S&S

Senses Sci 2019: 6 (1) 725-739
doi: 10.14616/sands- 2019-6-725739

Article

The association between periodontal disease and serum biomarkers levels in haemodialysis patients: a narrative review

Elisabetta Ferrara*, Roberta Grassi, Francesca Cesarano, Biagio Rapone, Gianna Maria Nardi

Affiliation: Department of Oral and Maxillo Facial Sciences, Dental School, University "La Sapienza" of Rome, Rome, Italy.

***Correspondence: Dr. Elisabetta Ferrara – E-mail: igieneeprevenzione@gmail.com**

Received: 28 February 2019; Accepted: 27 March 2019; Published: 31 March 2019

Abstract. The vast majority of studies has demonstrated that periodontal infection promotes significant systemic inflammatory status. The specific effects of these systemic alterations in response to periodontal inflammation have been comprehensively described and appear to be highly stereotyped, and it is well known the pathophysiological mechanism related to immune functioning linking periodontitis and pathologies such as diabetes or cardiovascular diseases, adverse pregnancy outcomes, and rheumatoid arthritis. More recently, it has been proposed that [illegible] mplications in [illegible] tory status in association to impaired nutritional status, emphasizing the role of periodontal infection in increase of C-reactive protein serum marker, a notably predictor of the cardiovascular risk. The aim of this narrative review was to summarize the currently literature evidence that has developed around the potential impact of periodontal inflammatory status on serum nutritional and inflammatory biomarkers concentration monitoring the severity of systemic conditions in HD patients, in which cardiovascular events and malnutrition are the most common causes of mortality and morbidity.

*Method*s**:** an electronic PubMed, Google Scholar and Cochrane database search complemented by a manual search of the bibliographies cited in all identified articles was performed between 2012 and 2019. The inclusion criteria were: all types of articles, articles published in PubMed, , Google Scholar and Cochrane and related only to humans. The exclusion criteria were: articles for which full text was not available, were not in English, or were grey literature. Keywords set: hemodialisys serum markers and periodontitis have been combined through the use of Mesh search. The terms then inserted in Pubmed were "serum markers", "hemodialisys", "periodontal disease" OR "periodontal infection" OR "periodontal inflammation".
Results: thirteen articles were identified. Studies currently available on the impact of periodontitis on the serum markers level in HD patients are analogous. Results confirmed the impact of subclinical inflammation related to periodontitis on C-reactive protein and albumin serum levels, supporting the emerging hypothesis of relationship between periodontal infection and HD status.
Conclusions: although many studies have suggested that the inflammatory cytokines release may play a key role in several clinical alterations related to HD maintenance, further studies are needed to investigate the long-term consequences of chronic inflammation caused by periodontitis. There is a paucity of data concerning to the impact of periodontal disease on maintenance hemodialysis patients and about mechanisms involved. Clinical trial and observational studies summarized here suggest but do not prove that persistent low level inflammation periodontitis-related are causing harm to hemodialysis maintenance.

Keywords: serum markers levels, periodontitis, periodontal inflammation, haemodialysis.

Introduction

How exposure to periodontal infection promotes general inflammation is an area of great interest and currently, investigation on the mechanistic link between periodontal inflammation and general diseases is the topic of intense research (1-2-3-4). This effort is encouraged by an amply literature about the link between inflammatory status periodontitis-induced and the risk of contribution for progression of severe pathologies such as diabetes or atherogenesis, adverse pregnancy outcomes, and rheumatoid arthritis. (5-6). It has been recognized the critical role of periodontitis in indirectly modulating immune response (7). The low-grade systemic inflammation supported and maintained by the worsened periodontal inflammation provides to the intensification of inflammatory signals from the periphery because of the perpetuate activating of the inflammatory cascade. According to the consensus report by the Joint European Federation of Periodontology (EFP) and American Academy of Periodontology (AAP) workshop, statistically significant additional risk was found for atherosclerotic cardiovascular disease in patients with periodontitis, independent of other co-morbidities (7-8). Specifically, it is now accepted that periodontitis is an independent risk factor that threatens the general immune system balance (9). Local periodontal stimuli and processes may transmit the inflammatory response to

other organs through two potentially mechanisms: (a) Direct migration and colonization of periodontal pathogens bacteria to distant organs eliciting an inflammatory reaction distant from the focus of infection (10); (b) establishment of systemic inflammation derived by metastatic periodontal inflammation or resulted by activated soluble inflammatory pathways by blood-borne periodontal bacteria (10-11).

There is strong evidence that chronic inflammation plays a significant role in determining the level of nutritional and inflammatory parameters and, specifically, of serum albumin, C-reactive protein, and other biomarkers in haemodialysis patients (12). High CRP level is a sign of inflammatory state and it is commonly associated to chronic disease, and is a relevant predicting factor of cardiovascular events and poor outcome (13). Hypoalbuminemia is associated with inflammatory burden in the body, liver disease, renal disease and malnutrition (14-15). Several evidences suggest that periodontal inflammation is associated to decrease of serum albumin levels but, concerning patients undergoing haemodialysis, there is paucity of knowledge regarding the potential relationship with nutritional status and involved mechanisms. In this brief narrative review the periodontal inflammation is presented as a potential amplifier factor of the serum biomarkers, such as CRP, albumin and other nutritional biomarkers, level alteration.

