Original Paper

Exploring Potential Correlations Between Oxidative Stress Markers and Inflammatory Pivotal Factors in Children with Hematological Malignancies

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ABSTRACT: Background: Hematological malignancies are associated to immune status alterations and an amplified systemic and local immune response, which can have a significant impact on oral health, especially concerning gingival and periodontal status. Along with cytokines, which play an important role in regulating local and systemic inflammation, oxidative stress factors also reflect a critical involvement in the evolution of periodontal alterations, especially in association to systemic conditions such as leukemia. This study aims to investigate certain inflammatory markers (such as IL-1β, IL-6, IL-17α and TGF-β) as well as oxidative stress factors (SOD, MDA, 8-OHdG), in order to identify any correlations between the two, in a comparative manner, in children with leukemia and individuals without this malignant disease. Methodology: The study evaluated inflammatory markers and oxidative stress factors both in plasma and gingival crevicular fluid of 97 children (47 in the study group, suffering from leukemia and 50 in the control group, without the oncological condition or any other inflammatory systemic disease). Results: In plasma, MDA seems to be the most powerful association, rising along with increased plasmatic values of IL-1β, IL-17α and TGF-β. In GCF, SOD and 8-OHdG associate with inflammatory indicators, suggesting a complex synergy between cytokine expression and oxidative stress mechanisms. Conclusions: Our analysis showed significant associations between the evaluated inflammatory markers and oxidative stress factors, both in plasma and gingival crevicular fluid. These observations might underline a potential role of certain biomarkers to act out as indicators of a complex interconnection between inflammatory status and oxidative stress.

KEYWORDS: *Cytokines, oxidative stress markers, children, hematological malignancy.*

Introduction

Malignant hemopathies are frequent accompanied by oral manifestations, periodontal complex being among the most vulnerable and affected network [1,2].

Periodontal disease is described as a chronic inflammatory condition, with a multifactorial etiology, that alters the support structures of the tooth. Research has been focused on understanding the underlying etiopathogenesis of this disease, which seems to be characterized by complex interactions between the bacterial determinant factor and the host immuno-inflammatory response to the microbial attack.

Literature shows that immune mediators and oxidative factors may be involved in the progression and severity of the pathological processes in periodontal disease [3,4]; however, the underlying molecular mechanisms still remain an intriguing subject.

Interleukins are cytokines with an essential role in regulating local and systemic inflammation processes; in the course of periodontal disease, they can shift the balance of the protective immune response to a destructive inflammatory state [5,6].

Among the most powerful pro-inflammatory mediators, IL-1β (interleukin 1 beta), IL-6 (interleukin 6) and IL-17 (interleukin 17) are acknowledged for leukocyte recruitment, matrix-metalloproteinases expression and osteoclastogenesis, processes which amplify the periodontal tissue breakdown [7].

Another key mediator is TGF-β (transforming growth factor β), which seems to be involved in limiting the inflammation and promoting tissue repairing processes [8].

Another critical factor in periodontal disease progression is oxidative stress, which translates an imbalance between oxygen reactive species production and antioxidant mechanisms.

Among the most important oxidative stress indicators, the literature recognizes MDA (malondialdehyde, an end-product of lipid peroxidation), 8-OHdG (8-hydroxy deoxyguanosine, a biomarker of oxidative DNA damage) and SOD (superoxide dismutase, an antioxidant catalyst) [9,10].

Literature depicts elevated values of these biomarkers during periodontal alterations,

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suggesting a direct contribution of oxidative stress in tissue degradation [11].

The importance of these biomarkers, albeit being inflammatory or oxidative stress factors, resides in their ability to reflect disease progression and severity; there is currently an increased interest in their use as prognostic indicators for periodontal disease evolution and treatment monitoring [9,12].

The biological and clinical relevance of the markers is especially highlighted in the context of associated systemic diseases, such as diabetes, cardiovascular conditions or hematological pathologies [13-15].

Altered immune responses and oxidative stress imbalances observed in systemic conditions can modulate the severity of periodontal changes and the treatment response; in these situations, heightened biomarker values can reflect a bidirectional interplay, with the amplification of both systemic and local inflammation boost [16,17].

Inflammatory and oxidative stress biomarkers are mostly investigated in adult population, suggesting correlations between periodontal damage and systemic conditions; however, research focusing on children are relatively scarce, with available data often limited by small sample sizes, methodological variability or inconsistent results [18-20].

In specific systemic conditions such as hematological malignancies, existing evidence is even more limited, with only a few studies evaluating inflammatory biomarkers or oxidative stress indicators related to periodontal changes triggered by the disease itself or the oncological treatment. Although plentiful studies have validated a correlation between inflammatory and oxidative stress pivotal factors, there remains a significant gap specifically addressing this association in juvenile population affected by leukemia, highlighting the need for subsequent further, focused research, in this vulnerable population.

Objective

The main goal of this study is to explore, in a comparative manner, any correlations that might emerge between inflammatory biomarkers and oxidative stress indicators, through parameter evaluation within plasma and gingival crevicular fluid of children with leukemia, relative to a control group consisting in children without such systemic condition.

This paper aims to analyze significant differences between certain cytokines and oxidative stress factors in order to identify a potential synergism between these markers, known to be deeply involved in the pathological mechanisms of periodontal disease as well as leukemia.

