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REVIEW OF THE CORRELATION BETWEEN SALIVARY PROINFLAMMATORY CYTOKINES IN CHRONIC KIDNEY DISEASE AND PERIODONTAL DISEASE IN CHILDREN

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ABSTRACT

Objectives: The purpose of this review was to evaluate the literature on saliva analysis in diagnosing chronic kidney disease or periodontal disease, as well as to establish a possible correlation between biomarkers analyzed in children with chronic kidney disease (CKD) and periodontal disease (PD). Emphasis was placed on some proinflammatory cytokines (tumor necrosis factor (TNF-α) and interleukin 6 (IL-6)), found in both chronic kidney disease and periodontal disease.

Material and method: We evaluated articles from the MedLine database, researched via PubMed, using MeSH terms.

Results: Since periodontal disease is a common oral pathology in patients with chronic kidney disease, it is essential to distinguish whether the modification of salivary biochemical markers is caused by the alteration of the general immune system, or the existent periodontal pathology. Also, an alternative, non-invasive process to blood analysis in children would be extremely beneficial.

Conclusions: Saliva analysis is a simple, non-invasive diagnostic test, fast and easy to accept by the paediatric patient and which could be a substitute for serum or plasma in the diagnosis of CKD, but in terms of the correlation between specific biomarkers seen in children with chronic kidney disease and periodontal disease, further studies are necessary to determine their interdependence and clinical relevance.

Keywords: children, chronic kidney disease, periodontal disease, proinflammatory cytokines

INTRODUCTION

Chronic kidney disease is a major health problem worldwide, given the continuing increase in incidence and prevalence, as well as the great potential for progression to the terminal stage. According to KDOQI (Kidney Disease Outcome Quality Initiative), chronic kidney disease is characterized by impaired kidney structure and function for a minimum of 3 months and is divided into 5 stages, depending on the level of glomerular filtration rate (GFR) as follows: in stage I GFR does not change (≥ 90 ml / min / 1.73 m2), in stage II the GFR is slightly affected (60-89 ml / min / 1.73 m2), stage III is characterized by moderately affected GFR (30- 59 ml / min / 1.73 m2), in stage IV GFR is severely affected (15-29 ml / min / 1.73 m2), and stage V is that of renal failure in the terminal stage (GFR <15 ml / min / 1.73 m2) (Levey A.S. et al., 2003).

The estimated incidence of chronic renal

failure in children, for the congenital form and also for the acquired form, is about 10-12 cases in 1 million children, with a prevalence of about 39-56 million cases globally (Trivedi and Pang, 2003).

Approximately 90% of patients with chronic renal failure have reported concomitant oral manifestations due to the impaired immune response (Saini et al., 2010).

In 2006, a study performed to assess the immune response in patients with CKD reported a high level of proinflammatory cytokines such as IL 6 or TNF-α, especially in the final stages of the disease, respectively stages 4 and 5 (Goicoechea M. et al., 2006). Moreover, Bleyer A.J. et al. have shown that these inflammatory markers can act as toxins, and their level varies depending on the impaired renal function (Bleyer AJ. et al., 2004).

Concerning oral conditions caused by the altered immune balance, associated with changes in IL-6 and TNF-α, an important role is played by periodontal disease (PD) (Nibali L. et al., 2012). PD has a high prevalence in pediatric patients with CKD and is the result of the action of proinflammatory cytokines, oral microbiota, local trauma and unsatisfactory oral hygiene conditions (a common occurrence among these patients). Hamissi J. et al., in a study conducted in 2009, showed that the prevalence of periodontal disease increases with the degree of impairment of kidney disease (Hamissi J. et al., 2009)

Salivary analysis of IL-6 and TNF-α in the pediatric patient with CKD and periodontal disease can be considered a non-invasive, fast and easy to accept test, with a role in establishing the diagnosis and degree of renal and periodontal damage in order to apply appropriate therapeutic measures.

In the past years, numerous clinical and experimental studies have demonstrated the powerful association between periodontal disease and some proinflammatory cytokines. Regarding the analysis of these salivary biomarkers in children with periodontal disease and especially in children with periodontal disease and CKD, the literature is relatively poor. Further studies are necessary to evaluate the relationship between the presence and activity of salivary biomarkers and periodontal disease and chronic kidney disease.

