, DHA</td>
<td>Chairperson</td>
</tr>
<tr>
<td>Dr. Mahera AbdulRahman Amir Rad</td>
<td>Project Manager, HQ - Medical Education Department</td>
<td>Member</td>
</tr>
<tr>
<td>Dr. Hamda Hassan Khansaheb</td>
<td>Specialist Registrar, PHC</td>
<td>Member</td>
</tr>
<tr>
<td>Dr. Nehad Hassan Mahdy Abd El Magid</td>
<td>Consultant, PHC</td>
<td>Member</td>
</tr>
<tr>
<td>Dr. Mouza Al-Sharhan</td>
<td>Head of Pathology Section, Dubai Hospital</td>
<td>Vice-Chairperson</td>
</tr>
</tbody>
</table>

DSREC wishes you every success in your research.

Yours faithfully,

Dubai Scientific Research Ethics Committee (DSREC),
Dubai Health Authority
Dubai, UAE.
Appendix II

Letter of approval from the Ministry of Health – Dubai
Appendix III

Study Consent sheets

Research Title: Oral Manifestations and Dentofacial Anomalies in beta thalassaemia major children in Dubai (UAE)

Dear parents /guardians:

We are a group of paediatric dentists from Dubai College of Dental Medicine currently studying the oral health status of healthy children and thalassaemic children in Dubai (United Arab Emirates). Recognizing the oral health problems in this group of children will help us structure a proper dental program according to their treatment needs. We will be visiting the schools and Dubai Genetic &Thalassaemia centre to conduct a clinical dental check-up, which will take on average ten minutes depending on the child’s cooperation and is free of charge. You will be provided with a copy of your child’s dental examination results. The collected data will be used for research purposes only and your child’s information will be kept confidential (The data will be scanned and save in the electronic file dedicated for the research data on Dubai Collage of Dental Medicine computer server).

This research will provide baseline data to be used by healthcare providers for the planning of the preventive and curative needs of thalassaemic children and help the families of thalassaemia children to access better healthcare for their thalassaemic child.

Your child’s voluntary participation will serve a great value to the community.

❖ If you are interested to participate, please sign below.
❖ Only children who meet the study’s inclusion criteria will be included.
❖ The child’s medical records maybe reviewed to obtain necessary information, which will be kept confidential.
❖ The Child’s information will be written in the data sheet for the purpose of collecting data ,after confirmation of completeness of data the name will be coded.
❖ Parents can withdraw their child from the study at any time without any liability on their part, and withdrawal will not affect any treatment they receive.
❖ The data of the child will be destroyed upon withdrawal from the study.
Name ________________________________________________
Relationship to child ___________________________________
Contact number – mobile: _________________________________
Signature _______________

In case of any inquires kindly call Dr. Shaikha Alraeesi: 044248624

This research study has been approved by the Research Ethics Review Committee in Dubai Healthcare City, Dubai-UAE
عنوان البحث: صحة الفم و الأسنان للأطفال الثلاسيما في دبى (دولة الإمارات العربية المتحدة).

عزيزي ولي الأمر :

نحن مجموعة أخصائيين (طب أسنان الأطفال) من كلية دبي لطب الأسنان، نجري دراسة حول صحة الفم و الأسنان لدى الأطفال الأصحاء وأطفال الثلاسيما في دبي - دولة الإمارات العربية المتحدة.

الهدف الأساسي من هذه الدراسة: التعرف على مشاكل صحة الفم و الأسنان التي تواجهها هذه الفئة في مجتمعنا، وكيفية وضع الحلول المناسبة عن طريق هيئة برامج طبي متكامل لصحة الفم و الأسنان لبيئتهما الاحتياجات العلاجية والوقائية، و مساعدة الأهالي على تفهم أهمية الجانب الوقائي و تشجيعهم على العناية بصحة الفم و الأسنان لأطفالهم.