Recently, based on the existing evidence, it has been proposed that this conceptualization could be extended to onset of clinical complications in HD patients because chronic inflammation has been shown to exert biological activity on pathogenesis of haemodialysis-related alterations (16-17-18). Indeed, environmental factors that might play a critical role in the aetiology of atherosclerosis and malnutrition in these individuals include exposure to general inflammation (19). Periodontitis is related with local and systemic rise in inflammatory cytokines and acute phase proteins and there is a few evidence that periodontitis, considering all available evidence on the contribute of chronic inflammation as promoting factor for systemic inflammation, might compromise clinical outcomes in patients undergoing hemodialysis (20). Hemodialysis patients are more prone to develop inflammation. It is multifactorial and may derive from few sites and chronic stimuli. Many authors underlined that onset of the inflammatory response in end-stage renal disease (ESRD) is associated with an increase of serum acute-phase proteins, involving CRP and elevated activation and release in blood of pro-inflammatory cytokines such as IL-6 and TNF-α that may induce muscle breakdown and hypoalbuminemia and may be implicated in atherogenesis process (21).

Increased levels of inflammatory markers such as CRP and IL-6 are known predictors of cardiovascular outcomes in the general population as well as in the HD population (22), where they are also linked to malnutrition and the role of these serum markers on endothelial dysfunction has been largely examined. Several dialysis-related traditional risk factors, such as bioincompatibility (23) between blood and dialyzer, the presence of endotoxins in dialysis fluid and access-related infections are responsible for high serum CRP levels (24), and contribute to onset of clinical complications in HD patients, but current research suggest that a variety of non-traditional risk factors may play a significant role in alterations in their immune and host-defence system. Impaired nutritional status and cardiovascular complications in HD patients are two of the most common leading causes of mortality and morbidity in this population. Attention however has now diverged with greater understanding of immunogenic pathways,

regarding the role of inflammation in HD, which has been questioned and studied. Clinical repercussion of cytokines circulation has been emphasized by Henderson et al. which formulated the interleukin hypothesis (25).

Periodontal disease can be a source of inflammatory response and, as demonstrated by meta-analytical studies, inflammation plays a key mediating role in positive association between periodontal disease and cardiovascular disease. Available data of atheromasique plaque specimen study (26) with in vivo studies demonstrate the many facets of periodontal inflammation contribute to the aetiopathogenesis of endothelial dysfunction. The role of periodontal infection on nutritional status in HD patients has been questioned by means of clinical investigations evaluating the basic inflammation and nutritional status markers fluctuation in HD patients affected by periodontal disease (27). More recently, numerous studies highlighted also the responsibility of microinflammation on contributing to malnutrition by several ways, including decrease in albumin synthesis and protein catabolism leading to loss of lean body mass (28-29). Specifically, on the basis of evidence obtained from experimental and clinical studies, it appears that chronic inflammation may be implicated in protein energy malnutrition and contribute to progressive atherosclerosis in HD patients (30). Several papers highlighted the role of systemic inflammatory response as responsible of increased protein catabolism and decreased protein intake with consequent malnutrition status (31). Negative nitrogen balance, weight loss and anorexia are more prevalent in HD patients due to inflammation. Malnutrition might originate from inflammatory status (32) and these conditions could interrelate establishing a composite clinical status in which inflammation and malnutrition each other reciprocally (33). An interesting contribute to this line of reasoning is evidence demonstrating the association between malnutrition, increased levels of CRP and prevalence of cardiovascular events in patients undergoing hemodilaysis, suggesting the presence of the syndrome defined Malnutrition-Inflammation-Atherosclerosis (MIA), responsible of premature death in this population (33-34). Periodontitis it has been shown a potential key role in systemic inflammation in HD patients, because of the positive correlation between C-reactive protein levels (CRP) and immunoglobulin G of periodontal pathogens (35). This narrative review was aimed to summarize the currently literature evidence that has developed around the potential impact of periodontal inflammatory status on serum nutritional and inflammatory biomarkers concentration monitoring the severity of systemic conditions in HD patients, in which cardiovascular events and malnutrition are the most common causes of mortality and morbidity.

Methods

An electronic PubMed, Google Scholar and Cochrane database search was assessed between 2002 and 2019. From the articles identified in the first search, additional references were identified by a manual search among the cited references. The inclusion criteria were: all types of articles, articles published in PubMed, Google Scholar and Cochrane and related only to humans. The

exclusion criteria were: articles for which full text was not available, were not in English, or were grey literature. Keywords set: hemodialisys serum markers and periodontitis have been combined through the use of Mesh search. The terms then inserted in Pubmed were “serum markers”, “hemodialisys”, “periodontal disease” OR “periodontal infection” OR “periodontal inflammation”.

Results

Thirteen articles were identified. Studies currently available on the impact of periodontitis on the serum markers level in HD patients are analogous.

