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Assessment of Periodontal Health in Patients with Sickle Cell Disease (SCD)

A Project Submitted to the College of Dentistry, University of Baghdad, Department of Periodontology in Partial Fulfillment for the Bachelor of Dental Surgery

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Certification of the Supervisor

I certify that this project entitled **"Assessment of Periodontal Health in Patients with Sickle Cell Disease (SCD)"** was prepared by fifth year student **Umniah Abdul-Salam Adnan** under my supervision at the College of Dentistry / University of Baghdad in partial fulfillment of the graduation requirements for the Bachelor Degree in Dentistry.

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Dedication

This research is dedicated to my supporting supervisor, my dear family and friends who always were by my side through my journey in dental school.

Thank you all.

Acknowledgement

This research was not possible without the guidance of my supervisor who was with me with every step until completion of this review of literature. I would also like to thank all of the teaching staff in the department of periodontics for their wealth of knowledge.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

Abbreviation	Meaning
ANSM	National Agency for the Safety of Medicines and Health Products
CBC	Complete blood count
CPI	Community periodontal index
DMFT	Decayed, missing and filled teeth
FDA	US food and drug administration
GAT	Guanine-adenine-thymine
GTT	Guanine-thymine-thymine
HbS	Sickle hemoglobin
Hg	Mercury
MDS	Myelodysplastic syndromes
RBCs	Red blood corpuscles
SCA	Sickle cell anemia
SCD	Sickle cell disease
SCT	Sickle cell trait
WHO	World health organization

Introduction

Sickle cell disease (SCD) is an inherited disease in individuals homozygous for hemoglobin S **(Majid, 2018)**.

Sickle cell disease (SCD) is caused by a mutant Hb S hemoglobin that modifies a normally shaped cell shape into a sickle shape (Brandão et al, 2018).

Sickle cell disease (SCD) is a common inherited disease characterized by morphologic changes in erythrocytes, caused by abnormal hemoglobin polymerization **(Al-Alawi et al, 2015)**.

Sickle-cell disease is particularly common among people whose ancestors come from sub-Saharan Africa, India, Saudi Arabia and Mediterranean countries (Majid, 2018).

The Eastern Province of Saudi Arabia is known to have one of the highest prevalence rates of SCD worldwide **(Al-Alawi et al, 2015)**.

Sickle RBCs have a shortened lifespan leading to vascular occlusion and ischemia resulting in damaging effect on many organs throughout the body **(Soualem et al, 2022)**.

A main feature of SCD is vaso-occlusive crisis of the microcirculation, which leads to limited blood supply to tissues and tissue necrosis. Patients with SCD usually report subjective pain in the form of acute pain crisis, which is considered to be one of the earliest clinical manifestations of this disease. Bone marrow hyperplasia and osteomyelitis of the jaw are general manifestations of SCD **(Majid, 2018)**.

For minor sickle cell syndrome, or heterozygous form, HbA (normal allele)/HbS (mutated allele), the patient is said to be only a carrier of the sickle cell trait and in this case, there are no symptoms. For major sickle cell syndrome

(MDS), the S/S form, or homozygous, is the most common. The allelic combinations are the cause of major sickle cell symptoms. The oral care of sickle cell patients requires specific precautions such as good management of local anesthetics, rigorous anti-infective prophylaxis as well as controlled prescription of analgesics **(Soualem et al, 2022)**.

Periodontal disease is a chronic inflammatory disease of periodontium and its advanced form is characterized by periodontal ligament loss and destruction of surrounding alveolar bone. It is the main cause of tooth loss and is considered one of the two biggest threats to the oral health **(Nazir, 2017)**.

A chronic oral infection such as periodontitis is a constant potential source of infection and has been considered as a separate risk factor for cardiovascular diseases, cerebrovascular diseases, peripheral arterial disease, respiratory diseases, and low birth weight **(Ohyama et al, 2009)**.

