Non-Malignant Blood Disorders and Their Impact on Oral Health: an Overview

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Abstract

Purpose of Review This review aims to summarize the literature on inherited hemoglobin and coagulation disorders, focusing on sickle cell disease (SCD), thalassemia, hemophilia, and von Willebrand disease (vWD), and their impact on oral health. Clinical dental management of patients with these conditions is also reviewed.

Recent Findings There is no evident association between caries and SCD. Despite limited available studies, there may be a possible association between caries and thalassemia, which could relate to salivary changes in immunoglobulin A and *Streptococcus mutans* reported in these patients. Controversial results on the caries experience of hemophilia and vWD patients are found in the literature, which are likely to reflect differences in the provided preventive dental care of these patients rather than a biological association. Current evidence does not support any association between periodontal disease and SCD. The literature on periodontal disease and thalassemia shows controversial results although some evidence suggests differences in the gingival inflammation of thalassemia patients with increased levels of inflammatory cytokines and matrix metalloproteinases, deserving further investigation. The available literature does not provide evidence of an increased risk for gingival bleeding or periodontal disease in patients with hemophilia or vWD. Dental management of these patients requires appropriate measures to prevent infection and excessive bleeding. The use of local hemostatic may often be sufficient; however, in severe bleeding disorders, systemic hemostatic or replacement therapy may be required, and procedures are recommended to be planned with the patient's hematologist.

Summary Maintaining good oral health through preventive dentistry is important for patients with inherited hemoglobin and coagulation disorders as that may prevent the risk of infection and the need for invasive dental treatments that can result in bleeding complications.

Keywords Hematologic diseases · Anemia · Blood coagulation disorders · Oral health · Periodontal diseases · Dental caries

Introduction

Non-malignant blood disorders are a group of diverse conditions ranging from rare inherited conditions like hemophilia and sickle cell disease (SCD) to common acute events with non-hereditary triggers such as venous thromboembolism. They are increasingly recognized as important illnesses, affecting millions of people

worldwide [1]. The estimated total cost for these disorders in 31 European countries was €11 billion in 2012 [2].

Regarding the inherited disorders, hemoglobinopathies and blood coagulation deficiencies are among the most common. Disorders of hemoglobin are classified into two main groups, the structural variants of hemoglobin and thalassemia. Sub-Saharan Africa has the highest burden of SCD, while Southeast Asia has of thalassemia [3]. Survey data from the World Federation of Hemophilia covering 90% of the world population showed that hemophilia A and B and von Willebrand disease (vWD) account for the majority of all bleeding disorders [4]. Further, registry data on hereditary coagulopathies reported that hemophilia A and B and vWD account for more than 95% of the inherited coagulopathies [5].

Blood transports vital components throughout the body, linking organs and systems together [6], and as such, the orofacial area is affected by blood disorders. General signs

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of anemia such as pallor of the oral mucosa are associated with hemoglobin disorders [7], while signs of bleeding or bruising are seen in the mucosa of patients with congenital bleeding disorders. Evidence of an effect of these disorders on the common oral diseases, caries and periodontal disease, is contestable, and is therefore discussed in this paper.

Dental management of this group of patients depends on the severity of disease, the type of dental procedure, and on the patient's ongoing medical intervention. Risk of infection is one of the main concerns in hemoglobinopathies. Patients may neglect dental care due to concerns of bleeding, which can result in the need for invasive dental procedures associated with a higher risk of bleeding [8]. The need for regular examinations and adequate preventive dental care is therefore emphasized for these patients [9, 10]. Clinical guidelines also recommend to plan and manage required dental procedures with the patient's hematologist [8].

Thus, this review aims to provide an overview of the impact on oral health posed by inherited hemoglobin and coagulation disorders, focusing on SCD, thalassemia, hemophilia, and vWD. Also, general aspects of the clinical dental management of patients with these conditions are reviewed.

Anemia and Oral Health

Anemia is the condition of reduced numbers of circulating erythrocytes (RBC) or decreased hemoglobin levels and diminished oxygen-carrying capacity in blood, estimated to have a global prevalence of 24.8% [11]. Anemia is broadly divided into nutritional, hemolytic, and aplastic forms. Nutritional anemia is mainly related to iron deficiency that results in low hemoglobin levels, but also deficiencies of other vitamins and minerals such as folate and vitamin B₁₂ [12]. Hemolytic anemia occurs due to premature RBC hemolysis and mainly includes sickle cell anemia, thalassemia, and autoimmune hemolytic anemia [13]. Aplastic anemia is a rare condition of bone marrow failure [14].

