PERIODONTAL STATUS IN ADULT PATIENTS WITH LEUKEMIA: A LITERATURE REVIEW

Condição periodontal em pacientes adultos com leucemia: revisão de literatura

Autores:
Lana Vitória Almeida Marques
Cirurgiã-dentista, Universidade Federal Fluminense (UFF) - Nova Friburgo, Brasil

Caroline Pessoa da Silva
Periodontista, Consutório Particular – Rio de Janeiro - Brasil

Christiane Mazurek da Cruz Ribeiro Moraes
Doutoranda, Universidade Estadual do Rio de Janeiro (UERJ) – Rio de Janeiro, Brasil

Eilzangela Partata Zuza
Professora Adjunta, Universidade Federal de Uberlândia (UFU) – Uberlândia, Brasil

Alessandra Areas e Souza
Professora Associada, Programa de Pós Graduação em Odontologia,
Universidade Federal Fluminense, Instituto de Saúde de Nova Friburgo (UFF/ISNF)– Nova Friburgo, Brasil

Instituição na qual o trabalho foi realizado: Universidade Federal Fluminense, Instituto de Saúde de Nova Friburgo (UFF/ISNF)

Endereço para correspondência: ISNF/UFF – Rua Doutor Silvio Henrique Braune, 22, Centro, Nova Friburgo, RJ, Brazil – CEP: 28060-160 – Tel: (22) 2568-7128/ (21) 98747-6672
E-mail para correspondência: alessandraareas@id.uff.br ou lecareas@gmail.com

RESUMO

A doença periodontal é uma doença inflamatória crônica altamente prevalente e que afeta os tecidos que sustentam os dentes, enquanto a leucemia é um tipo

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de câncer maligno que afeta a produção de células sanguíneas. Estudos recentes sugerem que a resposta imune e a disbiose microbiana relacionada a doença periodontal podem estar associadas a um risco aumentado de desenvolver leucemia e pode afetar o prognóstico da doença, assim como o tipo de leucemia e o tratamento também podem ter efeitos no periodonto, exigindo uma abordagem interdisciplinar desses pacientes. O objetivo deste estudo foi realizar uma revisão de literatura para avaliar a associação entre doença periodontal e leucemia em pacientes adultos. Foi realizada uma busca eletrônica em bancos de dados utilizando os descritores. Foram selecionados estudos clínicos com exame periodontal em indivíduos adultos com leucemia. Após busca na literatura, 9 estudos foram revisados. Sangramento gengival e bolsas periodontais foram achados frequentes. A prevalência da periodontite variou entre os estudos, sendo de 29% a 82,4% em pacientes diagnosticados com leucemia. A relação entre doença periodontal e leucemia é complexa e multifacetada e existem poucos estudos disponíveis em adultos, com protocolos de exames heterogêneos. Ainda assim, a alta prevalência de gengivite e periodontite encontrada nos estudos sugere que o diagnóstico e o tratamento periodontal podem ser uma ferramenta útil para prevenir maiores complicações no tratamento da leucemia.

Palavras-chave: doença periodontal, periodontite, gengivite, leucemia

ABSTRACT

Periodontal disease is a highly prevalent chronic inflammatory disease that affects the tissues that support the teeth, while leukemia is a type of malignous cancer that affects the production of blood cells. Recent studies suggest that immune response and microbial disbiosis related to periodontal disease may be associated with an increased risk of developing leukemia and may affect its prognosis, as well as leukemia type and treatment may also have effects on the periodontium, demanding a interdiscipinary approach of these patients. The aim of this study was to conduct a literature review to assess the association between periodontal disease and leukemia in adult patients. An electronic database serch using the descriptors was performed. Clinical studies with periodontal examination in adult individuals with leukemia were selected. After literature search, 9 studies were reviewed. Gingival bleeding and periodontal pockets were frequent findings. Periodontitis prevalence varied among studies, ranging from 29% to 82,4% in patients diagnosed with leukemia. The relationship between periodontal disease and leukemia is complex and multifaceted and there are few studies available in adults, with heterogeneous exam protocols. Still, the high prevalence of gingivitis and periodontitis found in the studies suggest that

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periodontal diagnosis and treatment could be a helpful tool to prevent further complications in leukemia treatment.

