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Special Issue on Periodontal Diseases

CONTENTS

Periodontal disease and systemic diseases: an overview on recent progresses.

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Periodontal diseases (PDs) affect about half of the adult population all over the world. PDs are caused by bacterial infection which induces an inflammatory response with progressive destruction of the periodontal tissues and finally the loss of teeth. Tobacco smoking (TS), alcohol consumption, and systemic diseases (SDs), are considered additional risk factors. This short review examines the potential causal association between PDs, TS and SDs. There is strong evidence that PDs are associated with an increased risk of SDs. In addition, many patients with SDs are also affected by PD, which can be mild or severe, and tobacco smokers manifest a greater risk of developing PDs. This paper includes many randomized controlled trials and reviews to test the effects of different periodontal therapies for patients with SDs.

For decades doctors and dentists have focused their attention on their respective fields of action. However, recent studies have strongly suggested that oral health may be indicative of systemic health. Currently, this gap between medicine and dentistry is rapidly shrinking, as there are many data supporting the idea of a close association between periodontal diseases (PDs) and systemic conditions, such as cardiovascular disease, diabetes, respiratory diseases, adverse reactions in pregnancy, osteoporosis, and tobacco smoking (TS). There is therefore reason to hope that the strong evidence of these studies could lead to significant improvements in the treatment of periodontal infections as well as an improvement of systemic conditions. For this reason, researchers must continue not only to discover more information on the correlation between PDs and systemic diseases (SDs), PDs and TS, but also focus their attention on the positive associations that may arise from the treatment of the oral cavity as a way to increase the healing of SDs.

The term 'periodontal diseases' (PDs) is generally used to describe diseases affecting the gums and tooth support tissues, causing damage to the connective tissue and alveolar bone (1). PDs are caused by specific bacteria of the biofilm formed by plaque. The bacteria leak into the periodontal ligament space, causing anaerobic infection and creating a cascade of events, which end with the production of inflammatory mediators and bacterial metabolites (2). At least two potential metabolic pathways could develop from the periodontal pocket which could lead to a localized infectious-inflammatory disease involving other organs. The first step is the passage of periodontal pathogens and their products through the ulcerated epithelium into the bloodstream, leading to bacteremia and/or causing a systemic immune response. The second step is the passage of inflammatory mediators from the periodontal pocket into the bloodstream (2). The pathological mechanisms by which PDs may contribute to the pathogenesis of systemic inflammatory diseases are currently the topic of intensive research.

Thousands of different kinds of bacteria and various viruses are associated with the composition of the plaque and are involved in the etiopathogenesis of PD. The most frequently identified include three

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species called "red complex": *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola* (3). The aim of this study is to explore the relationship between PDs, SDs - cardiovascular disease, diabetes and respiratory diseases - and TS.

Periodontal disease and cardiovascular disease

Cardiovascular disease (CVD) is a common cause of death, representing 29% of the mortality worldwide. Statistics for 2006 estimated that CVD is one of the world's main causes of death, with 17.1 million deaths per year. More than 70 million Americans have been diagnosed with various forms of CVD, including high blood pressure, coronary artery disease (acute myocardial infarction and angina pectoris), disorders of peripheral arteries etc. The main cause of these CVD is atherosclerosis, which is responsible for 50% of deaths in the United States, in Europe and in Japan (4).

After eliminating other risk factors, some studies indicate that severe PDs is associated with an increased risk of CVD ranging from 25% to 90%; 8.91% of patients with CVD are also affected by PDs, which can be mild or severe, while 66% of subjects who have CVD also manifest PD (5). This data must be explained also by the fact that CVD and PDs share similar risk factors such as smoking, diabetes mellitus, obesity and hypertension (6). In literature some studies demonstrated a mild-moderate association between CVD and PDs (7-13).

A recent randomized controlled trial concluded that the use of Triclosan-toothpaste has influence on biomarkers of cardiovascular risk. This study suggested that triclosan-toothpaste may influence some inflammatory biomarkers of CVD. However, it is unclear whether this influence is clinically significant. The reason why PD therapy could modify CVD management is still unknown (14).

On the contrary, a recent study found very little evidence to support or refute whether periodontal therapy can prevent long-term recurrence of CVD in patients with chronic periodontitis. No evidence on primary prevention was found (15-16).