C-reactive protein (CRP), Albumin and other serum markers level in HD patients and Periodontal Disease

C-reactive protein is an acute-phase protein and established non-specific indicator of inflammation. CRP is currently considered a key biomarker of systemic inflammation (36). It reflects the production and release of pro-inflammatory cytokines, such as Interleukine-1 (IL-1), IL-6 and TNF-α (37-38). Its blood concentration increases from less than about 1μg/ml to as high as 600/1000 1μg/ml during the height of an acute phase response. CRP is synthesized primarily in the liver by hepatocytes in response to the pro-inflammatory cytokines. An elevated level of CRP is a well-established marker for cardiovascular events risk on general population and HD patients. Since CRP is produced in response to inflammatory stimuli, several studies have shown that their levels are increased in subjects with periodontal disease when compared with healthy control population. Meta-analyses and systematic reviews of the relationship of CRP to periodontitis have shown consistently higher CRP levels in patients than in controls and that non-surgical periodontal treatment had a positive effect on reduction of the serum levels of C-reactive protein (39-40). Periodontal infection is implicated in increase of C-reactive protein concentration, suggesting a potential role of periodontitis as independent factor in addition to the documented risks for cardiovascular events. On the basis of this conceptualization many authors have focused their research about the ability of PD to became source of systemic inflammation favoring progression of complications in patients undergoing HD.

Specifically, Yazdi et al (41) conducted a clinical study to analyze the impact of non-surgical periodontal treatment on serum CRP levels on patients with periodontitis on maintenance hemodialysis. Results of this study showed a significant reduction in serum concentration of CRP after periodontal treatment ($p < 0.001$). Margaret et al. (42) at New York University undertaken a study to investigate whether periodontal inflammatory status could be associated to increase of

C-reactive protein (>10 mg/L) concentration in HD patients. The serum profiles for levels of immunoglobulin g (IgG) antibody of 86 subjects were drawn. Results showed that higher levels of IgG antibody significantly associated to periodontal pathogens P(=0.02) were associated to enhanced inflammatory response expressed in higher CRP levels (P=0.013). Kadiroglu et al. (2006) performed a prospective clinical study on 41 HD patients demonstrating a significant positive correlation between CRP levels and Plaque Index (PI) (r=0.319; P=0.045) and Gingival Index (GI) (r=0.317; P=0.046) (43). Further, an observational study of 253 HD patients conducted in Taiwan suggested that poor periodontal status could be a sign of malnutrition as well as chronic systemic inflammation. The results of this study showed a negative correlation between periodontitis and serum albumin level (r=-0.291; P<0.01) and blood urea nitrogen level (r=-0.161; P<0.01), but it was positively correlated with high-sensitivity C-reactive protein (r=0.212; P<0.01) (44). Of interest, Naghsh N et al (45) also provided data indicating that periodontal inflammation may affect general conditions in HD patients. In their cross-sectional study the authors evaluated whether the periodontal disease could modulate the alteration of some nutritional status serum markers level on patients undergoing hemodialysis. The authors observed that the mean serum levels of albumin (P=0.02) and ferritin (P=0.043) were significantly lower in subjects with periodontitis compared with subjects with gingivitis. Further, they detected a significant correlation between CAL and serum level of Calcium (P=0.046), Creatinine (P=0.02), Cystatin C (P=0.013), and Phosphorus (P=0.037) in patients with periodontitis. Siribamrungwong M et al. reported a positive correlation between hs-CRP and periodontal disease severity. They also found the negative association between CRP and hemoglobin and albumin. Further, they observed decreased CRP levels after periodontal treatment (46). Rahamati et al. conducted a study on 86 patients undergoing hemodialysis to evaluate the impact of periodontal inflammation on serum concentration of CRP, assessing levels of immunoglobulin G (IgG) antibody to six periodontal species. They showed that elevated levels of CRP were associated with resulting high Log serum IgG antibody levels to Porphyromonas gingivalis (P 0.013) (47). Vilela et al also examined the effect of periodontal treatment in chronic kidney disease patients versus control patients group. The study design was an interventional, controlled, nonrandomized clinical trial in which the participants, all of whom had a diagnosis of periodontal disease was analyzed for the following blood parameters: C-reactive protein, interleukin-6, and prohepcidin. Each patient was subjected to non-surgical periodontal treatment. The efficacy of PT was indicated by the significant decreases in the levels of ultrasensitive C-reactive protein, interleukin-6 and serum prohepcidin levels in both groups (48). The cross-sectional study conducted by Kshirsagar was aimed to examine the association between sera levels of albumin and CRP and periodontitis. 154 individuals undergoing haemodialisys were recruited. A multiple linear regression analysis of all biochemical parameters was applied to determine the association. Results showed that periodontitis was significantly independently associated with alteration of sera biomarkers (49). Depending on the approach followed, a number of different biochemical parameters have been employed as indices of nutritional status and inflammation in HD patients such as

serum albumin, phosphorus, creatinine, transferrin, ferritin, iron, alkaline phosphatase, calcium, potassium and haemoglobin (50).

Several studies have demonstrated that serum albumin concentrations are associated with general health. The amount of albumin serum concentration is depending on many factors, such as the rate of hepatic synthesis and secretion, exchanges between intra- and extravascular compartments, lymphatic uptake, alterations of the volume of distribution and protein degradation rate, and body lasses (51). Inflammation and malnutrition both reduce albumin concentration by decreasing its rate of synthesis. Albumin is a trace negative serum protein produced by the liver, that decreases significantly in concentration in inflammatory conditions. It is a marker of malnutrition that is widely employed in several studies. Remarkably, it became recognized that serum albumin concentration is determined by inflammation through its association with C-reactive protein (CRP) (52).

