REVIEW OF THE CORRELATION BETWEEN SPECIFIC BIOMARKERS IN LEUKEMIA AND PERIODONTAL DISEASE IN CHILDREN

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ABSTRACT

Objectives: The purpose of this review was evaluating the literature regarding a possible correlation between biomarkers analyzed in children with leukemia and periodontal disease, with emphasis on the antioxidant activity and oxidative stress markers, observed also in leukemia and in periodontal disease. **Materials and method:** Articles from Medline database were evaluated, searched via PubMed using MeSH terms. **Results:** Since periodontal disease is a very common oral pathology in patients with leukemia, it is crucial to distinguish whether the modification of biochemical markers is caused by the alteration of immune general system, or the existent periodontal pathology. **Conclusions:** Regarding the significance of specific biomarkers seen in children with leukemia and periodontal disease, further studies are necessary to determine their interdependence and clinical relevance.

Key words: children, leukemia, periodontal disease, oxidative stress marker.

INTRODUCTION

Oxygen reactive species have gained more and more attention in literature, mainly because of their important role in the progression of inflammatory diseases (Mittal et al., 2014).

In the past years, numerous clinical and experimental studies have demonstrated the powerful association between periodontal disease and oxidative stress. Regarding the analysis of these biomarkers in children with periodontal disease, and especially in children with periodontal disease and leukemia, the literature is relatively poor. Further studies are necessary to evaluate the relationship between the presence and activity of said biomarkers and periodontal disease and leukemia.

MATERIALS AND METHOD

Articles from Medline database (via PubMed) were evaluated, using MeSH search terms: ”oxidative stress markers” and ”leukemia” and ”children” and ”periodontal disease”. Literature was evaluated also by searching printed studies, with the same examination criteria as for the electronical search.

RESULTS

Numerous circulating biomarkers can indicate a pathological state in leukemia. Malignancy is associated with an elevated oxidative stress and decreased antioxidant factors. Various biomarkers, such as hematological, hepatic or renal indicators, as well as oxidative stress factors, electrolytes and vitamins (C, E) can be investigated. In their study in 2015, Rasool et al. have shown the presence of an elevated oxidative stress level, decreased levels of enzymatic and non-enzymatic antioxidants in adult leukemia patients, reflecting a pathological condition and an altered cellular control.

Oxidative stress is one of the potential malignancy mechanisms, due to the mutations that free radicals seem to produce in the DNA, resulting in neoplastic alterations. On the other hand, paradoxically, a high antioxidant defensive activity may stop the elimination of mutant cells and increase the development of a neoplastic modification.

Immune salivary factors play a very important role in maintaining normal functions of the oral mucosa. Patients with leukemia in general, and those under chemotherapy in particular, often have salivary alterations and a tendency to develop inflammatory conditions of the oral mucosa. Alteration of the immunological homeostasis leads to the development of pathological lesions described as mucositis. Oral mucositis is a complex pathology, resulted from the interaction of antineoplastic agents with the epithelial cells, actions of the proinflammatory cytokines, oral microbiota, overlaying local trauma, unsatisfactory oral hygiene and poor immunological status (Pinto, 2006). Initially, mucositis is observed as an erythematous plaque, developing into an ulceration. Oral mucositis is associated with pain, which leads to eating difficulties and speech impairments, that can go to cachexia. Moreover, these lesions can be a gateway to opportunistic infections: fungal, bacterial or viral (Valera, 2014).

In order to evaluate biomarkers in various pathologies, including some serious conditions, saliva analysis is increasingly more used. Some comparative studies suggest that saliva analysis can be an alternative to blood analysis in the evaluation of specific biomarkers (Pels, 2015). Due to the non-invasive collecting method, saliva analysis may be easily used in children, or in patients that suffer not only from the primary condition, but also from leukemic complications (Khalaf, 2014).

In 2015, Pels evaluated the effects of immunological alteration on the gingival status of children with acute lymphoblastic leukemia (ALL). Results of the study have shown that an increase of salivary proinflammatory IL-2 cytokines in children with ALL during treatment may cause pathological gingival alterations.

A study in 2014 (Du et al.) has also shown the presence of significantly high levels of IL-1β, IL-6, IL-10 in children with acute lymphoblastic leukemia. Moreover, the authors reported decreased levels of IL-2, TNF-α and IL-4.