Keywords: periodontal disease, periodontitis, gingivitis, leukemia

INTRODUCTION

Periodontal disease is a very prevalent chronic inflammatory condition that affects the supporting structures of the teeth. It can affect the gums, with clinical signs of bleeding (gingivitis) or also affect the surrounding tissues, with apical junctional epithelial migration, increase in pocket probing depth and bone loss (periodontitis), which can lead to tooth loss (KASSEBAUM et al., 2014). It is mainly triggered by the biofilm formed by dysbiotic bacteria that accumulate on the surface of the teeth and gums, and initiate a host immune response (PAPAPANOU et al., 2018; HAJISHENGALLIS et al., 2021).

According to the consensus report about the classification of periodontal conditions of the American and European Academy of Periodontics (CHAPPLE et al, 2018), hematological conditions can act as modifying systemic risk factors for biofilm-induced gingivitis, and can also cause malignant reaction processes such as a leukemic cell infiltrate in diseased gums not caused by biofilm.

Leukemia is a malignant neoplasm that affects hematological cells and is characterized by the abnormal accumulation of immature cells in the bone marrow, which proliferate and interfere with normal production of blood cells (HOSSAIN et al., 2019). Given this possible relationship between the two conditions, the investigation of the prevalence of periodontal disease in patients with leukemia and the subsequent assessment of the impact of periodontal disease on the progression and quality of life of these patients is essential. Some recent systematic reviews have emphasized the relation between these two conditions (ANGST et al., 2020; HAZINI, 2022; WU et al., 2020).

Every year, there is a significant increase in new cancer cases, especially in developing countries, which has brought new challenges to health systems (INCA, 2023). Both population aging and changes in lifestyle such as tobacco consumption, alcohol, sedentary lifestyle, pollution and poor diet have been identified as the causes for this growth in cancer cases, and oral symptoms may be the first one in these patients. When diagnosed early, a significant number of cancers can be cured through surgery, radiotherapy, or chemotherapy (SIEGEL et al., 2023).

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Recent evidence pointed that patients with periodontitis are at higher risk of developing different types of cancer, in a large sample of patients in a 5-year follow-up study (CHUNG et al., 2016). A dose-response meta-analysis revealed that each ten-tooth loss, which can be caused by periodontitis, was associated with a 3% increment of risk of hematopoietic cancer (SHI et al., 2017).

Thus, our aim was to evaluate the literature about periodontal disease in adult patients with leukemia and to verify whether the presence of periodontitis is associated with a worse prognosis and a higher incidence of complications in patients with this type of cancer, and also whether the immunosuppression caused by leukemia can increase the risk of developing or worsening periodontal conditions.

LITERATURE REVIEW

The present study was an integrative literature review. Searches in the PubMed, LILACS and SciELO databases were performed. The search strategy was carried out using descriptors selected according to the DeCS and MeSH descriptor lists, in English: periodontal disease, periodontitis, gingivitis, leukemia, followed by the Boolean AND operator, published between 2000 and 2023, in English or Portuguese. Articles that addressed the relationship between periodontal disease and leukemia were screened. Inclusion criteria were: 1) adults (> 18 years) with any type of leukemia; 2) periodontal examination. Studies evaluating children and other hematological diseases were excluded. After search by 2 independent reviewers (AAS and EPZ), data was inserted in Excel sheets. Duplicates were excluded and full text articles were selected for reading. 9 articles that met the criteria were finally described and are summarized in Table 1. Other relevant information about the topic is also presented.

LEUKEMIA

Leukemia is a type of cancer that affects blood and bone marrow cells, responsible for producing white blood cells, red blood cells and platelets. There is an excessive production of abnormal cells, which are not able to perform their functions and end up impairing the immune system and other body systems (SIEGEL et al., 2023). Leukemia can be caused by genetic mutations. Risk factors for leukemia include exposure to ionizing radiation, toxic chemicals, smoking, viral infections (Human T-Cell Lymphotropic Virus (HTLV-1) or Epstein Barr Virus (EBV)), genetic factors, family history, some genetic syndromes (Down syndrome, Fanconi anemia, Li-Fraumeni) and infections (SIEGEL et al., 2023).

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Leukemia symptoms include fatigue, weakness, weight loss, frequent infections, fever and night sweats (ARBER *et al*., 2016). There are four main types of leukemia: acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL) and chronic lymphocytic leukemia (CLL). Each type is classified according to the type of cell affected and the rate of disease progression (ARBER et al., 2016). Treatment of leukemia depends on the type and stage of the disease, and involves chemotherapy, radiotherapy, immunotherapy and bone marrow transplantation. The prognosis of leukemia also varies according to the type and stage of the disease, as well as other factors such as age, general health and response to treatment (HALLEK et al., 2018, HOCHHAUS et al., 2020).