The involvement of inflammation in plasma serum level decrease is strengthened by demonstrating the reduced synthesis of proteins and their increased catabolic rate (53). A series of available data indicate that periodontal inflammation exposure is positively associated to hypoalbuminemia. Periodontal disease, because of its chronicity could cause low-grade systemic inflammation and promote serum albumin levels decrease in these patients. Periodontal infection cause a marked activation of the immune system with the injection of the pro-inflammatory molecules, including cytokines such as tumor necrosis factor-α (TNF-α) and free radicals such as nitric oxide (54). In addition to significant inverse correlation between periodontal disease and serum levels of albumin, inflammation periodontitis-related it seems to interact with malnutrition status in HD patients (55). Kaur et al. (55) examining the effects of gingivitis and periodontitis on serum albumin concentration. This study was conducted on 60 patients, divided into two groups to distinguish healthy subjects and patients with periodontitis. Results showed a statistically association between serum albumin levels and Gingival Index ($P=0.002$) and Plaque Index ($P<0.001$) in patients with periodontitis compared to healthy subjects. Further, were emphasized a statistically highly significant differences between the serum albumin levels in two groups ($P < 0.001$). More recently, the association between periodontal status and serum calcium levels (sCa), phosphorus (sP), alkaline phosphatase (sAP), parathormone (PTH) have been also studied by Cholewa et al. Results of this study emphasized the previous highlighted negative correlation between serum albumin level and periodontal inflammation, and not significant correlation between phosphorus level and between calcium level and periodontal state was observed (56). Similarly, Rodrigues et al. (57) conducted a cross-sectional study, enrolling a total of 96 patients. They measured albumin, phosphorus, creatinine, transferrin, ferritin, iron, alkaline phosphatase, calcium, potassium and haemoglobin serum markers and executed periodontal clinical parameters examination, to evaluate if periodontitis could influence eventual changes of biomarkers. The prevalence rate of periodontitis registered was more of 50%. The authors revealed that there was significant linear relationship between periodontitis and albumin ($p=0.021$) and phosphorus ($p=0.024$) serum levels when compared to the group without periodontitis. The other biomarkers levels correlated positively with periodontitis, but showed no

significant correlation, were transferrin and haemoglobin. Despite these findings, in a randomized controlled trial of periodontal treatment effect on serum albumin levels and high-sensitivity IL-6 in patients receiving HD not benefits in these biomarkers concentration were observed in both groups (58). Patients were randomly assigned to the periodontal therapy group vs no treatment group. In contrast, results of Randomized Controlled Trial conducted by Wehmeyer et collegues (59) not showed evident impact of periodontal status on serum markers of inflammation in HD patients.

Moreover, periodontal treatment was not associated with a significant improvement in IL-6 pro-inflammatory mediator or in the concentration of serum albumin level, even after adjustment for potential confounding variables. Many investigations have used the serum albumin concentration and CRP as a markers of inflammatory activity and malnutrition status. A review of available data indicates that periodontal inflammation exposure is positively associated to hypoalbuminemia. Results confirmed the impact of subclinical inflammation related to periodontitis on C-reactive protein and albumin serum levels, supporting the emerging hypothesis of relationship between periodontal infection and HD inflammatory status (59-60).

Discussion

Periodontitis continues to mark very high indipendent risk for progression of several systemic disease and several clinical trials have revealed interesting findings about the association between periodontitis and inflammatory and nutritional serum biomarkers concentration in patients undergoing hemodialysis. The impact of periodontal inflammation on low-grade albuminuria has been amply investigated, especially in patients with kidney disease (61-62-63). A majority of clinical trials highlighted the positive effect of periodontal therapy on CRP and albumin levels as outcome measure after periodontal therapy, suggesting the potential role of microinflammation periodontitis-derivative on these biomarkers level. We have not randomized controlled trials on which to confirm this link, but clinical trials investigating the effectiveness of periodontal therapy on CRP and albumin serum levels indicate improvement of systemic conditions in HD patients (34-35). Periodontitis should be considering as a common and modifiable risk factor for systemic complications in patients undergoing hemodialysis. The mechanism linking periodontitis and systemic condition of HD individuals are complex and multifactorial (1-2-8-64). As discussed, it involves the critical impact on C-reactive protein and albumin dysregulation among others serum biomarkers concentration indicating nutritional and inflammatory status (65-66-67). The implications for research is that further understanding of the pathophysiological mechanisms supporting the impact of periodontal inflammation on HD general status is required so as to improve treatments (68-69-70). It would be interesting to see not only studies looking at underlying biological mechanisms but also clinical ones. Given the bidimensionality of these

conditions (71-72-73), it would be useful to clarify whether non-surgical periodontal treatment for HD can potentially contribute to improvement of HD systemic condition.