Saliva is the first defense line against free radicals mediated by oxidative stress. Hegde

et al. (2011) have discovered a decrease in salivary flow, salivary pH and global levels of salivary antioxidants, in children with leukemia comparative with healthy children. Their results suggest an alteration of oral status and gingival tissues, as well as an increased carious activity in children with leukemia, which implies the necessity of an interdisciplinary approach for the treatment of these patients.

In 2014, Wang et al. have emphasized the role of the immunological system in the homeostasis of oral status and structuring the oral microbiota, highlighted by salivary tests in healthy and leukemia children. They have discovered a structural imbalance, characterized by a reduced oral microbiota and an increased level of altered bacteria, which are involved in systemic infections.

Since periodontal disease is a very common oral pathology in patients with leukemia (Javed, 2012), it is crucial to distinguish whether the modification of biochemical markers is caused by the alteration of immunological system, or the preexistent periodontal pathology.

Numerous studies suggest that periodontal disease contributes to the local oxidative stress, and also to the systemic oxidative stress. Lipid peroxidation, protein and DNA alteration can be used as biological markers of oxidative stress associated with periodontal disease. Local and systemic activity of some antioxidant factors can, also, be influenced by periodontal disease.

In normal physiological conditions, there is a balance between oxidative activity and antioxidants. Oxidative stress appears only when antioxidant defensive systems cannot neutralize the increased production of oxidative factors (Sies, 1997).

Antioxidants are grouped in 2 main categories, by their method of action (Chapple, 2007): preventive antioxidant activity, like enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase and DNA repair enzymes, such as some metal ions sequestrants like albumin. The second antioxidant category is represented by cleaving antioxidants, like ascorbic acid (vit.C), carotenoids (including retinol – vit.A), uric acid, α-tocopherol (vit. E), reduced glutathione and polyphenols (flavonoids).

The activity of superoxide dismutase (SOD) and catalase (CAT) have been analysed in gingival tissues and were found to be more reduced in accordance to the depth of the periodontal pocket (Ellis et al., 1998).

Oxidative stress can be determined by measuring the decrease in total oxidative capacity or, more often, by estimating the alteration produced by lipid, protein and DNA oxidation. In 2016, Monisha et al. have shown that, in adults, we can evaluate periodontal disease by analyzing oxidative stress markers, considering the main causes of periodontal disease and increased oxidative capacity – smoking, diabetes and incorrect nutrition.

Periodontal disease is accompanied by high levels of lipid peroxidase and alteration of antioxidant status, alongside the depletion of antioxidant action of uric acid, reduced glutathione, vitamin C and α-tocopherol. Oxidative stress in periodontal disease, even if it is not an etiological factor, contributes to its aggravation. Oxidative stress markers are high in the saliva, but also in the blood (Nănescu, 2006).

MDA (malondialdehyde) is the most studied marker that indicates an increase of the oxidative stress (Monisha et al., 2016). Some studies have shown a significantly

increased activity of SOD (superoxide dismutase) in periodontal disease, which suggests a proportional increase with the intensity and progression of inflammation (Akalin et al., 2005).

In their study in 2006, Nănescu et al. suggest that it is improbable that oxidative process has a causal role in the etiology of periodontal disease, but it is likely to contribute to the disease progression. Crevicular fluid would add even more oxygen reactive species, determining a blind loop, which worsens the situation of the gingival status.

CONCLUSIONS

In periodontal disease, it has been shown that SOD (superoxide dismutase) and CAT (catalase) activity are more reduced, accompanied by an increase of oxidative stress, and a reduction of antioxidant capacity.

Also, it has been suggested that, although oxidative stress has no causal role in the etiology of periodontal disease, it probably contributes to the progression of the disease and the worsening of the gingival status.

Considering that there are studies in literature that confirm the association between some biochemical markers (salivary, hematological, hepatic or renal factors, as well as oxidative stress factors, electrolytes and vitamins) and periodontal disease and leukemia, but there are relatively few studies which follow this correlation in children with leukemia and periodontal disease, further studies are necessary to analyze the interdependency of these factors and their clinical relevance.

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