In Brazil, leukemia is the ninth most common malignant neoplasm in men and the tenth in women, according to the National Cancer Institute (INCA, 2023). The estimated number of new cases of leukemia for Brazil, for each year from 2023 to 2025, is 11,540 cases, which corresponds to an estimated risk of 5.90 new cases per 100,000 men and 4.78 per 100,000 women (INCA, 2023).

In terms of mortality, leukemia represents the fifth cause of cancer death in men and the fourth in women. Regarding leukemia subtypes, ALL is the most common in children and the second most common in adults. AML is more common in adults and represents about 80% of cases of acute leukemia in people over 60 years of age (INCA, 2023).

ORAL CONDITIONS AND LEUKEMIA

The general health of patients with leukemia influences the occurence and severity of oral manifestations. Before the diagnosis of leukemia, infiltration of the oral cavity by leukemic cells can cause a wide variety of oral lesions (ANTONINI et al., 2018). Periodontal manifestations of leukemia may vary depending on the type of leukemia, the stage of the disease, the age of the evaluated individuals and the presence of other risk factors. Conditions like gingivitis, periodontitis, tooth mobility, gingival hyperplasia and ulcerations can be found and cause pain and discomfort (MEYER et al., 2000; LÓPEZ-VALVERDE et al., 2019).

Most of the studies found in the literature search focused on children and adolescents with leukemia, evaluating caries, mucosal lesions and gingival condition (ANGST et al., 2020). In children with ALL, the most common inflammatory oral manifestations are gingival inflammation and mucositis. Leukemia patients are also more susceptible to infection due to immunosuppression caused by chemotherapy, which can induce a decrease in the number of blood cells, including white blood cells (SHANKARAPILLAI et al., 2010). This decrease in immunity can lead to an increased susceptibility to

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infections, including gingivitis (ANGST et al., 2011). The presence of gingivitis in patients with leukemia can lead to a higher incidence of opportunistic infections and systemic complications, which can aggravate the patient's condition. The gingiva may appear erythematous or cyanotic, with hyperplasia and hemorrhages, and may be covered by a pseudomembrane (DE SENA et al., 2022). These conditions may impair oral hygiene and perpetuate gingival inflammation, which can cause pain and discomfort and also lead to periodontitis.

Angst et al. (2020), in a systematic review, evaluated the prevalence of periodontal diseases and dental caries in patients with acute leukemia. They included 39 studies, mainly cross-sectional investigations in children/teenagers with ALL. Based on the data, young people with leukemia had higher prevalence of gingivitis and caries experience. Five studies described periodontal status in children and adolescents up to 15 years but did not find periodontal attachment loss, probably due to the use of partial periodontal examination, with indexes like the Community Periodontal Index, lack of proper periodontal probing and the fact that periodontitis is rare in this age group.

Hazini (2022), in a systematic review, evaluated the frequency of leukemia as a cause of gingival enlargement, gingival bleeding and periodontal clinical manifestations as an early sign of disease in adult and children population. They enrolled 24 studies. Inflammation and enlargement, when present, were at a mild or moderate level, on average around 50% of the population, with varying levels of inflammation. The authors concluded that around 60% of leukemic patients did show gum bleeding and also found a lot of discrepancies in studies and lack of controlling for confounding factors. About periodontitis, most studies didn't report periodontal findings, only 5 studies did. Ponce-Torres et al. (2016) evaluated children with leukemia and found that 91.84% showed signs of gingivitis, including gingival enlargement and bleeding while 16.32% of the patients showed signs of periodontitis. The other 4 studies (Shankara pillai et al. 2010, Rinčić et al. 2016, Busjan et al. 2018, Ptasiewicz et al. 2021) showed an average of 70% of patients affected by periodontitis at a mild or initial state. These studies are described with more details in the present review.

Schmalz et al. (2020) evaluated 39 adult patients suffering from acute leukemia and found dental treatment need for 75% of study participants, while 76% had a need for periodontal treatment, but authors did not report periodontal exam data. In this pilot study, dental and periodontal treatment need, as well as periodontal inflammation, was not associated with the outcome of induction therapy in adult patients with acute leukemia.

The impact of oral inflammation on leukemia treatment outcomes is not yet determined, but an available decision analysis model showed that additional

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death of 0.18% of patients could be avoided by dental treatment prior to chemotherapy, and a reduction in systemic infections by approximately one-third might be achievable (ELAD et al., 2008).