Methods

The study included 97 subjects between 3 and 18 years old, divided in two groups, consisting of children monitored in “St. Mary” Clinical Emergency Hospital for Children in Iasi, Romania (47 children with leukemia and 50 children with other non-inflammatory conditions), evaluated between October 2024 and May 2025. The inclusion criteria for the study group consisted of children under 18 years of age, with any form of leukemia and in any stage of cancer treatment, who have not been submitted to periodontal treatment 6 months prior to the examination. For the control group, inclusion criteria referred to children under 18 years of age, with non-inflammatory systemic conditions, who have not been submitted to periodontal treatment 6 months prior to the examination. Exclusion criteria for both groups consisted of subjects over 18 years of age, who were subject to periodontal treatment 6 months prior to the examination.

The inflammatory markers (IL-1β, IL-6, IL-17α and TGF-β) as well as oxidative stress parameters (SOD, MDA, 8-OHdG) were evaluated both in plasma and gingival crevicular fluid (GCF). Plasma samples were obtained from the routine blood tests during children’s hospitalization; the gingival fluid was collected following a standardized protocol, using calibrated paper cones inserted in the gingival sulcus for 30 seconds and then transported on ice, in sterile Eppendorf tubes, until GCF volume measuring on a calibrated Periotron device (Oraflow Inc, NY, USA). The cones were then inserted in 200μL of PBS (phosphate buffered saline solution) and stored at -80°C until biological markers analysis. At the evaluation moment, samples were thawed and biomarkers values were measured in plasma and GCF samples using ELISA (enzyme-linked immunosorbent assay) kits (Elabscience, Bionovation Inc., Houston, TX, USA), following instructions provided by the manufacturer’s protocol. The results were introduced in the statistical analysis software to evaluate distributions, group comparations, and the relationship between variables by applying Pearson correlation tests (IBM SPSS Statistics 26, IBM Corporation, Armonk, NY, USA) with $p<0.05$ for statistical significance.

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Results

Descriptive data

The main demographic characteristics of children in both groups are presented in Table 1; biomarker mean values, analyzed both in plasma and GCF for children in both groups, are presented in a comparative manner in Table 2.

Table 1. Age, gender and environment distribution of children in both groups.

Group	Parameter				
	Age	Gender (% of group)		Environment (% of group)	
		Male	Female	Urban	Rural
Study	8.71 (±0.53)	57.1%	42.9%	38.8%	24.0%
Control	12.16 (±0.51)	42.0%	58.0%	61.2%	76.0%

Table 2. Biomarker mean values in plasma and GCF for children in both groups.

Fluid	**Biomarker (unit)**	**Mean value (Standard Error)**	
		Study	**Control**
Plasma	IL-1β (pg/mL)	17.09 (3.33)	17.48 (1.51)
	IL-6 (pg/mL)	11.36 (2.11)	5.31 (0.36)
	IL-17α (pg/mL)	319.61 (43.13)	179.26 (29.82)
	TGF-β (ng/mL)	4.81 (0.53)	3.23 (0.26)
	SOD (U/mL)	6.359 (0.023)	6.095 (0.033)
	MDA (nmol/mL)	3.098 (0.356)	1.723 (0.196)
	8-OHdG (ng/mL)	43.840 (6.234)	20.659 (2.682)
GCF	IL-1β (pg/μL)	73.15 (8.92)	16.09 (0.45)
	IL-6 (pg/μL)	3.90 (0.41)	2.04 (0.10)
	IL-17α (pg/μL)	0.96 (0.14)	0.20 (0.01)
	TGF-β (pg/μL)	0.65 (0.10)	0.25 (0.03)
	SOD (U/mL)	6.296 (0.025)	6.091 (0.031)
	MDA (nmol/mL)	2.460 (0.322)	2.427 (0.298)
	8-OHdG (ng/mL)	2.714 (0.337)	1.228 (0.047)

The results pointed out differences between the two groups for nearly all analyzed biomarkers. Except for plasma IL-1β, cytokine levels from children in the study group were significantly elevated compared to those in the control group, both in plasma and GCF. Upon evaluation of oxidative stress markers, differences were significant for all plasma indicators, 8-OHdG in GCF and SOD in GCF, while gingival fluid MDA did not exhibit this pattern.

Correlation between inflammatory markers and oxidative stress markers in plasma

Pearson's correlation analysis between inflammatory markers and oxidative stress markers in plasma showed several statistically significant associations (Table 3).

MDA was the only oxidative stress marker significantly associated with inflammatory markers in plasma. Significant positive correlations were observed between MDA and IL-1β, IL-17α, and TGF-β1, with correlation factors ranging from r=0,360 to r=0,482. In contrast, IL-6 was not significantly correlated with any of the oxidative stress markers analyzed. Moreover, no significant correlations were identified between 8-OHdG or SOD and any inflammatory markers. These findings suggest that, from a statistical perspective, MDA may represent a more sensitive indicator of the relationship between inflammation and oxidative stress.

Table 3. Correlation between inflammatory markers and oxidative stress markers in plasma.

Inflammatory markers / Oxidative stress markers	**Plasma 8-OHdG**	**Plasma SOD**	**Plasma MDA**
Plasma IL-1β	r=0.053, p=0.609	r=-0.164, p=0.108	**r=0.365**, p=0.000**
Plasma IL-6	r=0.039, p=0.708	r=0.105, p=0.305	r=0.089, p=0.385
Plasma IL-17α	r=0.107, p=0.296	r=-0.081, p=0.432	**r=0.360**, p=0.000**
Plasma TGF-β1	r=0.126, p=0.218	r=-0.056, p=0.583	**r=0.482**, p=0.000**

*r=Pearson correlation coefficient; p=p-value; **=statistically significant correlation (p<0.01)*

Correlations between MDA and inflammatory markers in plasma

A significant positive association was observed between plasma IL-1β and MDA levels ($r=0.365$, $p<0.001$), with higher IL-1β values corresponding to higher MDA levels (Figure 1).