It is believed that due to increased susceptibility to infections. Individuals with SCD have a higher level of predisposition to developing periodontal disease which are infectious conditions trigged by the presence of periodontal pathogens and influenced by alterations in the host cellular and humoral immune response **(Javed et al, 2013) (Veiga et al, 2013)**.

However, most epidemiological studies refute this hypothesis **(Crawford et al, 1988) (Arowojolu, 1999) (Guzeldemir et al, 2011) (Passos et al, 2012) (Veiga et al, 2013).**

Moreover, the association of SCT with periodontal diseases is unclear.

Although SCT is described as benign, individuals with this condition may show significant clinical complications in situations of hypoxia where HbS molecules polymerize and cause morphological changes to the erythrocytes, making them less flexible and more adherent to the vascular endothelium, and

resulting in vaso-occlusive events and subsequent ischaemia, infarction and tissue necrosis similar to those associated with SCA **(Javed et al, 2013)**.

Venous thromboembolic events associated with SCT can lead to increased coagulation activity and increased levels of blood monocytes, which play an important role in tissue damage **(Goldsmith et al, 2013)**.

It is hypothesized that these changes, combined with bacterial challenge and consequent host immune response, may encourage the development of periodontal diseases. The increased susceptibility to infection of sickle-cell disease subjects provided the rationale for this review.

Aims of Review

- To assess the effects of sickle cell disease on periodontal health

Chapter One: Review of Literature

1. Chapter One: Review of Literature

1.1. Etiology

Sickle cell anemia (SCA) is an inherited multisystem disease caused by a defect in chromosome. The sickle mutation itself is the result of a single base change (GAT→ GTT) in the sixth codon of exon 1 of the β-globin gene on short arm of chromosome 11. This change, in turn, results in replacement of the normal glutamic acid with valine at position 6 of theβ-globin chain and the formation of sickle Hb. SCA is the homozygous state, where the sickle gene is inherited from both parents. If only one of the pair of chromosomes is affected then sickle-cell trait develops, while SCA reflects the involvement of both chromosomes. In SCD, amino acid substitution causes HbS to polymerase intracellularly when deoxygenated, thus changing the biconcave discoid shape of red blood cells (RBCs) to sickle shapes. This sickle hemoglobin causes: hemolytic anemia and hyperbilirubinemia due to the increased RBC destruction, It also predispose to bacterial infections, and painful vaso-occlusive crises due to the obstruction of blood flow **(Soualem et al, 2022)**.

1.2. Epidemiology

These patients also have a higher risk of developing dental caries due to the high prevalence of opacities in the teeth (alterations in enamel and dentin formation and calcification), frequently used medications containing sucrose and many episodes of hospitalization that make it difficult to perform adequate oral hygiene **(Brandão et al, 2018)**.

SCD is a disease that has been widely discussed in several ways that are important for understanding it. This recessive and hereditary disease was discovered in African black people; however, today it affects individuals with

other racial characteristics because of intermarriage **(Calvo-Gonzalez et al, 2010)**.

1.3. Effect on teeth

An association between SCD and pulp necrosis on clinically healthy teeth has been reported. The presence of healthy necrotic teeth is 8.25 times higher in a patient with SCD compared with a non-sickle cell patient, because of vascular occlusions of the pulpal microcirculation. Painful dental episodes in the past have been reported in the past. However, this feature is not essential and there are many cases of pulpal necrosis without any painful history **(Soualem et al, 2022)**.

1.4. Effect on alveolar bone

Sickle cells have a limited lifespan in the circulation (5–15 vs. 120 d). By the end of their life, the red cells are phagocytosed by macrophages. This causes an increase in the viscosity of the blood. The hemoconcentration is the origin of a blood stasis.