In cancer patients, oral and dental pretreatment has been shown to decrease the length of hospital stay, and to be associated with reduced oral complications (ELAD et al., 2008). Good oral hygiene has been reported to reduce the risk of mucositis and decrease the risk of fever or bacteremia and periodontal treatment in the intervals between chemotherapy cycles reduces febrile neutropenia in subsequent courses of chemotherapy and hematopoietic transplantation (SOGA et al., 2009; NISHI et al., 2022; MIRFENDERESKI et al., 2023).

PERIODONTITIS AND CANCER

There are some studies in the literature relating periodontitis to cancer in general (MICHAUD et al., 2017; PAI et al., 2023). Possible explanations for this association include the fact that periodontitis may increase the risk of cancer through chronic release of inflammatory mediators or dysregulation of the immune system. Poor oral hygiene and biofilm accumulation increases the formation of nitrogenous compounds by oral bacteria, which can influence carcinogenesis (LI et al., 2022).

Subgingival microorganisms can act as a focus for systemic infection in neutropenic cancer patients. Most anaerobic bacteria isolated from anaerobic bloodstream infections in neutropenic cancer patients were of oral source (VIDAL et al., 2000). Assessment of a patient's periodontal condition before the onset of profound neutropenia is critical to the diagnosis and management of these potentially life-threatening infections in cancer patients treated with high-dose chemotherapy (RABER-DURLACHER et al., 2002).

Narayanan et al. (2023) evaluated the relationship between periodontal microbiota and different clinical periodontal parameters and found strong correlations between presence of periodontal inflammation (bleeding on probing, gingival index, plaque index) and several species belonging to genera Prevotella, Treponema, and Mycoplasma in the cancer group.

Wang et al. (2022) in a meta-analysis concluded that there is a clear correlation between periodontal disease and total cancer mortality. Patients with periodontal disease had a 1.4 times higher risk of dying from total cancer than those without periodontal disease. Romandini et al. (2021b) reviewed 57 studies and concluded that periodontal disease increased the risk of all-cause mortality, including cancer mortality (RR = 1.38, 95% CI [1.24–1.53], $P < 0.001$).

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Once periodontitis can lead to tooth loss, studies linking cancer and number of teeth have reported that remaining teeth index values in patients with gastrointestinal cancer were lower, in a survey conducted for the Ministry of Health, Labor and Welfare in Japan (SAKAI et al., 2019).

PERIODONTITIS IN ADULTS WITH LEUKEMIA

Only a few studies so far evaluated periodontal status in adults with leukemia. The nine studies reviewed are summarized in Table 1 (Shankara pillai et al., 2010; Angst et al., 2012; Rinčić et al., 2016; Busjan et al., 2017; Angst et al., 2020; Ptasiewicz et al., 2022; Kim et al., 2022; de Sena et al., 2022; Skalljo et al., 2023).

Gingival and periodontal pathology, prior to chemotherapy was assessed in a cohort of young adult patients and found a statistically significant association between dental plaque levels and both gingival overgrowth and periodontal index (p < 0.001). More than one-third of patients were reported to have infections, most of which were of bacterial origin (Shankara pillai et al., 2010).

Another study found that periodontal status of the patients with acute and chronic leukaemia leukaemia showed a mild inflammation of the gingival margin. The individuals also presented a frame of moderate subgingival inflammation and attachment loss (Angst et al., 2012). These findings were corroborated by Rinčić et al. (2016), which showed worse periodontal status in CLL patients when compared to healthy subjects.

Studies describing periodontitis prevalence in leukemia adult patients were also described. Busjan et al. (2017) found moderate to severe periodontitis in 82.4% of leukemic patients and 79.5% of healthy controls. Angst et al. (2020) evaluated 55 patients and found that 55% of the sample had moderate or advanced periodontitis. Ptasiewicz et al. (2022) found in leukemic patients before chemotherapy that 74.51% patients showed periodontal issues. In 3.92% patients, periodontal pockets were deeper than 6 mm. In the majority of patients, both before and after chemotherapy, improper oral hygiene and severe generalized periodontitis were confirmed. de Sena et al. (2022) found that both paediatric and adult populations with leukemia exhibited dental caries (36.7%) and periodontal changes (34.6%) as the most frequent oral conditions.

Skalljo et al. (2023) described oral symptoms around disease onset reported by 43 patients (15.9%) while 153 patients (58.8%) reported oral complications during previous chemotherapy. In total, 124 (46.1%) patients had dental caries, 63 (29.0%) had one or more teeth with deep periodontal pockets, 147 (75.0%) had one or more teeth with bleeding on probing. Apical periodontitis was observed in

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almost 1/4 of the teeth in 17 (6.3%) patients. Oral mucosa lesions were observed in 84 patients (30.9%). A total of 45 (17.4%) of the 259 patients had at least one acute problem to be treated before host stem cell transplantation.