Conclusions

Periodontal disease is correlated with systemic inflammation (1-74-60-61). Literature data evolving to suggest the involvement of periodontal inflammation as contributing factor on decreased serum albumin level and CRP in haemodialysis patients (75-76-77). This potential mechanistic link might provide multiple interesting targets for new and multidisciplinary therapeutic interventions. Few reports suggested that control of local periodontal infection was associated with a decrease in levels of serum inflammatory markers in HD patients (78-79). In recent years, it has become evident that periodontal infection plays a pivotal role in various pathological systemic condition. Here we presented a short narrative review of the existing literature on the effect of periodontal inflammation on patients in hemodialisys maintenance (80-81-82). Depending on the approach followed, a number of different biochemical parameters have been employed as indices of nutritional status and inflammation in HD patients such as serum albumin, phosphorus, creatinine, transferrin, ferritin, iron, alkaline phosphatase, calcium, potassium and haemoglobin. Many investigations have used the serum albumin concentration and CRP as a markers of inflammatory activity and malnutrition status in HD population. Although the effects of PD on HD are mixed, we find that albumin levels are the most linked markers to PD , which supports the emerging hypothesis of correlation between periodontal inflammation on HD status. More longitudinal studies are also needed to evaluate the association of serum biomarkers levels with periodontitis in hemodialysis patients.

Conflict of interest

None

References

1. Manzon L et al. Oral health status of elderly people in Rome-Italy. Senses Sci 2014; 1 (4): 156-63 (https://sensesandsciences.com/index.php/Senses/article/view/122/114)
2. Dichicco A, Del Prete S, Putrino A et al. Identification of a research protocol to study orthodontic tooth movement. Senses Sci 2014; 1 (2): 44-50 (https://sensesandsciences.com/index.php/Senses/article/view/26/26)

3. Nardi GM, Sabatini S, F Guerra F, Tatullo M, L Ottolenghi L Tailored Brushing Method (TBM): An Innovative Simple Protocol to Improve the Oral Care. Journal of Biomedicine 2016; 1: 26-31. doi: 10.7150/jbm.16953
4. Bui FQ, Almeida-da-Silva CLC, Huynh B et al. Association between periodontal pathogens and systemic disease. Biomed J. 2019; 42(1):27–35.
5. Kim J, Amar S. Periodontal disease and systemic conditions: a bidirectional relationship. Odontology. 2006 Sep;94(1):10-21
6. Ide M, Linden GJ. Periodontitis, cardiovascular disease and pregnancy outcome–focal infection revisited? Br Dent J. 2014; 217:467–474
7. Iacopino A M and Cutler C W (2000), Pathophysiological Relationships Between Periodontitis and Systemic Disease: Recent Concepts Involving Serum Lipids. Journal of Periodontology, 2000; 71: 1375-1384.
8. Sanz M et al. Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International diabetes Federation and the European Federation of Periodontology Diabetes Research and Clinical Practice. 2018; (137):231-241. doi: 10.1016/j.diabres.2017.12.001. 137, 231–24
9. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105:1135–1143. doi.org/10.1161/hc0902.104353
10. Hayashi C, Gudino CV, Gibson FC, Genco CA. Review: Pathogen-induced inflammation at sites distant from oral infection: bacterial persistence and induction of cell-specific innate immune inflammatory pathways. Mol Oral Microbiol. 2010;25:305–316.
11. Schmitt A, Carra M C , Boutouyrie P, Bouchard P. Periodontitis and arterial stiffness: a systematic review and meta-analysis, Journal of Clinical Periodontology, 42, 11,(977-987), (2015).
12. Hirschfeld J, Kawai T. Oral inflammation and bacteremia: implications for chronic and acute systemic diseases involving major organs. Cardiovasc Hematol Disord Drug Targets. 2015;15:70–84.
13. Holtfreter B, Empen K, Gläser S, Lorbeer R, Völzke H, Ewert R, Kocher T, Dörr . Periodontitis is associated with endothelial dysfunction in a general population: a cross-sectional study.M PLoS One. 2013; 8(12)
14. Heidari B. C-reactive protein and other markers of inflammation in hemodialysis patients. Caspian J Intern Med. 2013;4(1):611–616.
15. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med. 2004;350(14): 1387–1397
16. Choi SR, Lee YK, Cho AJ, et al. Malnutrition, inflammation, progression of vascular calcification and survival: Inter-relationships in hemodialysis patients. PLoS One. 2019;14(5):e0216415.
17. Fernández, Javier et al. Effects of Albumin Treatment on Systemic and Portal Hemodynamics and Systemic Inflammation in Patients With Decompensated Cirrhosis Gastroenterology, Volume 0, Issue 0