Linear regression analysis ($y=1.64+0.04x$) showed that for every additional unit increase in IL-1β, the MDA level increased, on average, by 0.04 units, while the coefficient of determination ($R^2=0.133$) indicated that IL-1β explained 13.3% of the variability in MDA.

Overall, the association was weak, given the wide dispersion of the data points around the regression line, but statistically significant.

Similarly, plasma IL-17α showed a significant positive association with MDA levels ($r=0.360$, $p<0.001$), with elevated IL-17α levels being associated with higher MDA levels. The coefficient of determination ($R^2=0.129$) indicated that IL-17α explained 12.9% of the variability in MDA. Pearson's correlation analysis further pointed out that this association was weak to moderate, but statistically significant.

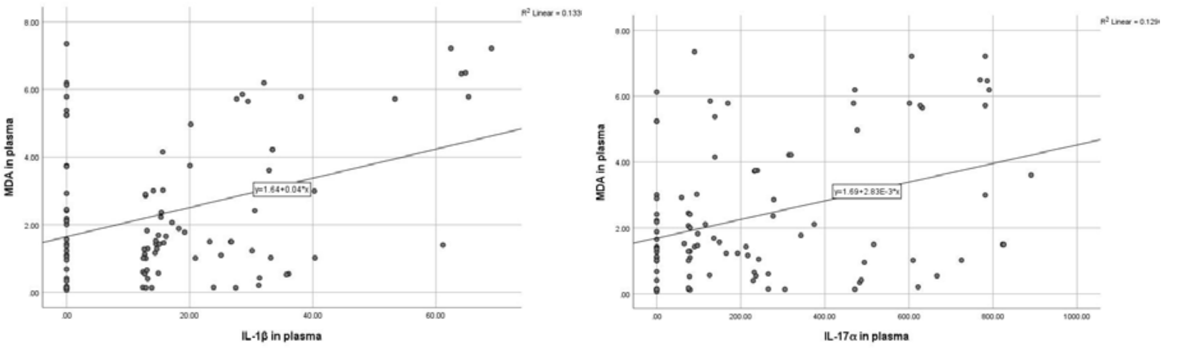

Figure 1. The relationship between and MDA and IL-1β, MDA and IL-17α in plasma.

A significant positive association was observed between plasma TGF-β1 and MDA levels ($r=0.482$, $p<0.001$), with higher TGF-β1 values corresponding to higher MDA levels (Figure 2).

Linear regression analysis showed a positive relationship ($y=1.02+0.34x$), and the coefficient of determination ($R^2=0.232$) indicated that TGF-β1 explained 23,2% of the variability in MDA. Overall, based on Pearson's correlation analysis, the association was moderate and statistically significant.

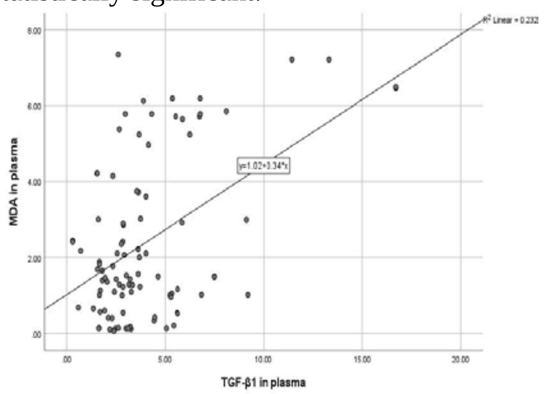

Figure 2. The relationship between MDA and TGF-β1 in plasma.

Correlation between inflammatory markers and oxidative stress markers in GCF

Pearson's correlation analysis between inflammatory markers and oxidative stress markers in GCF revealed several statistically significant associations (Table 4).

IL-1β showed a moderate positive correlation with SOD, whereas its correlations with 8-OHdG and MDA were not significant.

Both IL-6 and TGF-β1 showed a weak but significant positive correlation with 8-OHdG, while no significant association were observed with SOD or MDA. IL-17α was positively correlated with both 8-OHdG and SOD, but not with MDA.

Overall, 8-OHdG was the oxidative stress marker most frequently associated with inflammatory markers in GCF (IL-6, IL-17α, and TGF-β1), while SOD correlates strongly with IL-1β and IL-17α, confirming its role as an antioxidant compensatory mechanism. MDA did not show significant correlations with the inflammatory markers analyzed.

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Table 4. Correlation between inflammatory markers and oxidative stress markers in GCF.