Nishi et al. (2022) examined the relationship between oral environment using Periodontal Inflamed Surface Area (PISA) and Febrile Neutropenia (FN) in hematologic cancer patients undergoing chemotherapy. They evaluated retrospectively 157 patients, (81 males, 76 females; mean age 62.3 years, range 20–85 years), of which 69 had malignant lymphoma, 53 leukemia/myelodysplastic syndrome and 34 multiple myeloma. Individuals were divided into FN onset during chemotherapy (n = 75) and FN negative groups (n = 82). Pocket depth above 4 and 6 mm were found in 24% and 32% patients in FN group, respectively. Results were similar in the FN negative group. PISA results were 338,2 ± 328.3 in FN group against 159.7 ± 190.2 in the FN negative group (< 0.0001). Bleeding on probing was simliar in both groups, around 50% of sites. PISA was signicantly higher in the FN group than the FN negative group. There was a significant relationship between PISA and FN onset (P = 0.035).

Only one study (Ptasiewicz et al., 2022) evaluated the effects of chemotherapy on periodontal conditions and concluded that the cycle of chemotherapy used did not correlate with changes in oral hygiene periodontal status. It is still unknown if immunosuppression caused by leukemia can increase the risk of developing or worsening periodontal disease.

Kim et al. (2022) found in a large cohort of 713,201 participants that 53,075 (7,44%) had periodontitis. The cumulative incidence of cancer in the periodontitis group was 2.2 times greater than that in the control group. The periodontitis group had an increased risk of total cancer after adjusting for age, gender, comorbidities, body mass index, and smoking history (HR, 1.129; 95% confidence interval [CI], 1.089-1.171; P<0.0001).

Wu et al. (2020) did a meta-analysis to ascertain the correlation of periodontitis with risk of incident hematopoietic and lymphatic cancers. Six studies were included in qualitative synthesis. The pooled analysis revealed that periodontitis was significantly associated with an increased risk of hematopoietic and lymphatic cancers. Two studies evaluated only lymphatic cancers (Kristinsson et al; Bertrand et al., 2017). The other four evaluated hematopoietic and lymphatic cancer (Chung *et al., 2016;* Mai *et al., 2016;* Nwizu *et al., 201;* Michaud et al., 2018*).* The results on the association between periodontitits and the risk of hematopoietic and lymphatic cancer were not consistent. No associations were detected in four of the six included studies but two studies reported a higher risk of hematopoietic and lymphatic cancer among participants with periodontitis

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(Chung et al, 2016; Bertrand et al., 2017). Once periodontal findings involved not only leukemia, with mixed results, these studies were not described in our review.

Table 1. Studies about periodontitis in adults with leukemia

N	Author, year, country	Objective	Sample	Results
1	Shankara pillai et al. 2010, India	To assess gingival and periodontal pathology at the time of presentation, prior to chemotherapy, in a cohort of young adult patients with acute myeloid leukaemia (AML) at a cancer hospital in Kerala, southern India.	73 patients (40 males and 33 females), aged 18 -27 years, with AML and 100 matched controls. Used Oral Hygiene Index (Greene and Vermillion, 1964), the modified gingival hyperplasia index Angelopoulos and Goaz (Pernu et al, 1992) and the Russel Periodontal Index.	Patients with poor oral hygiene showed significantly more gingival enlargement than those with fair. Around three-quarters of the patients had either fair or poor oral hygiene. A statistically significant association between dental plaque levels and both gingival overgrowth (GO) and periodontal index was observed. Poor oral hygiene is a risk factor for leukaemic GO and for destructive periodontal disease. In patients showing high levels of oral hygiene, the GO tends to be mild and does not seem to be problematic, especially with respect to mechanical tooth cleaning. Periodontal parameters were not presented.
2	Angst et al. 2012, Brasil	To evaluate periodontal status in patients with acute lymphocytic leukaemia (ALL) , acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL) and chronic myeloid leukaemia (CML) and its correlation with haematological parameters.	68 patients (48 men, 20 women,37 with ALL and AML, aged 36,6 14,3 and 31 CLL and CML aged 51,4 14,4. Examiners assessed gingival swellng with Seymour index (SI) (Seymour et al. 1985), plaque index (PI) (Silness & Loe 1964), gingival index (GI) (Loe 1967) and bleeding on probing (BOP), probing depth (PD) and clinical attachment loss (CAL) on six sites on each tooth.	For total sample, the periodontal parameters were PI 1.28 ± 0.5, GI 0.74 ± 0.4, PD 2.27 ± 0.6, BOP 33%, CAL 2.31 ± 1.6. Fourteen patients were smokers. Forty-five per cent of the patients reported some type of oral manifestation at the time of leukaemia diagnosis, and gingival bleeding was the most prevalent (38.7%).No significant correlation was found between periodontal and haematological parameters, Periodontal status of the patients with leukaemia showed a mild inflammation of the gingival margin.
3	Rinčić et al., 2016, Croacia	To evaluate periodontal status of individuals with early-stage Chronic Lymphocytic Leukemia (CLL) and the relationship between periodontal and hematological parameters.	24 patients with CLL and at least 8 teeth aged 70.8±9.9 years; and 28 controls aged 65±9.6 years underwent a full mouth examination: periodontal probing depth (PD), gingival recession (REC) and clinical attachment loss (CAL), Approximal Plaque Index	Individuals with CLL had significantly higher mean values of periodontal indices (API 0.81 ± 0.18; PBI 2.72 ± 0.68; PPD 3.40 ± 0.53; REC 1.95 ± 0.87; CAL 4 .37 ± 0.80) in relation to individuals in the control group (API 0.69 ± 0.15; PBI 1.9 1 ± 0.45; PPD