كما هو معلوم فإن أي دراسة بحث تستلزم وجود أشخاص ينضمون و يشاركون في الدراسة، لذا سنقوم بزيارة المدارس و مركز الثلاسيما وإجراء فحص أسنان مجاني للأطفال و تسليم نتائج الفحص لكل طفل، علماً بأن هذا الفحص سيبقى معلماً بمعدل العشرة دقائق اعتمادًا على تعاون طفلكم.

البيانات التي سيتم رصدها ستستخدم لهذا الهدف و البحوث المستقبلية مع الاحتفاظ بالسرية التامة للمعلومات الشخصية لطفلك (حيث أن المعلومات سوف تحفظ في ملف الالكتروني الخاص بالبحث الجاري في كلية دبي لطب الأسنان).

مشاركة طفلك في هذه الدراسة هو عمل تطوعي و يعتبر خطوة فعلية نحو مجتمع نموذجي و صحي.

إذا كنت ترغب في المشاركة الرجاء التوقيع أدناه.

- يرجى العلم بأن الإستمارات الموجودة هي التي ستكون مؤهلة للمشاركة في الدراسة.
- الأطفال المستوفون لشروط البحث سوف يتم إدراجهم في هذه الدراسة.
- قد تحتاج لرجال العلامة الطبية لطفالك للحصول على المعلومات اللازمة، حيث سيتم ذلك بخصوصية تامة.
- المعلومات الطبية ستكون مكتوبة على ورقة البيانات بعد التأكد من أتمتة البيانات، اسم الطفل و بياناتاته ستكون مشفرة.
- ولي الأمر له الحق بإخراج طفله من الدراسة في أي وقت من غير أية تبعات دون أن يؤثر ذلك على علاج المريض.
- في حالة انسحاب الطفل من الدراسة سوف يتم التخلص من المعلومات بشكل نهائي.
لقد قرأت وفهمت المعلومات البارزة أعلاه وأوافق على مشاركة طفلي (الاسم: -------) في الدراسة البحثية.

يمكن أن تستخدم البيانات للمشاريع البحثية في المستقبل، شريطة أن هوية طفلك لن يتم التعرف عليها.

البيانات التي سيتم رصدها ستستخدم للبحوث المستقبلية، مع الاحترام للخصوصية والخصوصية. علم بأنه ستؤخذ موافقة أخرى من قبل لجنة مراجعة أخلاقيات البحوث الطبية في مدينة دبي الطبية للدراسات المستقبلية.

أوافق
لا أوافق

التوقيع:
اسم ولي الأمر:
النظام المتحرك:
الرقم:

لا ننسئ الرجاء الاتصال بالدكتور شيخنا الرئيسي على الرقم: 04.4286240

شكراً لتعاونكم معاً،

تتم الموافقة على هذه الدراسة البحثية من قبل لجنة مراجعة أخلاقيات البحث العلمي في سلطة مدينة دبي الطبية، دبي الإمارات العربية المتحدة.
Appendix V

Data sheet

<table>
<thead>
<tr>
<th>Child’s Name:</th>
<th>Age:</th>
<th>Sex:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Child’s condition:

<table>
<thead>
<tr>
<th>School/Area:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Permanent</th>
<th>Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 sound</td>
<td>A</td>
</tr>
<tr>
<td>1 decayed</td>
<td>B</td>
</tr>
<tr>
<td>2 filled &amp; decayed</td>
<td>C</td>
</tr>
<tr>
<td>3 filled, no decay</td>
<td>D</td>
</tr>
<tr>
<td>4 missing due caries</td>
<td>E</td>
</tr>
<tr>
<td>5 missing, other reason</td>
<td>-</td>
</tr>
<tr>
<td>6 sealant</td>
<td>-</td>
</tr>
<tr>
<td>7 bridge abutment, crown</td>
<td>G</td>
</tr>
<tr>
<td>8 interrupted</td>
<td>-</td>
</tr>
<tr>
<td>9 excluded</td>
<td>-</td>
</tr>
</tbody>
</table>

| Prim. Teeth | 0 | d | m | f | dmf |
| Perm. Teeth | O | D | M | F | DMF |

Codes for individual tooth status: small letters for primary teeth, capital letter for permanent teeth.