Ischemia very often affects the long bones, vertebrae, and the sternum. The bones of the face and maxilla are less affected. An incidence of 3%–5% of osteonecrosis in MDS is raised in the mandible, particularly the posterior regions. This is explained by a single homolateral vascularization throughout the inferior alveolar artery and the periosteal vascularization. The effect on alveolar bone comes down to irradiating bone pain, without any dental origin. A bone necrosis can be observed by radiologic examination **(Soualem et al, 2022)**.

1.5. Effect on Periodontitis

The effects of SCA on gum tissue and periodontium are unconclusive as studies are controversial on this subject. Some authors states that in subjects with major SCD we are seeing an increase in the release rates of proinflammatory

cytokines. There is a stimulation of destructive enzymes collagenases and metalloproteinases activities in periodontal tissues which predispose sickle cell subjects to periodontal disease **(Soualem et al, 2022)**.

1.6. Effect on Saliva

Reduced salivary flow may cause greater vulnerability to caries disease and oral infections and to changes in chewing, swallowing, tasting and speaking (World Health Organization, 2013). When the saliva is stimulated, it may promote positive actions in the oral cavity, such as potentiation of tooth remineralization capacity, removal of substances, neutralization of acids and antimicrobial action **(Tenovuo, 2002)**.

The continuous use of medications may cause xerostomia and thus increase the risk of caries disease development, as they lead to a decrease in salivary flow and cause changes in saliva **(World Health Organization, 2013)**.

Hydroxyurea, which is approved by the US Food and Drug Administration (FDA), is a drug currently used in the treatment of Hb SS **(Ware et al, 2009)**.

This drug has a strong positive impact on the quality of life of SCD patients by reducing many negative aspects of the disease including vaso-occlusive crises, the need for transfusions, the number of hospitalizations, the length of hospital stays, and acute neurological events; in addition, it has decisively demonstrated a reduction in the number of deaths resulting from neurological events or SCD when compared with the same number of patients in a group not using the drug **(Cançado et al, 2009)**.

Salvia et al. assessed 69 patients with a mean age of 26 years who had SCD. Among these patients, there were users and non-users of hydroxyurea. When evaluating the saliva, 75% of those taking the medication had low salivary flow and 18% had reduced buffer capacity **(Salvia et al, 2013)**.

1.7. Radiographic Manifestations

Dental radiographs of patients with SCD, may show enlarged medullary spaces and decreased number of trabeculations. As a result, the bone appears more radiolucent. The trabeculae between the teeth in patients with SCD may present as prominent horizontal rows, giving a "stepladder" appearance **(Soualem et al, 2022)**.

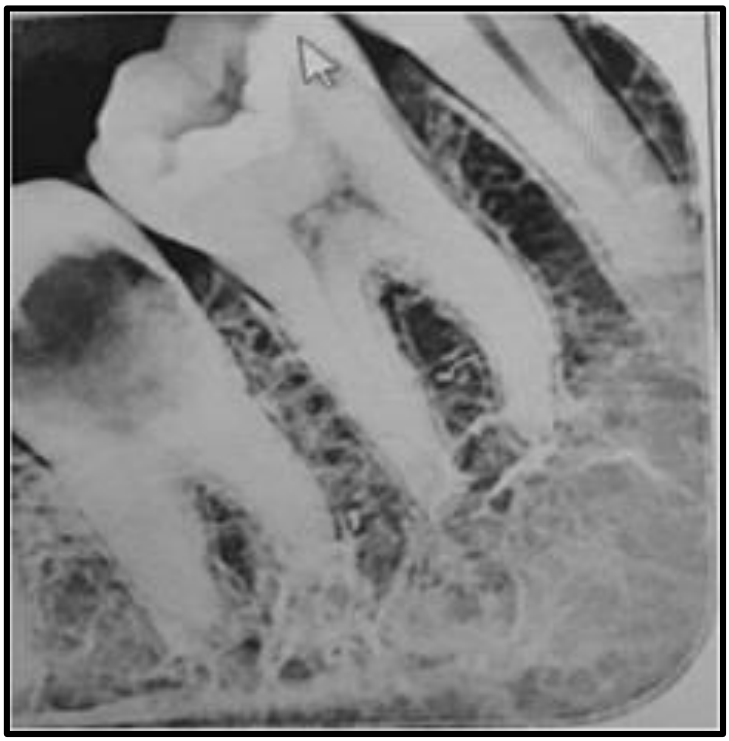

Fig 1.1: The trabeculae between the teeth in patients with major sickle cell disease may present as prominent horizontal rows, giving a "stepladder" appearance. The arrow indicates Localization of the mucosal paleness (Soualem et al, 2022).