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				2.51 ± 0.40; REC 0.99 ± 0.54; CAL 3.00 ± 0.58). Patients with CLL had a worse periodontal status than healthy subjects
			(API, Lange, 1986) and Papilla Bleeding Index (PBI, Saxer and Mühlemann, 1975) were also recorded.	
4	Busjan et al. 2017, Alemanha	To evaluate oral health of adult patients with newly diagnosed acute leukemia.	39 patients with newly diagnosed acute leukemia (L). 38 healthy individuals as controls (HC) (both genders, over 18 years). Oral examination comprised papillary bleeding index (PBI), periodontal probing depths (PPD), the occurrence of bleeding (bleeding on probing (BOP), and the clinical attachment loss (CAL). The stage of the periodontal disease was evaluated as: (1) no/mild periodontitis, (2) moderate periodontitis, and (3) severe periodontitis (Eke et al., 2012).	The leukemic group had a mean gingival inflammation (measured by PBI of 0.81 ± 0.82, which was significantly higher than the control group (0.30 ± 0.54, p = 0.005). PBI scores are also applicable for gingival bleeding. 82.4% of the leukemic patients and 79.5% of the healthy control group had a moderate to severe periodontitis. 82.4% of the L patients and 79.5% of the HC had a moderate to severe periodontitis. Within the L group, AML showed significantly higher prevalence for moderate (AML 56.5%, ALL 27.3%) and severe periodontitis (AML 39.1%, ALL 27.3%, p= 0.012). For all periodontal parameters (BOP,PPD,CAL), significantly higher values were found for the L compared t o the HC group and within the L patients for AML compared to ALL. Age tended to have an influence on periodontitis severity in both groups.
5	Angst et al 2020, Brasil	To evaluate the relation of quaity of life and periodontal status in patients with leukemia.	55 patients, aged 42.09±16.57 years. Data were collected at six sites per tooth for all teeth: PI, GI, PD, BOP and CAL. Gingival swelling was analysed according to Seymour index .Periodontal condition was: [no/mild gingivitis (GBI affecting ≤15% of sites) or gingivitis (GBI affecting >15% of sites)17; and absent/mild periodontitis (AMP), moderate periodontitis (MP), or severe periodontitis (SP) (Eke et al., 2012).	Patients had moderate (n = 18), absent/mild (n = 24) and severe (n = 13) periodontitis. Higher scores on the OHIP-14 quality of life questionnaire were not significantly associated with patients presenting > 15% sites with gingival bleeding or those with moderate/severe periodontitis.
6	Ptasiewicz et al 2022, Polonia	To assess and compare oral hygiene and periodontium status based on indices in leukemic patients before and after one cycle of	102 patients (51 males and 51 females), aged 22 -72 years. Oral examination: gingival bleeding on gentle probing, tooth mobility, and presence of supragingival and subgingival dental	The analysis of the SBI index in patients showed that all individuals had inflammation within the periodontal tissues. Before chemotherapy, in 59 subjects (57.84%), the SBI