0 = Sound tooth, d / D = Decayed tooth, m / M = Missed, f / F = Filled

D=
M=
F=
D+M+FT=

| d= |
| m= |
| f= |
| d+m+ft= |
### Oral Hygiene Status

Debris index (0, 1, 2, 3)  
Calculus Index (0, 1, 2, 3)

Oral Hygiene Index – Simplified = PI + CI

<table>
<thead>
<tr>
<th></th>
<th>Right molar</th>
<th>Anterior</th>
<th>Left molar</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Buccal</td>
<td>Lingual</td>
<td>Labial</td>
<td>Labial</td>
</tr>
<tr>
<td>Upper</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Debris Index = (The buccal-scores) + (The lingual-scores) / (Total number of examined buccal and lingual surfaces).

Calculus

<table>
<thead>
<tr>
<th></th>
<th>Right molar</th>
<th>Anterior</th>
<th>Left molar</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Buccal</td>
<td>Lingual</td>
<td>Labial</td>
<td>Labial</td>
</tr>
<tr>
<td>Upper</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Calculus Index = (The buccal-scores) + (The lingual-scores) / (Total number of examined buccal and lingual surfaces).

Oral Hygiene Index = Debris Index + Calculus Index
<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gingivitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gingival Hyperplasia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Debris</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Calculus</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

### Occlusion anomalies

#### Vertical:

1. Open
2. Deep

#### Transverse

1. Crossbite
2. Scissor

#### Spacing

1. Anterior
2. Posterior

Angle malocclusion classification:
- Class I
- Class II
- Class III

Primary Molar classification:
- Flush Terminal Plane
- Mesial step
- Distal step

Overjet = ................ mm

If reverse overjet = ................ mm
### Dentofacial abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Enamel defect</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>High arched palate</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Peg lateral</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Bulbous crown</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Retained teeth</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Lymphadenopathy</td>
<td></td>
</tr>
</tbody>
</table>

### Soft tissue abnormalities

<table>
<thead>
<tr>
<th>Oral lesion (yes / No)</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Atrophy of tongue papilla</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Median rhomboid glossitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Geographic tongue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fissure tongue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Irritation fibroma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Angular chilitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gingival hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gingival pigmentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ulcer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Trauma to soft tissue/lip</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix VI

Ethical approval from the Research Ethics Review Committee in Dubai Healthcare City

May 5th 2014

Dr. Sheikha Al-Raeesi
Dental Trainee-Pediatric Dentistry
Dubai School of Dental Medicine
Dubai Healthcare City
Dubai, United Arab Emirates

Subject: Ethical Approval for Research Protocol

Dear Dr. Al-Raeesi,

This is with reference to the initial protocol application for the research study entitled, "Oral Manifestations and Dental Anomalies in Beta Thalassemic Children in Dubai (UAE): A Case Control Study" which was submitted to the Dubai Healthcare City Authority-Research Ethics Review Committee (RERC) for review and approval.

It is hereby confirmed that the RERC has reviewed the above application on March 17th, 2014 and this was followed by further reviews upon submission of revised protocols. On May 5th, 2014, the RERC members have unanimously decided to approve your final submission which was made on April 1st, 2014.

Please note however, that this ethical approval is conditional to the following:

1. It is at the discretion of the principal investigator to ensure that all the scientific details and background information contained within the protocol are validated and substantiated with evidence to ensure credibility of the research outcome.
2. Other regulatory approval/s, needed to conduct the study is/are to be obtained and submitted to the RERC for record keeping.
3. No deviations from or changes to the protocol are to be implemented without prior review and documented approval of the RERC.
4. The research study documentation shall be periodically subject to RERC audit.
5. Upon completion of the study, a "Final Research Study Report" will be required for submission to RERC. Consequently, any abstract/publication should also be brought to the attention of the RERC.

Kindly collect your original Ethical Approval Letter from the CPQ Office after midday on Tuesday May 6th, 2014.

We congratulate you and wish you continued success in DHCC.

Best Regards,

Laheeb Al-Mutwalli
Director-Licensing Department
Center for Healthcare Planning and Quality
Dubai Healthcare City Authority