18. Veisa G, Tasmoc Aì, Nistor I et al. The impact of periodontal disease on physical and psychological domains in long-term hemodialysis patients: a cross-sectional study, International Urology and Nephrology2017; 49(7):1261-1266. doi: 10.1007/s11255-017-1571-5
19. Tbahriti HF, Meknassi D, Moussaoui R, et al. Inflammatory status in chronic renal failure: The role of homocysteinemia and pro-inflammatory cytokines. World J Nephrol. 2013;2(2):31–37.
20. Fernández-Reyes MJ, Alvarez-Ude F, Sánchez R, Mon C, Iglesias P, Vázquez A. Nutritional status, comorbidity, and inflammation in hemodialysis. Nefrologia. 2000; 20(6):540-9.
21. Choi SR, Lee YK, Cho AJ, et al. Malnutrition, inflammation, progression of vascular calcification and survival: Inter-relationships in hemodialysis patients. PLoS One. 2019;14(5):e0216415.
22. Di Comite M, Crincoli V, Fatone L, Ballini A, Mori G, Rapone B, Boccaccio A, Pappalettere C, Grassi F.R., Favia A. Quantitative analysis of defects at the dentin-post space in endodontically treated teeth. Materials 2015;8,3268-3283. Published online 2015 Jun 4. doi: 10.3390/ma8063268.
23. Kalemaj Z, Scarano A, Valbonetti L, Rapone B, Grassi FR. Bone response to four dental implants with different surface topography: a histologic and histometric study in minipigs. Int J Periodontics Restorative Dent. 2016 Sep-Oct; 36(5):745-54. doi: 10.11607/prd.2719.
24. Rapone B, Nardi GM, Di Venere D, Pettini F, Grassi FR, Corsalini M. Oral hygiene in patients with oral cancer undergoing chemotherapy and/or radiotherapy after prosthesis rehabilitation: protocol proposal. Oral Implantology 2016 Dic ;9 (01 suppl): 90-97 doi: 10.11138/orl/2016.9.1S.090.
25. Corsalini M, Di Venere D, Rapone B, Stefanachi G, Laforgia A, Pettini F. Evidence of signs and symptoms of Craniomandibular Disorders in Fibromyalgia patients. The Open Dent Journal 2017; 11: 91–98. Published online 2017 Feb 14. doi: 10.2174/1874210601711010091.
26. Di Venere D, Pettini F, Nardi GM, Laforgia A, Stefanachi G, Notaro V, Rapone B, Grassi FR, Corsalini M. Correlation between parodontal indexes and orthodontic retainers: prospective study in a group of 16 patients. Oral Implantology 2017 Apr 10;10(1):78-86. doi: 10.11138/orl/2017.10.1.078. eCollection 2017 Jan-Mar.
27. Di Venere D, Nardi GM, Lacarbonara V, Laforgia A, Stefanachi G, Corsalini M, Grassi FR, Rapone B, Pettini F. Early mandibular canine-lateral incisor transposition: Case Report. Oral Implantology 2017 April; 10(2):181-189. doi: 10.11138/orl/2017.10.2.181.
28. Di Venere D, Corsalini M, Nardi GM, Laforgia A, Grassi FR, Rapone B, Pettini F. Obstructive site localization in patients with Obstructive Sleep Apnea Syndrome: a comparison between otolaryngologic data and cephalometric values. Oral Implantology 2017 Jul-Sep; 10(3): 295–310. Published online 2017 Nov 30. doi: 10.11138/orl/2017.10.3.295.
29. Grassi FR, Rapone B, Scarano Catanzaro F, Corsalini M, Kalemaj Z. Effectiveness of computer-assisted anesthetic delivery system (STA™) in dental implant surgery: a prospective study. Oral Implantology 2017; 10(4):381-389. ISSN:1974-5648. doi: 10.11138/orl/2017.10.4.381.
30. Notaro V, Rapone B, Cagnetta G, Sportelli P, Nardi GM, Corsalini M. Resonance frequency evaluation on immediate loading implants with angled abutments: case series. Annali di

Stomatologia 2018 May-August; 9(2): 91–96. doi: 10.11138/ads/2018.9.2.091.

31. Quaglia E, Moscufo L, Corsalini M, Coscia D, Sportelli P, Cantatore F, De Rinaldis C, Rapone B, Carossa M, Carossa S. Polyamide vs silk sutures in the healing of postextraction sockets: a split mouth study. Oral Implantology 2018 April-June; 11(2): 115-120. doi: 10.11138/orl/2018.11.2.115.
32. Nardi GM, Grassi R, Grassi FR, Aragona SE, Rapone B, Della Vella F, Sabatini S. Use of photobiomodulation induced by polarized polychromatic non-coherent light in the management of adult chronic periodontitis. J Biol Regul Homeost Agents. 2019 Jan 22;33(1).
33. Corsalini M, Di Venere D, Carossa M, Ripa M, Sportelli P, Cantatore F, De Rinaldis C, Di Santantonio G, Lenoci G, Barile G, Rapone B. Comparative clinical study between zirconium-ceramic and metal-ceramic fixed rehabilitations. Oral Implantology 2018 Jul-Sep; 11(3): 150–160. Published online 2019 Mar 16.
34. Corsalini M, Di Venere D, Sportelli P, Magazzino D, Ripa M, Cantatore F, Cagnetta C, De Rinaldis C, Montemurro N, De Giacomo A, Laforgia A, Rapone B. Evaluation of prosthetic quality and masticatory efficiency in patients with total removable prosthesis: study of 12 cases. Oral Implantology 2018 Oct-Dec; 11(4): 230–240. Published online 2019 Mar 26.
35. Corsalini M, Rapone B, Di Venere D, Petruzzi M. Removable prosthetic treatment in oral pemphigus vulgaris: Report of three cases. J Int Soc Prevent Communit Dent 2019. doi:10.4103/jispcd.JISPCD_421_18.
36. Deo V, Bhongade ML Pathogenesis of periodontitis: role of cytokines in host response. Dent Today. 2010; 29(9):60-62
37. Nascimento MM, Pecoits-Filho R, Lindholm B, Riella MC, Stenvinkel P: Inflammation, malnutrition and atherosclerosis in end-stage renal disease: A global perspective. Blood Purif. 2002; 20:454-458
38. Lazarus JM, Owen WF. Role of bioincompatibility in dialysis morbidity and mortality. Am J Kidney Dis. 1994; 24(6):1019-32.
39. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003;(111):1805–1812
40. Russa D, Pellegrino D, Montesanto A, et al. Oxidative Balance and Inflammation in Hemodialysis Patients: Biomarkers of Cardiovascular Risk?. Oxid Med Cell Longev. 2019; 8567275.
41. Haynes, W.G., Stanford, C. Periodontal disease and atherosclerosis (From dental to arterial plaque). Arterioscler Thromb Vasc Biol. 2003; 23:1309–131
42. Wrigge H, Zinserling J, Stüber F, Von Spiegel T, Hering R, Wetegrove S, Hoeft A, Putensen C. Effects of Mechanical Ventilation on Release of Cytokines into Systemic Circulation in Patients with Normal Pulmonary Function. *Anesthesiology* 2000;93(6):1413-1417.
43. Figuero E, Sánchez-Beltrán M, Cuesta-Frechoso S, Tejerina JM, del Castro JA, Gutiérrez JM, Herrera D, Sanz M.J Detection of periodontal bacteria in atheromatous plaque by nested polymerase chain reaction. Periodontol. 2011; 82(10):1469-77
44. Chen, Li-Ping et al Does Periodontitis Reflect Inflammation and Malnutrition Status in Hemodialysis Patients? American Journal of Kidney Diseases. 2006; 47 (5): 815 - 822

45. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD: Malnutrition-inflammation complex syndrome in dialysis patients: Causes and consequences. Am J Kidney Dis. 2003; 42:864-881
46. Kalantar-Zadeh K, Kopple JD, Humphreys MH, Block G: Comparing outcome predictability of markers of malnutrition-inflammation complex syndrome in haemodialysis patients. Nephrol Dial Transplant 2004; 19:1507-1519
47. Kaysen, George A. et al. Inflammation and reduced albumin synthesis associated with stable decline in serum albumin in hemodialysis patients. Kidney International. 2004; 65(4):1408-15
48. Kadiroglu A, K, Kadiroglu E, T, Sit D, Dag A, Yilmaz M, E: Periodontitis Is an Important and Occult Source of Inflammation in Hemodialysis Patients. Blood Purif 2006;24:400-404.
49. Naghsh N, Sabet NK, Vahidi F, Mogharehabed A, Yaghini J. Relationship Between Periodontal Disease and Serum Factors in Patients Undergoing Hemodialysis. Open Dent J. 2017;11:701–709.
50. Pecoits-Filho R, Lindholm B, Stenvinkel P, The malnutrition, inflammation, and atherosclerosis (MIA) syndrome – the heart of the matter, *Nephrology Dialysis Transplantation*,2002,17; 28–31
51. Stenvinkel P, Chung SH, Heimburger O, Lindholm B. Malnutrition, inflammation, and atherosclerosis in peritoneal dialysis patients. Perit Dial Int. 2001;21 (3):157–162.
52. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. Am J Kidney Dis. 2003;42:864-81.
53. Demmer RT, Trinquart L, Zuk A, Fu BC, Blomkvist J, Michalowicz BS, Ravaud P, Desvarieux M. The influence of anti-infective periodontal treatment on C-reactive protein: a systematic review and meta-analysis of randomized controlled trials. PLoS One. 2013; 8(10)
54. Gonzalez-Jaramillo V, Portilla-Fernandez E, Glisic M, et al. Epigenetics and Inflammatory Markers: A Systematic Review of the Current Evidence. Int J Inflam. 2019; 6273680.
55. Black S, Kushner I, Samols D. C-reactive protein. *The Journal of Biological Chemistry*. 2004;279(47):48487–48490. doi: 10.1074/jbc.R400025200
56. Arnaud C, Burger F, Steffens S, et al. Statins reduce interleukin-6-induced C-reactive protein in human hepatocytes: new evidence for direct antiinflammatory effects of statins. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2005;25(6):1231–1236.
57. Escobar GF, Abdalla DR, Beghini M, et al. Levels of Pro and Anti-inflammatory Citokynes and C-Reactive Protein in Patients with Chronic Periodontitis Submitted to Nonsurgical Periodontal Treatment. Asian Pac J Cancer Prev. 2013 ;19(7):1927–1933.
58. Lalla E, Kaplan S, Yang J, et al. Effects of periodontal therapy on serum C-reactive protein, sE-selectin, and tumor necrosis factor-alpha secretion by peripheral blood-derived macrophages in diabetes. A pilot study. J Periodontal Res. 2007;42:274–82
59. Yazdi F K, Karimi N, Rasouli M, Roozbeh J . Effect of Nonsurgical Periodontal Treatment on C-Reactive Protein Levels in Maintenance Hemodialysis Patients, Renal Failure. 2013; 35:5, 711-717