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			chemotherapy and whether the therapy had an impact on these parameters.	deposits. Periodontal pockets and their depth were assessed. The following índices: sulcus bleeding index (SBI), approximal plaque index (API), and community periodontal index (CPI) were used to assess oral hygiene and periodontal status.	value ranged from 50 to 100%. After hematological treatment, the SBI value was in the same range of 50–100% in 63 subjects (61.76%). None of the patients had a healthy periodontium (code 0). In 30 patients (29.41%), gums bleeding after gentle probing were observed. There were 25 individuals (24.50%) who had supra and subgingival calculus and overhanging fillings, and 17 patients (16.6%) had pathological gingival pockets with a depth of 3.5–5.5 mm. In four persons (3.92%), gingival pockets were deeper than 6 mm. The CPI index did not change after hematological treatment.
7	Kim et al. 2022, Korea		To assess cancer risk in a population-based retrospective cohort study using data from the Korea National Health Insurance Cohort Database obtained between January 2003 and December 2015.	713,201 individuals from the Korea National Health Insurance Cohort Database. Periodontitis was assessed using the Community Periodontal Index (CPI). Periodontal disease was defined as a CPI score ≥ 3.	Of the 713,201 participants, 53,075 (7,44%), aged 39-60 years, had periodontitis; the remaining 660,126 subjects were included as controls. Overall, the cumulative incidence of cancer in the periodontitis group was 2.2 times greater than that in the control group. Periodontitis was associated with increased risks of gastrointestinal cancers (such as stomach cancer, colon cancer), lung cancer, bladder cancer, thyroid cancer and leukemia. Even after controlling for confounding factors, such as sex, income, smoking history, BMI, and comorbidities, periodontitis was found to be a modest but obvious risk factor for cancer.
8	de Sena et al. 2022, Brasil		To assess oral status in cancer patients.	781 leukemia/lynphoma patients. 449 males,332 females. 235 had acute lymphoblastic leukemia, ALL, 204 acute myeloid leukemia AML, 173 non hodgkin lymphoma, mean age 31,4 ± 21,9 years. Periodontitis were charcterized as present	Both paediatric and adult populations exhibited the same three most frequent oral findings: dental caries (n=104/34.4% and n=183/38.2%), periodontal changes (n=80/26.5% and n=190/39.7%), and oral mucositis (n=171/56.6% and n=142/29.6%).

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			or absent, with no further esplanation.	Overall, dental caries (36.7%) and periodontal changes (34.6%) were the most frequent oral conditions. Oral mucosal infiltrates occurred in 25 (3.2%) subjects. Lesions mainly involved the gingiva (80%) and patients diagnosed with AML (64%). Death and worse periodontal condition were more frequent among adults with oral mucosal infiltrates.
9	Skalljo *et al.* 2023, Multicenter	To evaluate the impact of oral risk factors in patients who would receive hematopoietic stem cell transplantation (HSCT) in 5 sites from 2011-2018.	272 individuals aged 18 -76 years. Level of periodontal disease was documented by number of teeth with probing pocket depth (PD) >5mm and bleeding on probing (BOP), registered on four tooth surfaces, when possible.	235 patients (85.5%), were assessed two weeks or more before planned HSCT, 10 patients (3.6%) were evaluated less than one week before. Oral symptoms around disease onset were reported by 43 patients (15.9%) and 153 patients (58.8%) reported oral complications during previous chemotherapy. In total, 124 (46.1%) patients had dental caries, 63 (29.0%) had one or more teeth with deep periodontal pockets, 147 (75.0%) had one or more teeth with bleeding on probing. Apical periodontitis was observed in almost 1/4 of the teeth and partially impacted in 17 (6.3%) patients. Oral mucosa lesions were observed in 84 patients (30.9%). A total of 45 (17.4%) of the 259 patients had at least one acute problem to be treated before HSCT.

AML: acute myeloid leukaemia; GO: gingival overgrowth; ALL: acute lymphocytic leukaemia, AML: acute myeloid leukaemia. CLL: chronic lymphocytic leukaemia, CML: chronic myeloid leukaemia; SI: Seymour index; PI: plaque index, GI: gingival index; BOP: bleeding on probing; PD: probing depth; CAL: clinical attachment loss; REC: gingival recession; API: Approximal Plaque Index; PBI: Papilla Bleeding Index; HSCT: hematopoietic stem cell transplantation.

DISCUSSION

The different types of leukemia are frequent conditions in oncology services, affecting different age groups (INCA, 2023). Likewise, periodontitis is a highly prevalent non-communicable chronic inflammatory disease, associated with numerous systemic conditions (CHAPPLE et al., 2018). On the other hand, leukemia can also affect the oral health of patients, causing ulcerations in the oral mucosa, bleeding and infections. In addition, the treatment of leukemia, which

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usually includes chemotherapy and radiotherapy, can cause side effects such as oral mucositis, xerostomia and tooth loss (ALJOHANI, 2018; SKALLSJÖ et al, 2023; MIRFENDERESKI et al., 2023).