Inflammatory markers / Oxidative stress markers	8-OHdG in GCF	SOD in GCF	MDA in GCF
IL-1β in GCF	r=0.171, p=0.094	**r=0.401**, p<0.001**	r=0.040, p=0.695
IL-6 in GCF	**r=0.219*, p=0.031**	r=0.015, p=0.885	r=-0.075, p=0.463
IL-17α in GCF	**r=0.213*, p=0.036**	**r=0.437**, p<0.001**	r=-0.061, p=0.555
TGF-β1 in GCF	**r=0.216*, p=0.034**	r=-0.008, p=0.939	r=-0.044, p=0.668

r=Pearson correlation coefficient; p=p-value;
**=statistically significant correlation (p<0.05); **=statistically significant correlation (p<0.01)*

Correlations between 8-OHdG and inflammatory markers in GCF

A weak but statistically significant positive association was observed between IL-6 and 8-OHdG levels in GCF (r=0.219, p=0.031), with higher IL-6 values corresponding to slightly higher 8-OHdG levels (Figure 3).

Linear regression analysis (y=1.43+0.18x) indicated that each additional unit increase in IL-6 was associated with an average increase of 0.18 units in 8-OHdG. The coefficient of determination (R^2=0.048) indicated that IL-6 explained 4.8% of the variability in 8-OHdG.

The wide dispersion of data points around the regression line is consistent with the weak strength of this association.

Similarly, the positive association between IL-17α and 8-OHdG levels in GCF (r=0.213, p=0.036) was weak, but statistically significant, with higher IL-17α values corresponding to slightly higher 8-OHdG levels. Linear regression analysis (y=1.66+0.50x) indicated that each additional unit increase in IL-17α was associated with an average increase of 0.50 units in 8-OHdG. The coefficient of determination (R^2=0.045) indicated that IL-17α explained 4.5% of the variability in 8-OHdG, consistent with a weak association. The wide dispersion of data points around the regression line is in line with the limited strength of this relationship.

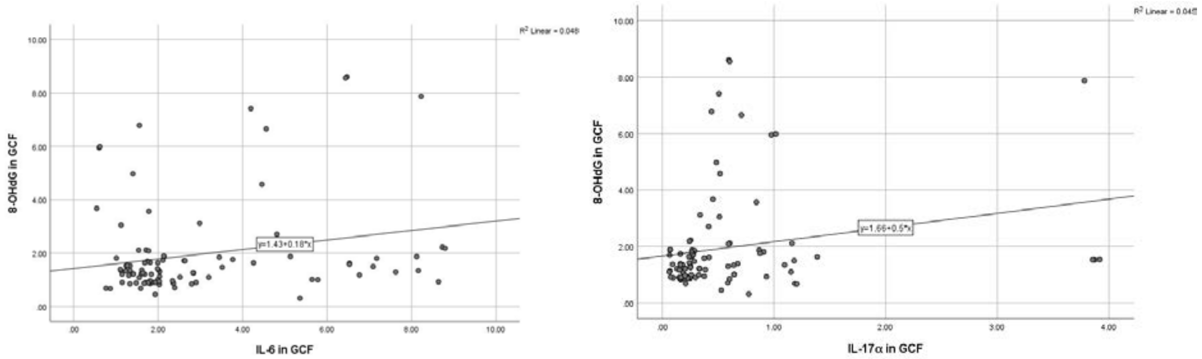

Figure 3. The relationship between 8-OHdG and IL-6, 8-OHdG and IL-17α in GCF.

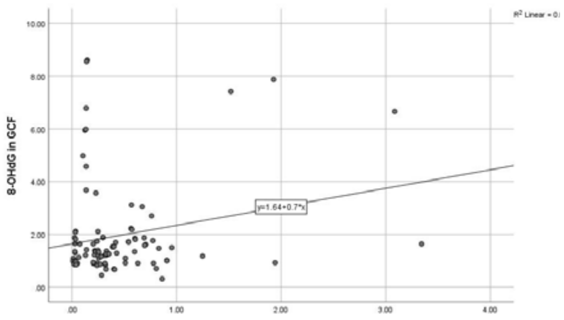

Figure 4. The relationship between 8-OHdG and TGF-β1 in GCF.

A weak but statistically significant positive association was observed between TGF-β1 and 8-OHdG levels in GCF (r=0.216, p=0.034), with higher TGF-β1 values corresponding to higher 8-OHdG levels (Figure 4).

Linear regression analysis (y=1.64+0.70x) indicated that each additional unit increase in TGF-β1 was associated with an average increase of 0.70 units in 8-OHdG. The coefficient of determination (R^2=0.046) indicated that TGF-β1 explained 4.6% of the variability in 8-OHdG. The wide dispersion of data points around the regression line is consistent with the weak strength of this association.

Correlations between SOD and inflammatory markers in GCF

In GCF, SOD showed significant positive associations with both IL-1β and IL-17α (Figure 5).

Linear regression analysis indicated that higher IL-1β levels were associated with higher SOD levels (y=6.11+0.00175x; R^2=0.161), with IL-1β explaining 16.1% of the variability in SOD. Similarly, higher IL-17α levels were associated with higher SOD levels (y=6.12+0.13x; R^2=0.191), with IL-17α explaining 19.1% of the variability in SOD.

Overall, both associations were positive and statistically significant, with the relationship between IL-17α and SOD appearing slightly stronger than that observed for IL-1β.