MATERIAL AND METHOD

Articles from MedLine database (via PubMed) were evaluated, using MeSH search terms:): “proinflammatory cytokines” and “chronic kidney disease” and “children” and “periodontal disease”. Literature was also evaluated by searching printed studies, with the same examination criteria used for the electronical search.

RESULTS AND DISCUSSIONS

Chronic kidney disease is a progressive and irreversible condition characterized by a reduced kidney’s ability to filter, therefore causing uraemia (elevated levels of urea) expressed by an accumulation of substances in the blood, which must be filtrated and expelled by kidneys (Pallos D. et al., 2015). Uraemia provokes immunodeficiency due to the increase of toxic substances in the bloodstream, therefore patients with this disorder have suppressed humoral and immune responses.

Oral manifestations have a prognostic value and are determined by nitrogen retention (uric acid, creatinine), metabolic and hydroelectric disorders and chronic uremia syndrome, all of which are actually symptoms of CKD aggravation (Sociedade Brasileira de Nefrologia, 2013).

Immune salivary factors play a very

important role in maintaining normal functions of the oral mucosa. Patients with CKD in general, and those on hemodialysis in particular, often have salivary alterations and a tendency to develop inflammatory conditions of the oral mucosa.

Among the CKD-induced oral manifestations, disorders of the salivary flow have been reported, which in dialysis patients is manifested by a 25% reduction in salivary flow rate, xerostomia, alterations that can be explained by the fibrous changes in salivary acini and accumulation of lipid deposits in salivary tissues (Kao C.H. et al., 2000).

Dioguardi et al. (2015) have studied other symptoms in CKD patients: uremic fetor caused by high quantities of urea (especially in the uremic stage of the disease), taste alterations (a metallic, bitter taste), dry mouth sensation and rash (at food contact).

Children with CKD are frequently diagnosed in the dental office with gingivo-periodontal diseases like gingivitis, periodontitis, high calculus and plaque deposits, observed in the initial and also the late stages of the disease (Kim et al., 2017).

The results of a study which assessed the periodontal status in patients on dialysis treatment showed that 80% of patients had poor oral health, with a high degree of periodontal damage (Chen L.P. și colab., 2006).

In 2017, Slots, J. et al., showed that periodontal changes are manifested by alterations of the supporting tissues of the tooth, causing attachment loss, periodontal pockets and bone resorption, the appearance being characteristic to the evolutionary stage of the disease (Slots, J. et al. ., 2017).

In 2013, Di Benedetto A. et al. reported an increased prevalence of gram-negative organisms in PD. These gram-negative organisms produce endotoxins which are capable of invoking inflammatory and immune responses mediated by cytokines, chemokines, and other biomolecules (Di Benedetto, A. et al., 2013).

In 2011, Preshaw P. et al. conducted a study to identify proinflammatory cytokines with a role in regulating the immune response in PD. The results showed that IL 1-β, TNF-α, IL 6, along with other cytokines, play a key role in this mechanism (Preshaw P. et al., 2011).

Likewise, Lutfioglu M. et al., studying the relationship between CKD and PD, showed that hyperparathyroidism, a common complication of CKD, is associated with elevated levels of proinflammatory cytokines in gingival tissue (Lutfioglu M. et al., 2010).

Periodontal disease is the result of the interaction between the bacterial complex in the dental plaque and the host's immune response. The role of the immune response is a very important factor because it influences both the progression of the disease and its severity (Seymour G.J. et al., 1993).

Regarding the difficulty of determining the active form of periodontal disease by traditional diagnostic means such as the level of loss of periodontal attachment or the depth of periodontal pockets, periodontal biomarkers are used nowadays, namely proinflammatory cytokines that can guide the dentist in determining the degree of activity of the disease itself. (Gümüş P. et al., 2013).

Cytokines are soluble proteins that play an important role in the initiation and maintenance of inflammatory and immune response (Nibali L. et al., 2012). Some of the prior studies have found that inflammmatory cytokines such as IL-6 and TNF-α are elevated both in periodontal and end-stage CKD disease (Khozeymeh F. et al. 2016, Singh P. et al. 2016, Rodrigues R.P. et al.. 2019).