Some recent systematic reviews have shown that the presence of gingival bleeding and inflammation can negatively affect the prognosis and quality of life of patients with leukemia, increasing the risk of complications, such as infections and bleeding (ANGST et al, 2020; WU et al, 2020, HAZINI 2022). Most studies described in these reviews focused on gingival exams in children. Only a few studies evaluated periodontitis in adults with leukemia and are described in the present study.

Published articles on leukemia and periodontal condition are very heterogeneous, as they include individuals with different types of leukemia, different age groups, different stages of treatment and with varied periodontal examination protocols, which makes it difficult to compare them and estimate periodontal disease prevalence and impact on leukemia prognosis. The range of periodontal disease prevalence in the analysed studies varied from 29% to 82,5%. Considering that gingivitis and periodontitis are highly prevalent in adult populations, with estimates over 50% prevalence (KASSEBAUM et al, 2014), efforts to diagnose and treat these conditions as soon as possible may help to minimize other systemic complications.

The relationship between periodontal disease and leukemia is complex and involves several factors, such as immunosuppression resulting from leukemia and oncological treatment, the use of immunosuppressive drugs, the presence of infections and chronic inflammation, and the deterioration of oral health (LI et al., 2022). A possible explanation for this correlation may be the chronic inflammation that characterizes periodontal disease, which can affect the body's immune response, stimulating the production of pro-inflammatory cytokines, which can affect the production and regulation of blood cells, allowing cancer cells to develop ((LI et al., 2022). Along with immune system suppression, changes in saliva and decreased blood flow to the mouth were also suggested (SKALLSJÖ et al, 2023; MIRFENDERESKI et al., 2023).

The presence of periodontopathogenic bacteria, which are able to reach the bloodstream and lodge in the bone marrow is also importante (VIDAL et al., 2000). These bacteria can interfere with the production of blood cells, which can lead to the development of leukemia and have been reported in other types of cancer (MICHAUD et al., 2017; LI et al., 2022). Studies showing increased mortality associated with periodontitis points out the importance of diagnosis and treatment (ROMANDINI et al., 2021).

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It is important to emphasize that oral manifestations of leukemia patients can be an early sign of the disease and, therefore, regular evaluation of oral health can help with the early diagnosis of leukemia. About 65% of patients with leukemia present signs and symptoms in the oral cavity during the course of the disease or even when this pathology is not yet clinically diagnosed (ANTONINI et al., 2018). In addition, it is important that leukemia is diagnosed and treated as soon as possible, to control disease progression and also reduce oral symptoms. Angst et al. (2020) found that, despite the presence of periodontal disease (gingivitis and/or periodontitis), leukemia patients were more concerned about their systemic condition than with their oral condition. There is insufficient evidence about the effects of chemotherapy on periodontal conditions (PTASIEWICZ et al., 2021).

Even though a recent study demonstrated no benefit of dental and periodontal treatment on leukemia treatment outcomes (Schmalz et al., 2020), a previous report showed that reduction of systemic inflammation could reduce cancer mortality (ELAD et al, 2006). Although some studies suggest that periodontitis may be a risk factor for cancer related mortality due to the potential for systemic inflammation and infection, this causal relationship has not yet been determined (ANGST et al., 2020).

Despite the divergences, it is agreed that patients with leukemia may benefit from regular dental care. Treating caries and gingival inflammation, through restaurations and good oral hygiene and performing periodontal treatment, if necessary, is important to reduce gingival bleeding and help to reduce microbial counts and the inflammatory burden in the oral cavity. Regular follow-up with a dentist and a hematologist is essential for the control of oral and general health conditions, to ensure a good prognosis for leukemia treatment (ELAD et al., 2008).

Further investigations about the relationship between periodontal diseases and leukemia is necessary for a better understanding of this association and the development of effective prevention and treatment strategies.

CONCLUSION

The relationship between periodontal disease and leukemia is complex and multifaceted, and even though studies have demonstrated a possible association between them, no conclusions can be withdrawn based on the few studies available, once they are very heterogeneous. Still, due to the high prevalence of gingivitis and periodontitis found in the studies, it is important that patients with leukemia receive regular dental care, including diagnosis of periodontitis and

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other oral manifestations like mucositis, ulcers and gingival bleeding and treatment of these conditions, which can be a helpful tool to prevent further complications in leukemia treatment.

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