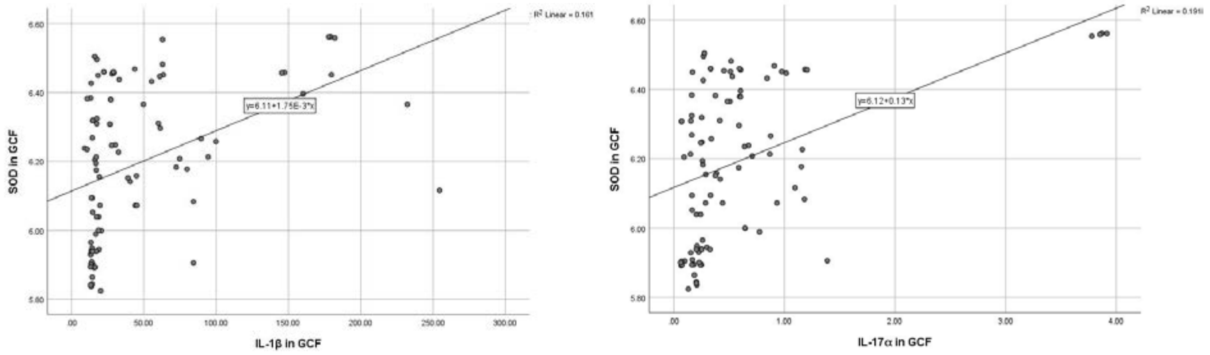

Figure 5. The relationship between SOD and IL-1β, SOD and IL-17α in GCF.

Discussion

In our study, the distribution of demographic data concerning age, gender or environment seems to be aligned to other findings in literature, targeting children affected by hematological malignancies. We have found younger children with leukemia as compared to children in the control group, similar to other studies [21-25]; moreover, a slightly increased prevalence of boys affected by the oncologic disease have emerged, just as described by some authors [26,27], while rural area being better represented in both study groups, in accordance to other studies [28,29].

Children with hematologic malignancies often present oral changes, either related to the disease itself or the oncological treatment, with various degrees of involvement of gingival and periodontal tissues [2].

A recent meta-analysis has evaluated pediatric patients with leukemia and found oral manifestations predominantly during and after oncologic therapy [30].

Among the main alterations of oral tissues outlined in childhood leukemias, Cammarata-Scalisi et al. have identified petechiae, gingival bleedings, mucosal ulcerations, gingival enlargement with or without necrosis, infections and others [31].4/14/2026 5:08:00 PM4/14/2026 5:08:00 PM4/14/2026 5:08:00 PM

Gingival and periodontal alterations observed in pediatric leukemia most likely appear as a result of gingival tissue infiltration by the leukemic cells, associated to hematological disturbances and specific malignancy immunosuppression, which support the gingival inflammation, bleeding and periodontal infection susceptibility [31].

However, the picture of pathologic sequences during periodontal disease in the context of such a severe systemic disorder as leukemia, is far from being clear, the underlying immunological mechanisms being yet to be explored.

Literature has identified interactions between cytokine networks and oxidative mechanisms, described as key elements in the pathogenesis of periodontal disease, in adults as well as children [18,32,33].

The relationship between inflammation status and oxidative stress has sometimes been described as a bidirectional, self-perpetuating, destructive cycle [34].

Consistent evidence of the interdependence between the interleukin-mediated inflammatory response and the oxidative stress imbalance, both in periodontal disease and oral manifestations have been depicted during the evolution of systemic conditions. Moreover, a new field in periodontology seems to be emerging, related to the concept of „periodontal medicine”, which highlights a close association between periodontal disease and oral and systemic health [35].

A relatively recent approach evaluated proinflammatory cytokines such as IL-6 and

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MMP-9 (matrix metalloproteinase-9) and certain oxidative stress markers (MDA, SOD and 8-OHdG), recording a possible connection between increased values of inflammatory mediators and oxidative imbalance in radicular cysts [36].

Despite reporting a strong correlation between pain scores and serum 8-OHdG and MDA values, which could suggest an interrelation between inflammation and oxidative stress mechanisms, Kazan et al. (2023) did not find significant associations between MDA, 8-OHdG and IL-6 in subjects with temporo-mandibular joint disorders compared to healthy individuals [37].

Periodontal disease seems to be related to systemic expression of interleukins, as Kajihara et al. reported in their study in 2022. These authors have even observed a positive relationship between periodontal health deterioration, IL-6 expression and regulatory T cells increase in oncological adult patients, suggesting an involvement of periodontal impairment in cancer progression [38].

Other authors have linked periodontal disease with an increased risk for acute myocardial infarction, suggesting that oxidative stress could represent the main pathogenic bridge between the two conditions, in the absence of IL-1β levels differentiation [39].

In the present study, plasma biomarker values illustrated certain statistically significant relationships between the evaluated cytokines and oxidative stress factors. Among the consistent associations, MDA values stand out as a rather sensitive indicator of the connection between inflammatory status and oxidative stress. This lipid peroxidation marker seems to raise in plasma along with increased plasmatic values of IL-1β, IL-17α and TGF-β.

As gingival crevicular fluid is an exudate reflecting the local response of periodontal tissues to the bacterial invasion and inflammation, certain biological markers identified in this fluid may be used to estimate local inflammatory status as well as oxidative imbalance in periodontal disease [14].

Literature depicts direct connections between local levels of oxidative stress biomarkers and periodontal disease, highlighting the important role of oxidative stress in the evolution and development of this condition [40].

Regarding the complex interplay between inflammatory pillars and oxidative stress factors expressed local in GCF, within periodontal disease and systemic conditions, research is quite narrow and rather focused on adults than children and adolescents. One recent study evaluated the connection between IL-6 and TNF-α (tumor necrosis factor alpha) gingival fluid values in colorectal cancer, suggesting an association between the severity of periodontal disease, the inflammatory markers and the oncologic pathology severity [41].