Inherited hemoglobin disorders are the most common monogenic diseases worldwide and result from abnormalities in its synthesis or structure [15]. SCD is a collection of disorders caused by abnormal beta-globin alleles carrying the sickle mutation on the HBB gene. Sickle cell anemia (SCA) is the most common and severe form of SCD, which results from inheritance of β^S from both parents. Sickle cell trait (SCT) is related to the inheritance of both HbA and HbS, and is not strictly a form of SCD. Sickled erythrocytes are involved in vaso-occlusion, which leads to acute and chronic complications as a result of repeated ischemia and inflammation. Acute complications involve, among others, infection and anemia, whereas chronic complications can affect almost every organ system [16]. Thalassemia stems from abnormalities in the hemoglobin synthesis, where there is an imbalance in the α/β -globin chain ratio leading to

ineffective erythropoiesis, anemia, and iron overload. The disease has a multimorbidity profile affecting several organ systems, such as heart and liver [15].

Both diseases are associated with alterations in the orofacial area, though most of the changes are not specific to these diseases. Several dental complications have been described in SCD including delayed dental eruption, pallor of the oral mucosa, neuropathy, malocclusions, and infections [7, 17]. Thalassemia patients can present facial deformities, malocclusions, and affected dentition with altered tooth size and dental discoloration [18–21]. Mucosal changes include general signs of anemia such as mucosal pallor and atrophic glossitis. Parotid enlargement and altered salivary levels of phosphorus and immunoglobulin A (IgA) are also found in thalassemia patients [22, 23].

The association between SCD and caries is debatable. Okafor and co-workers observed a lower prevalence of caries in SCD compared with controls [24]. This finding was partially substantiated by another study that found a lower occurrence of caries in children with SCD, but similar prevalence between teenagers with SCD and controls [25]. However, on the other hand, lack of a difference or higher prevalence of caries in SCD has also been reported. Laurence et al. [26] found that low-income adults with SCD were more likely to have more decayed and fewer filled teeth than matched controls, which was also observed in Saudi men with SCD [27]. Further well-designed studies are needed to clarify the possible relationship between SCD and caries.

Kaplan, Werther, and Castano [28] reported that decayed missing filled teeth (DMFT) index in patients with thalassemia major was slightly higher than in a comparable study done on children (8.3 vs 7.0). Subsequent studies found that patients with thalassemia have higher dental caries experience than healthy controls [23, 29, 30]. Furthermore, patients with thalassemia major are found to have significantly higher DMFT in comparison to those with thalassemia intermedia [31]. Of note, DMFT index has been reported to be higher in thalassemia patients than in SCD [29, 32]. It has been suggested that this increased caries experience in thalassemia might be due to lower concentrations of IgA in saliva, which could allow increased microbial proliferation [23]. Luglie et al. [33] also showed that *S. mutans* in saliva was detected more frequently in thalassemia major patients compared with controls, but they found no difference in the DMFT index between groups.

It is important to highlight a possible role played by medications, especially antibiotics, taken by SCD patients in the association with caries. It has been reported that caries indices in children with SCA under oral penicillin therapy, who had pneumococcal vaccination or a combination of penicillin and vaccination, were lower than in children with SCA who did not receive those treatments. This was paralleled by lower counts of *S. mutans* in saliva from SCA children who received

prophylactic antibiotic therapy [34]. In fact, penicillin prophylaxis in SCA patients could prevent the acquisition of *S. mutans* leading to the reduced caries prevalence in these patients [35]. As a probable result of the long-term antibiotic therapy, higher counts of yeasts are found in the oral cavity of SCA patients [36], and biofilms of *C. albicans* isolates from these patients display greater caries-associated virulence, as evidenced by increased production of lactic acid, extracellular polysaccharides, and proteins than isolates from healthy controls [37]. Together, these results provide an explanation for the putative association of SCA with caries, highlighting the necessity to take into account the medications used to manage the disease.