This is due to a persistent proliferation of erythrocytes in the marrow, to compensate the destruction of erythrocytes. This causes the widening medullary spaces, creating abnormal trabecular spacings **(Yawn et al, 2014)**.

Osteomyelitis is an inflammatory condition of the bone, beginning in the medullar cavity and extending to involve the periosteum of the affected area. It is more common in the long bones. Osteomyelitis of the jaws secondary to SCD is

rare; however, when it occurs, the mandible is the most commonly affected facial bone because of its relatively poor blood supply **(Mendes et al, 2011, Stanley et al, 2013).**

In case of osteomyelitis, intra-oral examination, can show swelling of the maxilla, or the mandible with suppuration and the exposure of bone. Radiologic examination can reveal a large bone sequestration. It is often very difficult to differentiate early bone infarction from osteomyelitis. However, the treatment is the same and consists of an adapted, long-term antibiotic therapy associated with surgical drainage **(Soualem et al, 2022)**.

1.8. Indirect Correlation

Due to the lack of specialized care in the different areas of dentistry, such as pediatric dentistry, endodontics, prosthesis, periodontics and orthodontics, the patients who demand/require these specific treatments are not always given the appropriate attention. In Brazil and in other countries it has been observed that in the most severe cases of the disease, the patients who are most affected systemically require hospitalizations for transfusions and treatments. These patients require primary oral health care, such as daily tooth brushing after main meals and careful selection of the type of diet consumed, both of which may lead to a lower level of predisposition for developing oral diseases **(Passos et al, 2012, Laurence et al, 2006, Okafor et al, 1986)**.

1.9. Dental Management

Dental routine care can be provided, but several recommendations should, be a priority to avoid hemorrhagic and infectious complications **(Mulimani et al, 2019, Habibi et al, 2015, Lionnet et al, 2015)**.

The French recommendations for adult sickle cell patients call for an annual consultation to ensure that a dental examination and the necessary care are performed each year **(Javed et al, 2013)**.

1.9.1. Bleeding Tendency

The blood formula count (BFS) will be systematic before any oral surgery in patients with SCD. The biological examinations are then used to monitor the basal state: blood count and reticulocytes. The interpretation of CBC in patients with SCD should take into account the change in references compared with the healthy subject (Table 1). The hemorrhagic risk is evaluated thanks to the preoperative assessment with the thrombocythemia (Table 1) and the rate of prothrombin (Table 2).

Table 1.1 - Proposal of preoperative CBC for the major sickle cell patient (Sepúlveda et al, 1989).

	Red blood cells (g/L)	**Platelets (10^3/mm)**	**Leukocytes (/mm^3)**	**Recticulocytes (10^3/mm)**
Healthy patient	12–16	150–400	4000–10,000	50–100
MDS	7–9	250–400	800–20,000	200–600
Clinical interest	If RBc value <7, all surgery must be done in a hospital environment	In case of decrease in platelets suspect hepatic involvement	Sickle cell disease is a disease One of the markers is hyperleukocytosis A decrease in leukocytes should be alarming about bone marrow necrosis	Chronic hemolysis induces a strong bone marrow regeneration to compensate for anemia, which leads to an increase in the number of reticulocytes A value <200 is a sign of bone marrow necrosis, which will lead to Thrombocytopenia

Table 1.2: Proposed prothrombin rate of a major sickle cell patient (Soualem et al, 2022).

