Periodontitis and bone metabolism

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Summary

Periodontitis is a plaque induced disease characterized by tissue destruction. The extent of the alveolar bone loss depends on the host response stimulated by bacterial infection. Recently researchers have focused on the role of the immune system, of RANK/RANKL/OPG pathway and of cytokines network. Another recent field of interest is osteoimmunology that try to explain the relationship between immune and bone cells in activating bone resorption. Advances in the understanding of the pathogenic mechanisms allowed a better understanding of the relationship with other diseases like osteoporosis and also to hypothesize new therapies based on modulation of host response (host modulatory therapy - HMT). The purpose of this mini-review is to briefly discuss these topics.

KEY WORDS: periodontitis; alveolar bone; osteoporosis; osteoimmunology.

Background

Periodontitis is defined by the American Academy of Periodontology (AAP) as "Inflammation of the supporting tissues of the teeth. Usually a progressively destructive change leading to loss of bone and periodontal ligament. An extension of inflammation from gingiva into the adjacent bone and ligament" (1). The disease is an opportunistic infection associated to plaque on soft (gingiva) and hard (tooth) tissue (2-4). Plaque is an organized mass, consisting mainly of microorganisms that adheres to teeth, prostheses and oral surfaces (1). The subgingival bacterial plaque is necessary, but not sufficient to develop the disease. In fact, if on the one hand we find the infection determined by the plaque on the other we find the host defense. The latter will be determined by modifiable or not-modifiable (genetic) risk factors (5-10).

The role of the immune system: T cells

In the past, for many years, Authors analyzed the role of bacterial plaque. Today, since it was introduced the concept of "Osteoimmunology", the Authors have focused on the signaling between cells of the immune system and cells of the bone (11, 12).
The early stages of infection activate the non-specific immune defenses. These include mechanical barriers and initial inflammatory response. Later, lymphocytes T and lymphocytes B are activated when bacteria invade the tissues or when macrophages and other cells (APCs) present the antigen. Recently, researchers are considering T cells as regulators of bone turnover, not only in the case of periodontal disease but also in other diseases (13). In fact T cells activates the macrophages, can activate indirectly the osteoclasts and their precursors and also directly expressing RANKL (14). Brunetti et al. demonstrate that the samples of lymphocytes T from patients affected by periodontitis show over-expression of RANKL and TNF-alfa compared to healthy controls (13). The role of RANKL and TNF-alfa in activating osteoclasts is demonstrated also for other diseases like osteoporosis and rheumatoid arthritis (15).
The T cells can be activated also by the toll like receptors (TLRs), which bind bacterial structures. The heterodimers TLR2/TLR6 and TLR2/TLR1 determine mandibular bone resorption mediated by PGE2 in periodontal disease (16, 17). Moreover activated TLRs start an intracellular cascade that leads to the production of cytokines involved directly or indirectly in osteoclasts activation (18).
It is know that T cells produce "pro-resorptive" cytokines (IL-1, IL-6, IL-11) when properly stimulated. Cytokines act in a network with the cells, however the relationship with clinical manifestations of periodontal diseases is not clear (19, 20). During the last years researchers have focused on Th-17, a subpopulation of lymphocytes T characterized by the production of IL-17. This cytokine seems to be strongly correlated to tissue destruction (21).
These recent findings suggest a primary role of the immune system in alveolar bone resorption due to periodontal disease.

RANK/RANKL/OPG pathway in periodontal disease

The current knowledge suggest that RANK/RANKL/OPG pathway seems to be the bottle-knee, of metabolic ways of inflammation, to activate bone resorption in patients affected by periodontal disease (22, 23); RANKL activates bone resorption, while OPG has inhibition functions. Different Au-

thors have investigated RANKL/OPG ratio in periodontitis. Some studies have demonstrated a RANKL/OPG ratio augmented in serum/plasma of patients affected by periodontitis reporting low level of OPG (24-26). Cochran in a review of literature has found that RANKL/OPG ratio is augmented in saliva and gingival crevicular fluid (GCF) of patients affected by periodontitis compared with healthy controls, however there is heterogeneity between selected studies (20). In another review Belibasakis and Bostanci have reported increased RANKL/OPG ratio underlining that RANKL is up-regulated, whereas OPG is down-regulated in periodontitis compared to healthy control, that the ratio is further up-regulated in smokers and diabetics, and that is not affected by conventional periodontal treatment (27). Nowadays there are not sufficient data to correlate RANKL/OPG ratio in biofluids (saliva, GCF, serum/plasma) to clinical expression of periodontitis, so the RANKL/OPG ratio cannot be considered a valid marker of pathology.