An association between SCD and pulp necrosis has been observed, where the presence of necrotic pulp in clinically healthy teeth was 8.3 times higher than in healthy patients [38]. Maxillary teeth, except the canines, with confirmed pulp vitality from SCD patients exhibit lower arterial oxygen saturation, probably as a result of vaso-occlusion due to the accumulation of sickled red blood cells in the large medullary spaces of bones [39]. The effect of SCD in the pulpal microcirculation might result in necrosis without any other etiological factor [40]. A study assessed the expression of cytokines in the periapical interstitial fluid from SCA patients with apical periodontitis and found that interferon (IFN)- γ , tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , IL-17A, and IL-10 were significantly higher in SCA than in the healthy individuals with vital pulp, but not compared with healthy individuals with apical periodontitis [41]. An evaluation of the pulp condition in patients with SCA should be routine [38].

Most of the evidence so far does not support an association between SCD and periodontitis [42–45]. In fact, the workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions concluded that no significant association has been reported between SCD and attachment loss [46]. On the contrary, the oral hygiene status instead of SCD correlates with the periodontal status [44]. de Carvalho et al. [47] analyzed the association between periodontal disease and SCA and SCT, and found that SCT was related to periodontitis. The authors speculated that trabecular bone changes frequently found in SCT patients may lead to decreased bone density, which makes it more susceptible to bone loss. Interestingly, gingival enlargement was reported more frequently in SCD children than in healthy controls (55.1% vs 15.4%), although no difference was seen in the oral hygiene status [43].

Conflicting results have been found regarding the association between thalassemia and periodontal disease. While no difference in plaque index, gingival index, or periodontal probing depth was found between thalassemia patients and healthy controls [30], other studies reported a worse periodontal condition in thalassemia [29, 48, 49]. These discrepant results might be explained by the age difference of the included participants between the studies. Patients with thalassemia

were shown to have increased levels of several inflammatory markers in gingival crevicular fluid and in saliva, such as IL-6, IL-8, matrix metalloproteinase (MMP)-8, MMP-9, and tissue inhibitor of metalloproteinase (TIMP)-1, compared with a systemically healthy group suggesting an exacerbation of the local immune response in these patients, which could affect the periodontal condition [48, 50]. Whether there is a difference in periodontal status between thalassemia and SCD is not clear, though it has been shown that thalassemia patients have more missing teeth than SCD patients [32].

A series of bone manifestations have been described in SCD. Bone pain results from vascular occlusive attacks leading to bone ischemia and the appearance of necrotic areas [7]. Osteomyelitis of the jaws secondary to SCD is rare [51]. Normally, it is difficult to differentiate osteomyelitis from early bone infarction, and in both cases bone pain is associated with fever. Occurrence of pathological fractures or the appearance of a chronic osteitis that can cause fistula are complications of osteomyelitis [7]. In addition, jaw trabecular bone changes with a step-ladder appearance and spider web-like pattern as well as alterations in the lamina dura are seen more frequently in patients with SCA [52]. As a result of the changes in the bone structure, malocclusion is believed to be more common in SCD. In fact, an association between SCA and moderate and very severe malocclusion in permanent dentition has been reported [53].

In thalassemia, skeletal deformities and low bone mass are present and result from increased proliferation of erythroid precursors in the bone marrow that leads to medullary expansion [15, 54]. Prominent cheek bones and protrusive premaxilla with depression of the bridge of the nose are known orofacial manifestations of the disease [18, 28]. Cephalometric evaluation revealed vertical growth direction of the mandible, short mandibular body and ramus length and eversion of the upper and lower lips as the main features of thalassemia patients [18, 55]. Also, spiky-shaped and short roots, attenuated lamina dura, thin cortex of the mandible, absence of inferior alveolar canals, and small maxillary sinuses have been reported in thalassemia [56]. As seen in SCD, malocclusion is more prevalent in thalassemic children than in healthy controls [28, 57]. Bisphosphonate-related osteonecrosis of the jaw has been reported in thalassemia patients; thus, dental check-up prior to and during treatment is recommended [58].