Hepatic check	Healthy patient	MSD	Clinical interest
Rate of prothrombin (%)	100	>60	If for MSD 60 <TP <30 exploration of TCA and coagulation factors because the risk of hemorrhage is increased

A periosteal flap is not recommended because local vascular rupture increases the risk of flap necrosis or MDS hemostasis is done using the most airtight sutures possible. A collagen hemostatic sponge that is not very irritating to the bone such as Pangen can be added, allowing the formation of the blood clot and therefore perfect healing as quickly as possible. The use of biological glues for coaptation of the banks and stability of the clot. In case of resumption of bleeding, hemostasis will be obtained by direct compression using a gaze or a thermoformed splint **(Soualem et al, 2022)**.

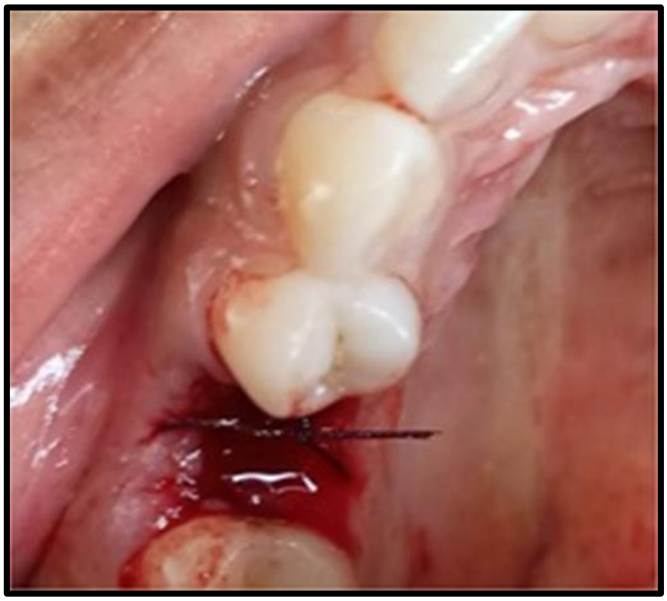

Figure 1.2: Intraoral view showing the extraction site, sutured hermetically with simple O-shaped sutures to minimize the risk of tearing of the edges (Soualem et al, 2022).

1.9.2.Risk of infection

In SCD, splenic function is reduced in people with SCD, thus reducing their immunity especially against encapsulated bacteria and increasing their susceptibility to infection. Thus, the prevention of infection by antibiotic prophylaxis is a priority in oral SCD management. Antibiotic prophylaxis is prescribed for periodontal, periapical, and oral mucosal surgery. MDS and sickle cell patients have functional asplenia or have undergone splenectomy must receive antibiotic prophylaxis.

According to ANSM, the protocol is: 2 g of Amoxicillin/if allergy 500 mg Azithromycin 1 hour before the procedure. In cases of osteomyelitis in the mandibular region, various treatments can be considered: curettage, debridement, corticotomy or partial bone resection. Appropriate, long-term antibiotic coverage and follow-up are indicated **(Soualem et al, 2022)**.

1.9.3.Considerations of Anesthesia

Locoregional anesthesia is possible and preferable to general anesthesia. The use of vasoconstrictors is also possible. On the other hand, it is preferable to obtain deep local anesthesia to avoid situations of stress which may be responsible for subsequent occlusive vascular pain. If general anesthesia is unavoidable, some precautions should be considered. Anemia must be corrected preoperatively (Hg >10 g/dL). General anesthesia should allow all oral care in one session to avoid reintervention **(Habibi et al, 2015, Santos et al, 2015)**.

1.9.4.Analgesia

Pain management is difficult because patients with MDS are already dependent to analgesics **(Mulimani et al, 2019)**.

In the management of postoperative pain, certain medications should be taken with caution. Steroidal anti-inflammatory drugs are contraindicated because of the risk of triggering serious pathologies **(Andrews et al, 1983)**.