60. Snaedal, Sunna et al. Comorbidity and Acute Clinical Events as Determinants of C-Reactive Protein Variation in Hemodialysis Patients: Implications for Patient Survival American Journal of Kidney Diseases. 2009 ;53(6):1024-33. doi: 10.1053/j.ajkd.2009.02.008
61. Kadiroglu A, K, Kadiroglu E, T, Sit D, Dag A, Yilmaz M, E: Periodontitis Is an Important and Occult Source of Inflammation in Hemodialysis Patients. Blood Purif 2006;24:400-404.
62. Chen, Li-Ping et al. Does Periodontitis Reflect Inflammation and Malnutrition Status in Hemodialysis Patients? American Journal of Kidney Diseases. 2006; 47(5):815-22.
63. Naghsh N, Sabet NK, Vahidi F, Mogharehabed A, Yaghini J. Relationship Between Periodontal Disease and Serum Factors in Patients Undergoing Hemodialysis. Open Dent J. 2017;11:701–709.
64. Siribamrungwong M, Kutchaporn P. Treatment of Periodontal Diseases Reduces Chronic Systemic Inflammation in Maintenance Hemodialysis Patients. Renal Failure 2012; 34:2,171-175
65. Rahmati, Margaret A. et al. Serum markers of periodontal disease status and inflammation in hemodialysis patients. American Journal of Kidney Diseases, Volume 40, Issue 5, 983 – 989
66. Vilela EM, Bastos JA, Fernandes N, Ferreira AP, Chaoubah A, Bastos MG. Treatment of chronic periodontitis decreases serum prohepcidin levels in patients with chronic kidney disease. Clinics (Sao Paulo). 2011;66(4):657–662.
67. Kshirsagar A. V et al. Severe Periodontitis Is Associated with Low Serum Albumin among Patients on Maintenance Hemodialysis Therapy CJASN 2007, 2 (2) 239-244
68. Ogawa H, Yoshihara A, Amarasena N, Hirotomi T, Miyazaki H.J Association between serum albumin and periodontal disease in community-dwelling elderly. Clin Periodontol. 2006; 33(5):312-6.
69. Infusino I, Braga F, Mozzi R, Valente C, Panteghini M. Is the accuracy of serum albumin measurements suitable for clinical application of the test? Clin Chim Acta 2011;412:791–2.
70. Wu MT, He SY, Chen SL, et al. Clinical and prognostic implications of pretreatment albumin to C-reactive protein ratio in patients with hepatocellular carcinoma. BMC Cancer. 2019;19(1):538.
71. De Mutsert R, Grootendorst DC, Indemans F, Boeschoten EW, Krediet RT, Dekker FW,Association between serum albumin and mortality in dialysis patients is partly explained by inflammation, and not by malnutrition.Netherlands Cooperative Study on the Adequacy of Dialysis-II Study Group..J Ren Nutr. 2009; 19(2):127-35
72. Zekeridou A, Mombelli A, Cancela J, Courvoisier D, Giannopoulou C. Systemic inflammatory burden and local inflammation in periodontitis: What is the link between inflammatory biomarkers in serum and gingival crevicular fluid?. Clin Exp Dent Res. 2019;5(2):128–135.
73. Kaur N, Kaur N, Sarangal V.A study to evaluate the correlation of serum albumin levels with chronic periodontitis. Indian J Dent Res. 2015;;26(1):11-4.
74. Cholewa M, Madziarska K, Radwan-Oczko M. The association between periodontal conditions, inflammation, nutritional status and calcium-phosphate metabolism disorders in hemodialysis patients. J Appl Oral Sci. 2018;26 doi.org/10.1590/1678-7757-2017-0495

75. Rodrigues, VP, Libério, SA, Lopes, FF, Thomaz, EBFA, Guerra, RNM, Gomes-Filho, IS, Pereira, ALA. Periodontal status and serum biomarkers levels in haemodialysis patients. J Clin Periodontol 2014; 41:862– 868.
76. Freitas CO, Gomes-Filho IS, Naves RC, et al. Influence of periodontal therapy on C-reactive protein level: a systematic review and meta-analysis. J Appl Oral Sci. 2012;20(1):1–8.
77. Menon V, Wang X, Greene T, Beck GJ, Kusek JW, Marcovina SM, et al. Relationship between C-reactive protein, albumin, and cardiovascular disease in patients with chronic kidney disease. Am J Kidney Dis. 2003;42(1):44–52
78. Wehmeyer MM, Kshirsagar AV, Barros SP, et al. A randomized controlled trial of intensive periodontal therapy on metabolic and inflammatory markers in patients With ESRD: results of an exploratory study. Am J Kidney Dis. 2012;61(3):450–458.
79. Schroder J, Mygind ND, Frestad D, et al. Pro-inflammatory biomarkers in women with non-obstructive angina pectoris and coronary microvascular dysfunction. Int J Cardiol Heart Vasc. 2019;24:100370.
80. Shimada Y, Komatsu Y, Ikezawa-Suzuki I, Tai H, Sugita N, Yoshie H.J The effect of periodontal treatment on serum leptin, interleukin-6, and C-reactive protein. Periodontol. 2010; 81(8):1118-23
81. Proctor R, Kumar N, Stein A, Moles D, Porter S. Oral and dental aspects of chronic renal failure. J Dent Res. 2005;84(3):199–208
82. Strippoli GF, Palmer SC, Ruospo M, et al. Oral disease in adults treated with hemodialysis: prevalence, predictors, and association with mortality and adverse cardiovascular events: the rationale and design of the ORAL Diseases in hemodialysis (ORAL-D) study, a prospective, multinational, longitudinal, observational, cohort study. BMC Nephrol. 2013;14:90.