Moreover, oxidative stress reflected by gingival crevicular fluid specific markers' values seem to be involved in the relationship between periodontal disease and diabetes [42-45].

Most studies which focused on systemic diseases and underlying mechanisms related to periodontal disease, such as inflammatory cascades and oxidative stress imbalance, are usually not based on causality, linking the conditions through bidirectional associations.

This would also be the case of chronic kidney diseases, where some authors have linked periodontal inflammation with increased systemic inflammatory mediators and oxidative stress factors [46].

In our study, gingival crevicular fluid SOD and 8-OHdG values proved to be the most powerful correlation factors, when evaluating the interdependence between cytokines and oxidative stress markers at a local level, in the gingival fluid. These two markers associate with inflammatory indicators evaluated in GCF, suggestive for a complex synergy between cytokine cascade and oxidative stress mechanisms.

There are clear limitations for our study that should be acknowledged, considering the relative narrow subject size and the inability to distinguish whether the observed changes and associations are primarily attributable to periodontal impairment or to hematological malignancy itself. The interplay between these conditions remains to be clarified and warrants further research in large scale approaches.

Additionally, although differences in oxidative imbalance and cytokine levels were identified in leukemia children, the investigation of the relationship between interleukins and oxidative stress markers was conducted on the entire study population, without differentiating between leukemia juvenile subjects and healthy controls.

Conclusions

The present study highlights the relationship between inflammatory and oxidative stress markers in children with hematologic malignancies, both at systemic and periodontal level.

Plasma findings suggest that MDA may represent a sensitive marker of the association between oxidative stress and inflammation, as it exhibited positive correlations with IL-1β, IL-17α, and TGF-β1, while GCF analyses evidenced 8-OHdG and SOD as oxidative stress markers most closely associated with inflammatory cytokines.

These results support the view that periodontal alterations in children with leukemia may reflect an intricate connection between immune dysregulation and oxidative stress.

However, the relatively small subject size may limit the strength of these conclusions, further larger studies being necessary for enforcing our findings.

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None to declare.

Author Contributions

Conceptualization, C.I.F. and A.E.A.; Methodology, C.I.F. and L.G.; Investigation, A.E.A., C.I.F., and L.G.; Data analysis, D.C. and A.D.C.; Manuscript writing and initial draft preparation, C.I.F., A.M.T., and E.O.C.; Manuscript review and editing, A.E.A. and L.G.; Supervision, D.C. All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare no competing interests.

Institutional Review Board

The study was conducted according to the guidelines of the Declaration of Helsinki; the study and the protocols utilized therein were approved by the Ethics Committee of the Grigore T. Popa University of Medicine and Pharmacy Iasi (approval no.477/16 September 2024) and the Ethical Committee of the "St. Mary" Clinical Emergency Hospital for Children in Iasi (approval no.34161/14 October 2024).

Consent Statement

All human subjects involved in this study provided a written informed consent prior to participation, including the consent of publishing their anonymized data.

Data availability

All data presented in the manuscript are available from the authors upon request.

References

1. Cammarata-Scalisi F, Girardi K, Strocchio L, Merli P, Bernardin AG, Galeotti A, Magliarditi F, Inserra A, Callea M. Oral Manifestations and Complications in Childhood Acute Myeloid Leukemia. Cancers, 2020, 12(6):1634.
2. Quispe RA, Aguiar EM, De Oliveira CT, Neves ACX, Santos PSDS. Oral manifestations of leukemia as part of early diagnosis. Hematology, Transfusion and Cell Therapy, 2022, 44(3):392-401.
3. Medara N, Lenzo JC, Walsh KA, Reynolds EC, Darby IB, O'Brien-Simpson NM. A review of T helper 17 cell-related cytokines in serum and saliva in periodontitis. Cytokine, 2021, 138:155340.
4. Patil RT, Dhadse PV, Salian SS, Punse SD. Role of Oxidative Stress in Periodontal Diseases. Cureus, 2024, 16(5):e60779.
5. Pirih FQ, Monajemzadeh S, Singh N, Sinacola RS, Shin JM, Chen T, Fenno JC, Kamarajan P, Rickard AH, Travan S, Paster BJ, Kapila Y. Association between metabolic syndrome and periodontitis: The role of lipids, inflammatory cytokines, altered host response, and the microbiome. Periodontology 2000, 2021, 87(1):50-75.
6. Omran TZ, Jasmi FSOA, Obaid KM, Ghareeb AKR, Alsailawi HA, Mudhafar M. The interleukin gene landscape: understanding its influence on inflammatory mechanisms in apical periodontitis. Mol Biol Rep, 2025, 52(1):365.
7. Beklen A, Ainola M, Hukkanen M, Gürgan C, Sorsa T, Konttinen YT. MMPs, IL-1, and TNF are Regulated by IL-17 in Periodontitis. J Dent Res, 2007, 86(4):347-51.
8. Martínez-García M, Hernández-Lemus E. Pro-Inflammatory and Anti-Inflammatory Interleukins in Periodontitis: Molecular Roles, Immune Crosstalk, and Therapeutic Perspectives. IJMS, 2025, 26(20):10094.
9. Liu Z, Liu Y, Song Y, Zhang X, Wang S, Wang Z. Systemic Oxidative Stress Biomarkers in Chronic Periodontitis: A Meta-Analysis. Disease Markers, 2014, 2014:1-10.
10. Valavanidis A, Vlachogianni T, Fiotakis C. 8-hydroxy-2′ -deoxyguanosine (8-OHdG): A Critical Biomarker of Oxidative Stress and Carcinogenesis. Journal of Environmental Science and Health, Part C, 2009, 27(2):120-39.
11. Stoica AM, Dako T, Monea MD, Beresescu L, Benedek C, Vlasa A, Stoica OE. The role of oxidative stress in periodontal disease: a narrative review and clinical perspectives. RJOR, 2025, 17(2):753-9.