The combination of paracetamol and codeine is the best analgesic solution for these patients (Gregory et al, 1994, Chekroun et al, 2019). The use of morphine and derivative analgesics is also possible (buprenorphine, fentanyl, hydromorphone, nalbuphine, oxycodone, and pethidine). These central analgesics are reserved for intense pain that often requires hospitalization. The use of morphine at home is contraindicated as there is a risk of overdose and death.

Because of the association of slowing the blood circulation and vasoconstriction due to the cold. The use of an ice pack (cold) is contraindicated postoperatively because this would increase the chances of occurrence of a phlebitis **(Chekroun et al, 2019)**.

Chapter Two: Discussion

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It was believed that all individuals were uniformly susceptible to developing periodontal disease and that accumulation of plaque, poor oral hygiene and perhaps occlusal trauma were sufficient to initiate periodontitis. However, during the past four decades, it has become accepted that periodontal disease is caused by specific bacterial infections, and those individuals are uniformly susceptible neither to these infections nor to the damage caused by them. It has been suggested that the low socioeconomic level is considered a positive risk factor for development of aggressive periodontitis. Besides, smoking is considered the more established of the modifiable risk factors for periodontal disease **(Imran et al, 2010)**.

It has been reported that hygiene and oral care are important factors that influence the severity of periodontal disease and can prevent complications and infections in patients with SCA **(Javed et al, 2013)**.

Passos et al. (2012) found no association between sickle cell disease and periodontal disease when evaluating 190 patients, 99 with systemic alteration and 91 controls. Fernandes et al. (2016) found that only the adolescents showed the presence of gingival bleeding, but no significant differences were observed between the SCD and control groups. Carvalho et al. (2015) evaluated several criteria indicative of periodontal diseases in patients with SCD, patients with the trait of the disease and patients without the disease. They observed that none of these criteria were associated with the patients with SCD, suggesting no association between these two pathologies.

Mahmoud, Ghandour and Atalla (2013) evaluated the association between periodontal disease and SCD in 113 adolescents aged 12 to 16 and found no statistically significant differences between the groups; but when evaluating the

disease group, they were able to verify an increase in the prevalence of gingival inflammation in adolescents with SCD when compared with the control group.

Tonguç, Unal and Aspaci (2018) also verified a lack of differences in the periodontal health status of 49 children with SCD and 39 systemically healthy children in the control groups. The most important finding of their study was that gingival enlargement was more prevalent in children with SCD.

Al-Alawi et al. (2015) did a prospective case-control study included 66 Saudi men (33 patients with SCD attending Al-Qatif Central Hospital and 33 apparently healthy male individuals selected from the general population). The two groups had similar socioeconomic backgrounds and were age matched. All dental examinations were standardized according to the World Health Organization (WHO) standardized index and the decayed, missing, and filled teeth (DMFT) index. Gingival bleeding, calculus, and periodontal pocket depth were measured with a Williams periodontal probe according to the community periodontal index (CPI). The Silness–Löe plaque index was also used to measure oral hygiene status. Although we found no significant difference in mean DMFT index between patients with SCD and control subjects, the prevalence of decayed and filled teeth differed significantly between groups. Tooth decay was more prevalent and the number of filled teeth was lower among patients with SCD than among healthy control subjects. This assumption was that patients with SCD were aware of the high risk of tooth decay, but did not take timely and appropriate action due to frequent hospitalization and vaso-occlusive crises, which deterred them from seeking regular dental consultations.

Majid A et al. (2018) found that that Plaque index score and Gingival index score are significantly raised in patients with sickle cell disease as compared to normal healthy individuals. This predicts that patients with sickle cell disease are more prone to periodontal diseases. The results were statistically significant.