Tumour necrosis factor (TNF) is a pleiotropic molecule that plays an important role in inflammation, immune system development, apoptosis and lipid metabolism.

This proinflammatory cytokine, TNF-α, released by macrophages, with a substantial role in bone resorption by activation of the osteoclasts, can be detected in saliva and crevicular fluid, both in healthy patients and those with periodontal disease (Boyce BF et al., 2005). Increased values of TNF- α in periodontal disease are closely correlated with tissue destruction and host immune response, as well as the presence of systemic disease. (Teles R.P. et al., 2009),

IL-6 is another proinflammatory cytokine that can be identified in the oral cavity. It is produced by numerous cells in the periodontium in response to IL1-β and TNF-α secretion, playing a major role in the activity of immune cells and osteoclasts and the inlammatory response to bacterial plaque formation. (Preshaw P. et al., 2011, Irwin C. et al., 2008).

Increased IL-6 levels have been reported in some studies in patients with periodontal disease (Ebersole J. et al., 2012, Prakasam S. et al., 2013), but not in other studies such as those performed by Rathnayake, N. et al. in 2012 or Teles R. et al. in 2009.

Numerous studies have reported that certain systemic diseases, including chronic kidney disease, produce changes in detectable inflammatory biomarkers in saliva (Raimann J.G. et al. 2011, Goli S. et al., 2014).

Saliva is a biological fluid secreted by the salivary glands, that plays an important role in oral and systemic health. 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 (Renda R. et al., 2017).

Collection of blood for serum analysis is an invasive procedure, associated with fear and anxiety in pediatric patients. Frequently, blood sampling among CKD children results in severe anemia and an increased risk of infection (Kaushik A. et al., 2013), therefore a non-invasive, low-risk, inexpensive, easy-to-use diagnostic test that can accurately evaluate the disease status would be of tremendous value to children patients and clinicians. According to Schafer C.A. and co., saliva sampling is appropiate for all age groups and can be repeated more frequently. It also offers a cost–effective method for the screening of large populations (Schafer C.A. et al., 2014).

Fisher et al. demonstrated the existence of an interrelation between periodontal disease and CKD – meaning that each is a risk factor for the other (Fisher M.A. et al., 2011). However, few studies have evaluated the effect of periodontal disease treatment on inflammatory biomarkers (Wehmeyer M.M. et al., 2013, Dasanayake A.P. et al., 2009), so further studies are needed to assess the benefits of periodontal disease treatment in CKD patients. Wehmeyer M.M. et al. stated that in the complex interdisciplinary treatment of the child with CKD, close cooperation between the pedodontists and the pediatric nephrologists is necessary.

Ariyamuthu V.K. et al. claim that in the context of the altered immune system, in children with chronic renal failure, periodontal disease, ulcerative lesions, bacterial plaque and calculus can be gateways for microorganisms to enter the blood system. Therefore, early assessment of the oral status of children with CKD, diagnosis of periodontal disease and its treatment are essential to limit systemic inflammatory levels. (Ariyamuthu V.K. et al., 2013).

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

preexistant periodontal pathology.

Conclusions

Blood analysis is an invasive and painful procedure, especially for children, and an alternative process would be extremely beneficial. In this regard, the salivary analysis is a non-invasive test, fast and easy to accept by children patients.

The existence of a local or general pathology changes the salivary level of the analyzed biomarkers, so the salivary biomarkers TNF-α and IL 6 could be used as alternatives to plasma biomarkers in children with CKD and periodontal disease, to establish the diagnosis and assess the prognosis of the disease.

Considering that there are some studies in literature that demonstrate the association between CKD and PD, but there are few studies confirming the association between certain biochemical markers (TNF-α, IL-6) and periodontal disease, respectively some chronic kidney disease in adults and very few studies which follow this correlation in children with CKD and periodontal disease, further studies are necessary to analyze the interdependency of these factors and their clinical relevance.

Contributions:

All authors contributed equally to the development of this article.

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