An adverse impact of the oral health status on SCD and thalassemia has not been thoroughly investigated so far. However, the possibility of dental infections triggering a sickle cell crisis has been discussed in the literature [59]. Laurence, Haywood and Lanzkron [60] investigated the association between dental infections (periodontal or periapical/pulpal infections) and likelihood of hospitalization admission in SCD patients. They showed that among SCD patients with a sickle cell crisis, having a dental infection was associated with a 72% increased likelihood of being admitted to a

hospital. A preliminary report in thalassemia showed that triglycerides and cholesterol/high-density lipoprotein ratio correlated positively with the periodontal parameters, suggesting that periodontal health might affect the lipid profile of thalassemia patients [49].

Regarding the dental treatment for patients having SCD, infection risks are one of the main concerns. Antibiotic prophylaxis is considered in cases of invasive dental treatment for patients with functional asplenia or who underwent splenectomy [7]. It is important to minimize stressful situations, which might result in subsequent occlusive vascular pain. Conscious sedation is preferable to general anesthesia. Analgesics are frequently prescribed, but steroidal anti-inflammatory drugs are contraindicated [7]. French guidelines for the management of adult with SCD recommend an annual dental check-up [9]. A systematic review was performed to evaluate methods of treating dental complications in people with SCD; however, no randomized clinical trial or quasi-RCT was identified. The authors highlighted the need for well-designed studies to identify the most effective and safe method for treating dental complications [17•]. Many of the concerns for the dental treatment of patients with thalassemia are similar to those for SCD [61].

Coagulation Defects and Oral Health

Coagulation disorders are conditions that affect the hemostatic capacity of the blood resulting in either hemorrhage or thrombosis. Conditions that result in extensive bleeding include congenital deficiencies in factor VIII (hemophilia A), factor IX (hemophilia B), and von Willebrand disease (vWD), as well as thrombocytopenic conditions [62]. Thrombophilias are, on the contrary, hypercoagulable states that include rare inherited thrombophilic conditions, but more commonly acquired states such as venous thromboembolism. Hemophilia A and B are X-linked recessive disorders caused by a deficiency or dysfunction in the coagulation protein factor VIII and factor IX, respectively. The diseases are characterized by recurrent hemorrhages that affect soft tissue, muscles, and joints, and patients are in need of intravenous replacement therapy with coagulation factor concentrates [63]. vWD is characterized by reduced levels or dysfunctional von Willebrand factor (vWF) resulting in deficient adhesion and aggregation of platelets. There are three main types of vWD, type 1, 2, and type 3. Type 1 vWD is the most common form. In type 1 the vWF levels are too low, but still functional. Type 2 vWD is the second most common form affecting the size and function of vWF, but not the levels. Type 3 vWD is rare and is the most severe form of the disease characterized by little or no vWF. Symptoms of vWD include, among others, hematoma, nasal, and oral mucosa bleedings as well as post-operative bleedings [64].

Manifestations in the oral mucosa of patients with hemophilia and vWD are mainly mucosal signs of bleeding or bruising, such as petechiae. Regarding caries, the reviewed literature does not support an association with congenital bleeding disorders although some contradictory results have been published. Some studies have reported an increase in the dmft/DMFT scores of young hemophilia patients [65–67]. However, other reports found comparable caries indices in hemophilia patients as in healthy individuals [68, 69]. In fact, even a lower prevalence of caries has been shown in young hemophilia patients compared to the general population of Northern Ireland [70]. Similarly, Sonbol et al. [71] presented data from UK showing a greater proportion of caries-free children with severe hemophilia compared with controls, and decreased caries scores along with a decreased mean number of colony forming units for *S. mutans* in hemophilia patients compared with controls. Similar findings were presented by Jangra and Goswami [72] from India showing lower caries indices in hemophilia patients compared with controls. It is possible that differences in the reported caries experience between countries reflect differences in the provided oral care and interventions, as well as preventive dental measures for hemophilia patients. Little has been reported on caries in patients with vWD. A study on dmfs/DMFT scores in young type 3 vWD patients reported high caries burden compared with the hemophilia patients reported in the study by Sonbol et al. The authors speculated that the increased caries burden might be a result of the mucosal bleeding in vWD type 3, which may lead to avoidance of brushing to escape from mucosal bleeding [73].