12. Relvas M, Mendes-Frias A, Gonçalves M, Salazar F, López-Jarana P, Silvestre R, Viana Da Costa A. Salivary IL-1β, IL-6, and IL-10 Are Key Biomarkers of Periodontitis Severity. IJMS, 2024, 25(15):8401.
13. Chen S, Gao X, Song J. Oxidative stress-related biomarkers in chronic periodontitis patients with or without type 2 diabetes: A systematic review and meta-analysis. J of Periodontal Research, 2023, 58(4):780-90.
14. Lazar L, Popescu DM, Popa S, Gheorghe DN, Martu A, Rîca AM, Rauten AM. Inflammatory markers and oxidative stress in association with periodontal disease and systemic conditions. Rom J of Oral Rehab, 2021, 13(1):50-6.
15. Caloian CS, Șurlin P, Ciurea A, Pop D, Caloian B, Leucuța DC, Țigu AB, Rasperini G, Micu IC, Stanomir A, Soancă A, Roman A. Exploring Periodontal Conditions, Salivary Markers, and Systemic Inflammation in Patients with Cardiovascular Diseases. Biomedicines, 2024, 12(6):1341.
16. Tattar R, Da Costa BDC, Neves VCM. The interrelationship between periodontal disease and systemic health. Br Dent J, 2025, 239(2):103-8.
17. Shang J, Liu H, Zheng Y, Zhang Z. Role of oxidative stress in the relationship between periodontitis and systemic diseases. Front Physiol, 2023, 14:1210449.
18. Salman BN, Darvish S, Goriuc A, Mazloomzadeh S, Hossein Poor Tehrani M, Luchian I. Salivary Oxidative Stress Markers' Relation to Oral Diseases in Children and Adolescents. Antioxidants, 2021, 10(10):1540.
19. Guízar-Mendoza J, LÓpez-Ayuso C, Anguiano-Flores L, Fajardo-Araujo M, Amador-Licona N. Correlation between interleukin-1β and matrix metalloproteinase-1 levels in crevicular fluid with a proposed periodontal disease index in children. J Indian Soc Periodontol, 2018, 22(3):209-214.
20. Acar B, Cagdas D, Tan Ç, Özbek B, Yaz İ, Yıldırım YD, Özşin-Özler C, Karaatmaca B, Gür-Çetinkaya P, Soyak E, Karabulut E, Tezcan İ, Berker E. Evaluation of periodontal status and cytokine/chemokine profile of GCF in patients with severe congenital neutropenia. Odontology, 2021, 109(2):474-482.
21. Liu S, Hu B, Zhang J. Epidemiological characteristics and influencing factors of acute leukemia in children and adolescents and adults: a large population-based study. Hematology, 2024, 29(1):2327916.
22. Nakata K, Okawa S. Age-specific leukaemia incidence rates in children and adolescents in the world. Japanese Journal of Clinical Oncology, 2023, 53(2):184-185.
23. Al Shamahy HA. Prevalence of Different Types of Leukemia and Associated Factors among Children with Leukemia in Children's Cancer Units at Al-Kuwait Hospital, Sana'a City: A Cross-Sectional Study. GJPNC, 2021, 3(4).
24. Bachir F, Bennani S, Lahjouji A, Cherkaoui S, Harif M, Khattab M, Nassereddine I, Zafad S, El Aouad R. Characterization of Acute Lymphoblastic Leukemia Subtypes in Moroccan Children. International Journal of Pediatrics, 2009, 2009:1-7.
25. Al-Hashimi M. Incidence of Childhood Leukemia in Iraq, 2000-2019. Asian Pac J Cancer Prev, 2021, 22(11):3663-3670.
26. Williams LA, Richardson M, Marcotte EL, Poynter JN, Spector LG. Sex ratio among childhood cancers by single year of age. Pediatric Blood & Cancer, 2019, 66(6):e27620.
27. Namayandeh SM, Khazaei Z, Lari Najafi M, Goodarzi E, Moslem A. GLOBAL Leukemia in Children 0-14 Statistics 2018, Incidence and Mortality and Human Development Index (HDI): GLOBOCAN Sources and Methods. Asian Pac J Cancer Prev, 2020, 21(5):1487-1494.
28. González García H, Garrote Molpeceres R, Urbaneja Rodríguez E, Gutiérrez Meléndez P, Herráiz Cristóbal R, Pino Vázquez MA. Differences in incidence and survival to childhood cancer between rural and urban areas in Castilla y León, Spain (2003-2014): A Strobe-compliant study. Medicine, 2018, 97(41):e12797.
29. Onyije FM, Olsson A, Baaken D, Erdmann F, Stanulla M, Wollschläger D, Schüz J. Environmental Risk Factors for Childhood Acute Lymphoblastic Leukemia: An Umbrella Review. Cancers, 2022, 14(2):382.
30. Bastos Silveira B, Di Carvalho Melo L, Amorim Dos Santos J, Ferreira EB, Reis PED, De Luca Canto G, Acevedo AC, Massignan C, Guerra ENS. Oral manifestations in pediatric patients with leukemia. The Journal of the American Dental Association, 2024, 155(10):858-870.e30.
31. Cammarata-Scalisi F, Girardi K, Strocchio L, Merli P, Bernardin AG, Galeotti A, Magliarditi F, Inserra A, Callea M. Oral Manifestations and Complications in Childhood Acute Myeloid Leukemia. Cancers, 2020, 12(6):1634.
32. Pan W, Wang Q, Chen Q. The cytokine network involved in the host immune response to periodontitis. International Journal of Oral Science, 2019, 11(3):30.
33. Borges Jr. I, Moreira EAM, Filho DW, De Oliveira TB, Da Silva MBS, Fröde TS. Proinflammatory and Oxidative Stress Markers in Patients with Periodontal Disease. Mediators of Inflammation, 2007, 2007:1-5.
34. Hosseini S, Diegelmann J, Folwaczny M, Frasheri I, Wichelhaus A, Sabbagh H, Seidel C, Baumert U, Janjic Rankovic M. Investigation of Impact of Oxidative Stress on Human Periodontal Ligament Cells Exposed to Static Compression. IJMS, 2024, 25(24):13513.
35. Isola G, Santonocito S, Lupi SM, Polizzi A, Sclafani R, Patini R, Marchetti E. Periodontal Health and Disease in the Context of Systemic Diseases. Brzozowski T, editor. Mediators of Inflammation, 2023, 2023:1-19.
36. Malik A, Chawla S, Tauseef A, Sohail H, Ijaz F, Malik A, Rahman F, Muhammad G, Khakwani S. Association of Oxidative Stress and Production of Inflammatory Mediators Matrix Metalloproteinase-9 and Interleukin 6: Systemic Events in Radicular Cysts. Cureus, 2020, 12(4):e7822.
37. Kazan D, Baş B, Aksoy A, Atmaca E. The evaluation of oxidative stress and inflammation markers in serum and saliva of the patients with temporomandibular disorders. Turkish Journal of Medical Sciences, 2023, 53(6):1690-1696.