Periodontitis and osteoporosis

For patients suffering form of aggressive periodontitis or for patients not responding to classical therapy is recommended a deep clinical investigation. Considering the age of the patients, we search for other diseases that can be linked to periodontitis; one of these diseases is the osteoporosis (Figure 1). In literature we can find numerous studies and also some systematic reviews which analyze the relationship between osteoporosis and periodontitis. Groen in the late '60 was the first Author to propose the association (28).
Considering the common risk factors like age, genetics, smoke, alcohol, diabetes, and that, despite different etiology, the diseases have a common final step which is bone resorption, researchers developed two hypothesis. An hypothesis suggests that osteoporosis can accelerate alveolar bone resorption in case of periodontitis. Vice versa the other hypothesis suggests that infections by parodontopathogens can promote directly and indirectly an inflammatory systemic status, which activates the osteoclast cells (29-31).

Data retrieved from literature are about three areas of interests:
- clinical parameters of periodontitis (PD, CAL) and diagnosis of osteoporosis;
- systemic and alveolar bone mineral density;
- effects of the osteoporosis medications on periodontitis and vice versa.

In a recent review Guglia et al. (32) searched for studies relating systemic BMD to clinical parameters of periodontitis (pocket depth, clinical attachment level, alveolar bone height and teeth loss). The included studies report conflicting results, however different Authors suggest a positive relationship between the diseases. The results of this review are difficult to analyze because of methodological variability, small samples and different parameters of diagnosis for periodontitis. Considering different parameters of diagnosis, Passos et al. (33) showed that in the same group of patients the prevalence of periodontitis ranged from 24 to 98,6%.
In literature there are different index of bone mandibular density measured on routine dental radiography proposed by researchers. Independently by the method used almost all studies found an association between mandibular bone density and systemic bone density measured at spine or femur (32, 34). Therefore it is possible for dentists to do screening of osteoporosis on the basis of routine dental radiography.
Although there are many drugs to treat osteoporosis, the effects of osteoporosis medications on periodontal disease are the least investigate. The hormone replacement therapy (HRT) seems to reduce the number of teeth lost due to periodontitis, to improve mandibular bone density and reduce gingival bleeding (35, 36). The administration of teriparatide in an animal model of periodontitis reduces the alveolar bone resorption, however augments the prevalence of osteosarcoma (37-39). Two RCTs on human demonstrate that patient affected by periodontitis and treated with periodontal therapy and administration of alendronate (10mg/die for 6 months)

Age <20 years	Age 20-40 years	Age >45 years
- Diabetes	- **Diabetes**	- **Diabetes**
- Leukemia	- HIV/AIDS	- HIV/AIDS
- Neutropenia	- Pregnancy	- Pregnancy
- Down Syndrome	- Drugs	- Drugs
- Kindler Syndrome	- **Hyperthyroidism**	- **Hyperthyroidism**
- Papillon-Lefevre Syndrome	- **Hyperparathyroidism**	- **Hyperparathyroidism**
	- Bruxism	- Bruxism
		- **Osteoporosis**
		- **Liver disease**

Figure 1 - Diseases that can promote periodontitis.

suffer less alveolar bone resorption compared to patients treated with only periodontal therapy (34, 39). These data are few to draw any conclusions.

Future treatments

The treatment of periodontitis widely accepted is based on:
- infection control obtained removing supragingival and subgingival plaque (scaling, root planing or debridement);
- instructions for oral hygiene at home;
- interventions on modifiable risk factors.

Recently, considering the better understanding of the role of immune system and of the RANK/RANKL/OPG pathway, is emerged the modern concept of Host modulatory therapy (HMT). The HMTs aims to reduce the tissue destruction and to inhibit over-expression of inflammatory response (40, 41).
The HMT offers local or systemic possibilities (42):
- Systemic administered:
  - agents acting against MMPs (sub-antimicrobical administration of doxicicline, 20mg/die for 180 days as approved by FDA);
  - tetracycline analogues;
  - agents acting against arachidonic acid metabolites (NSAIDs);
  - lipid inflammatory mediators as target for HMT (resolvine, protectine, maresine);
  - agents acting on cytokines;
  - agents acting against bone resorption (bisphosphonate, OPG);
  - modulation of nitric oxide synthase (resveratrol);
  - probiotics, periodontal vaccines, nutrients.
- Local administered: enamel matrix proteins; PDGF; local bisphosphonate; local NSAIDs; hypochlorous acid and taurine-N-Monochloramine; Cimetidine.

Different Authors reported that the administration of OPG in an animal model of periodontitis is protective for alveolar bone resorption (43, 44). HMTs seem to offer the potential to move periodontal treatment to a higher level, however data are few and inconsistent.

Conclusion

Periodontal disease is characterized by the destruction of the supporting tissues of the tooth. The mechanisms that lead to bone resorption are similar to those of other diseases such as osteoporosis. Despite recent acquisitions regarding the role of the immune system, the cytokine network and RANK/RANKL/OPG pathway, we need further studies to better explain bone resorption mechanisms.
Most of the Authors suggest a correlation between osteoporosis and periodontal disease but the clinical relationship still has not been well demonstrated, however dentist can screen the osteoporosis on routine dental radiography.
The HMTs seem to be promising to stabilize and improve the results of classical periodontal therapy.

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