Gingival bleeding has often been regarded as a symptom of congenital bleeding disorders; however, the periodontal status of these patients has often been overlooked. Sonbol et al. [71] reported no difference in the gingivitis scores between hemophilic patients and controls. In vWD, comparable, or even lower gingival bleeding indices were reported compared with controls, and similar amount of bleeding on probing [74, 75•]. Analysis of factors associated with gingival bleeding showed that plaque was more related to gingival bleeding than the levels of vWF [76]. Regarding the oral hygiene, some studies have found differences in hemophilic patients with less frequent brushing [66], which has been speculated to be due to the fear of bleeding during oral hygiene measures. But on the contrary, Sonbol et al. [71] reported higher plaque scores in the controls. This may reflect differences in the preventive health care and education given for this group of patients. Small (< 1 mm) differences in the alveolar bone loss were reported in patients with congenital bleeding disorders; however, these were not considered clinically significant [77]. The periodontal status of hemophilic patients has not been shown as a risk for postsurgical bleeding after tooth extraction as comparable indices for gingivitis and plaque were reported in patients with and without bleeding [78]. Intensive

periodontal treatment has been shown to increase vWF the first day after treatment [79]; however, in a review by D'Aiuto, Orlandi, and Gunsolley [80], limited evidence was found for an effect on vWF by periodontal therapy. In summary, the available literature does not provide evidence for an increased risk of gingival bleeding or periodontal disease in patients with congenital bleeding disorders.

In a retrospective study, Franchini et al. [81] reviewed dental procedures and associated bleeding complications carried out during a 10-year period in patients with congenital bleeding disorders. The incidence of bleeding complications was low, and occurred mainly in conjunction with multiple tooth extractions. Treatment recommendations for dental management of patients with inherited bleeding disorders have evolved over the years. Stubbs and Lloyd [82] provided treatment protocols based on non-surgical dental treatment carried out in 30 patients with hemophilia A, 1 patient with hemophilia B, and 15 patients with type 1 vWD over a 24-month period. The recommendations largely depended on the severity of disease, but also on the type of dental procedure ranging from infiltration anesthesia and inferior alveolar nerve block, supragingival scaling, subgingival scaling, or restorative treatment with the use of matrix band to minor soft tissue abscess/swelling. The recommended measures for hemophilia A included the use of oral tranexamic acid or factor replacement or a combination of both, and the use of oral tranexamic acid, prothrombinex-HT, or combination of both for hemophilia B.

For vWD the protocol included the use of oral tranexamic acid, desmopressin or factor VIII, or a combination of oral tranexamic acid and factor VIII. A later consensus report by hospital dentists published slightly adjusted recommendations [8]. For instance, the risk of hematoma during anesthesia is now considered lower in mild and moderate hemophilia and vWD types 1 and 2, but caution should be taken in severe hemophilia patients and vWD type 3. Furthermore, there is no recommended cover for routine endodontic, restorative, and orthodontic treatment in vWD or mild and moderate hemophilia, but it should be carried out with caution in patients with severe hemophilia. For scaling and cleaning, tranexamic acid mouthwash is recommended, but severe periodontal disease cases with vWD type 3 are recommended to be handled at hemophilia treatment centers or by hospital dental service. For invasive dental procedures in mild hemophilia and vWD type 1 and 2 patients, careful extraction, tranexamic acid, and an absorbable hemostat usage together with tightly suturing with absorbable sutures is recommended. Oral surgery in vWD type 3 patients and those with moderate and severe hemophilia is recommended to be handled at hemophilia treatment centers or by hospital dental service. For pain control, aspirin should not be used and the use of non-steroidal anti-inflammatory drugs should be discussed with the patient's hematologist [83].

Conclusions

The impact of inherited hemoglobin and coagulation disorders on oral health is not well established, and clinical management of these patients in dentistry remains to be a challenge. For SCD the risk of infections is a concern and antibiotic prophylaxis may be needed for compromised patients in cases of invasive dental treatment. Dental management of patients with bleeding disorders requires appropriate measures to prevent excessive bleeding. The use of local hemostatic measures may often be sufficient; however, in severe bleeding disorders, systemic hemostatic or replacement therapy may be required. It is recommended to consult with the patient's hematologist to plan the dental procedures for patients with inherited hemoglobin and coagulation disorders. Maintaining good oral health is of outmost importance as this may prevent the risk of infection and the need for invasive dental interventions associated with bleeding or risk of infections, and potential subsequent complications.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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