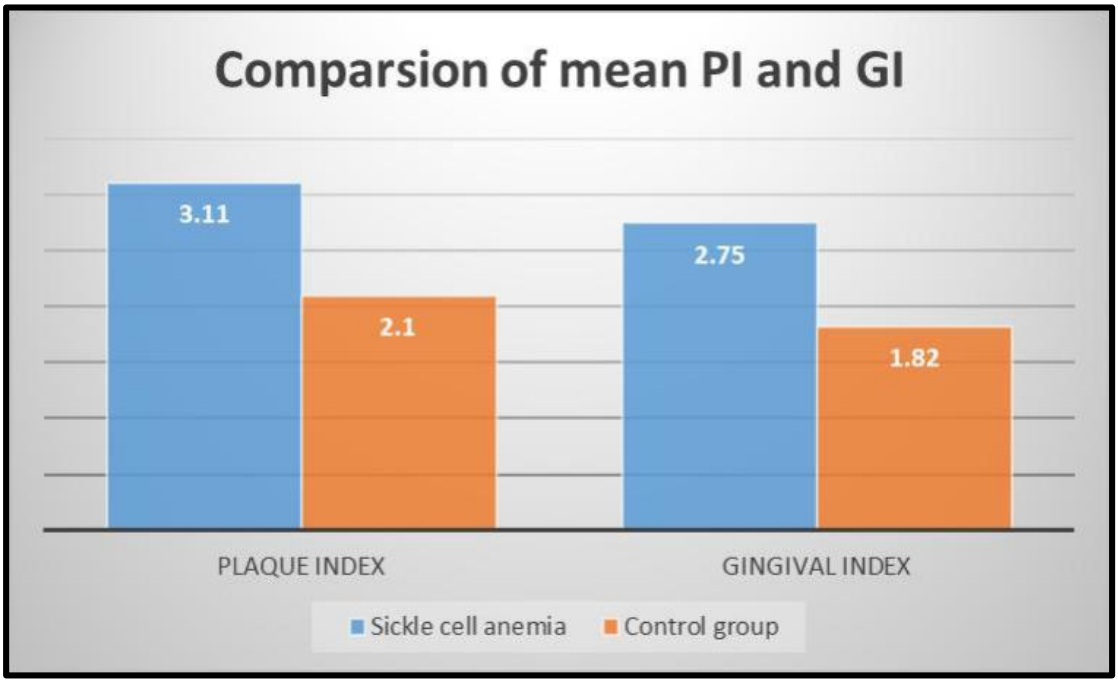

Figure 2.1: Comparative analysis of mean plaque index and mean gingival index in patients with sickle cell anemia and control group (Majid, 2018).

Chapter Three: Conclusion and Suggestions

3. Chapter Three: Conclusion and Suggestions

3.1. Conclusion

- Sickle cell disease patients needed better and continuous oral health care integrated with the clinical aspects of their systemic health.
- Because there are insufficient studies and controversies between the different recommendations for oral management of SCD patients, clinicians need to use their clinical judgement and refer to lower-level evidence (eg, observational studies, case reports, expert opinion) for selecting the best and most suitable form of intervention for treating the dental complications in SCD patients
- The biological mechanisms of SCA and its genetic etiology make it possible to understand the complications linked to this pathology. Knowledge of these complications is essential because they will have direct or indirect consequences on oral health, on the diagnosis of oral lesions and on the management of patients with MDS.
- It is necessary to make dental surgeons and specialists in oral surgery aware of the specificities of diagnosis and treatment of SCD
- The oral care of sickle cell patients requires specific precautions such as good management of local anesthetics, rigorous anti-infective prophylaxis as well as controlled prescription of analgesics.
- Patients with SCD are more susceptible to dental caries compared to general population in this community, with a higher prevalence of tooth decay and lower prevalence of filled teeth

3.2. Suggestions

- Periodontal study with a sample including sickle cell gene carriers should be conducted

- Establishment of a more frequent dental examination schedule for all individuals
- Hospitals can promote oral hygiene practices by providing these hospitalized SCD patients with products such as appropriate toothbrushes, toothpaste, and mouthwash

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