38. Kajihara R, Sakai H, Han Y, Amari K, Kawamoto M, Hakoyama Y, Nagashio S, Yamada S ichi, Sanjo H, Kurita H. Presence of periodontitis may synergistically contribute to cancer progression via Treg and IL-6. Sci Rep, 2022, 12(1):11584.
39. Díaz CM, Bullon B, Ruiz-Salmerón RJ, Fernández-Riejos P, Fernández-Palacín A, Battino M, Cordero MD, Quiles JL, Varela-López A, Bullón P. Molecular inflammation and oxidative stress are shared mechanisms involved in both myocardial infarction and periodontitis. J of Periodontal Research, 2020, 55(4):519-528.
40. Chen M, Cai W, Zhao S, Shi L, Chen Y, Li X, Sun X, Mao Y, He B, Hou Y, Zhou Y, Zhou Q, Ma J, Huang S. Oxidative stress-related biomarkers in saliva and gingival crevicular fluid associated with chronic periodontitis: A systematic review and meta-analysis. J Clinic Periodontology, 2019, 46(6):608-622.
41. Râmboiu S, Nicolae FM, Soancă A, Gheorghe DN, Popescu DM, Ungureanu BS, Mărgăritescu DN, Turcu-Știolica A, Boldeanu MV, Șurlin VM, Gheonea DI, Șurlin P. Periodontal status and inflammatory markers in gingival crevicular fluid of patients with periodontitis and colorectal cancer. Journal of Mind and Medical Sciences, 2023, 10(2):347-355.
42. Miki A, Ricordi C, Sakuma Y, Yamamoto T, Misawa R, Mita A, Molano RD, Vaziri ND, Pileggi A, Ichii H. Divergent antioxidant capacity of human islet cell subsets: A potential cause of beta-cell vulnerability in diabetes and islet transplantation. Fiorina P, editor. PLoS ONE, 2018, 13(5):e0196570.
43. Luong A, Tawfik AN, Islamoglu H, Gobriel HS, Ali N, Ansari P, Shah R, Hung T, Patel T, Henson B, Thankam F, Lewis J, Mintline M, Boehm T, Tumur Z, Seleem D. Periodontitis and diabetes mellitus co-morbidity: A molecular dialogue. Journal of Oral Biosciences, 2021, 63(4):360-369.
44. Olteanu M, Surlin P, Rauten AM, Popescu RM, Nițu M, Carmen GC, Caraivan O. Gingival inflammatory infiltrate analysis in patients with chronic periodontitis and diabetes mellitus, Rom J Morphol Embryol, 2011, 52(4):1311-1317.
45. Bogdan M, Tica I, Gheorghe DN, Silosi I, Solomon S, Martu I, Surlin P, Chiscop I, Budacu C. Effect of 0.2% Chlorhexidine's Use for Treatment of Localized Gingival Lesions in Patients with Type 2 Diabetes. Rev Chim, 2016, 67(12):2651-2653.
46. Li L, Zhang YL, Liu XY, Meng X, Zhao RQ, Ou LL, Li BZ, Xing T. Periodontitis Exacerbates and Promotes the Progression of Chronic Kidney Disease Through Oral Flora, Cytokines, and Oxidative Stress. Front Microbiol, 2021, 12:656372.

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