Diabetes mellitus and periodontal disease

The direct correlation between diabetes mellitus (DM) and PDs is supported by different etiopathogenetic mechanisms. Patients suffering from DM have an exaggerated response to inflammation; thus, the chronic presence of pathogenic bacteria in periodontal pockets together with an exaggerated inflammatory response could trigger the destruction of periodontal tissue, leading to PDs. In diabetic patients, proteins become glycated to form advanced glycation end products (AGE) (17).

The AGE accumulated in the periodontal tissue may change the structure of the cell and of the extracellular components. Collagen degradation is easily provoked by the activity of matrix metalloproteinase (MMP), the production of which is higher in DM patients. AGE acts on bone collagen also, resulting in alterations of bone metabolism. Glycation of collagen proteins may affect bone turnover, leading to reduced bone formation, and delaying the formation of new bone (18, 19). This phenomenon reduces osteoblastic differentiation and extracellular collagen matrix production (20-22). Patients with DM have high levels of AGE receptor. Such cell surface receptor and its ligands are expressed in the periodontium of individuals with DM. Even in PDs high levels of AGE are present, activating their receptors with increased production of proinflammatory cytokines such as IL-6 and TNF-α, worsening progression of PDs (10). Furthermore, DM slows the healing of tissues. This phenomenon can be explained by increased apoptosis of fibroblasts (23).

Periodontal tissue is mainly formed by fibroblasts, whereby PDs are particularly aggressive in these patients (9). Alteration of immune functions, such as phagocytosis and chemotaxis of neutrophils, may predispose to the most severe manifestations of PDs (24-33).

Respiratory diseases and periodontal disease

The oral cavity could represent a reservoir of pathogenic bacteria that can infect the pulmonary tree mucosa. A pathogen is expected to exceed immune defence mechanisms to reach the lower respiratory airways. The immune defence mechanisms are so efficient, that the lower respiratory airways are sterile, despite the upper airway bacterial load being huge (34-46). Pulmonary tract infected by oral biofilm

pathogenic bacteria can occur when the immune system defence is decreased and the pathogens are particularly virulent. The pathogens can enter via inhalation, but the most accepted hypothesis is that infection of the lung mucous is caused by aspiration of oropharyngeal secretions. It is therefore plausible that oral microorganisms may infect the pulmonary tract.

Infections of the lower respiratory tract can start by the colonization of pathogenic bacteria of the oral and oropharyngeal mucosa. Pathogens are successively mixed in the oral secretions in addition to oral bacteria, hydrolytic enzymes and proinflammatory cytokines. The content of these secretions may contaminate and cause modifications on the epithelial surface of the lower respiratory airway mucosa. Since periodontal disease is characterized by chronic inflammation, inflammatory mediators, released at the level of saliva, can reach the respiratory epithelium. It is therefore likely that periodontal disease may contribute to the development and progression of RDs. This idea is supported another studies (47-58) stating that incidence of RDs by oropharyngeal colonization is more frequent in dentate patients and patients wearing denture, than in totally edentulous patients not wearing dentures. In addition, another study (59-72) reported that periodontal enzymes may cause the loss of fibronectine from the epithelial cell surface, uncovering mucosal surface receptors for respiratory pathogen adhesions, and favouring a better adhesion of periodontal pathogens to respiratory mucosa.

Smoking and periodontal disease

There are many studies evidencing that TS increases PDs progression and slows healing after periodontal therapy (73-85). These studies are unanimous in demonstrating a positive relationship between TS and periodontitis severity. These findings were confirmed by a recent systematic review, which showed a causal association between TS and tooth loss and an evident decrease in the risk of tooth loss after smoking cessation (86-93). The relationship between TS and PD is evident even if smokers, paradoxically, show less clinical signs of gingivitis such as bleeding on probing and oedema. It is presumed that TS may decrease gingival bleeding and crevicular fluid volume as a result of changes in the proportion of blood vessels and vascular alterations in periodontal tissues.

TS may influence the microbiological findings of periodontal pockets of smokers, in fact, higher levels of anaerobic bacteria were found in smoker's periodontal pockets. An anaerobic environment could conceivably promote the growth of Gram- negative periodontal pathogens in the sub gingival plaque. However, there is no significant difference in oral bacteria between smokers and non-smokers. Perhaps TS modifies the immune response to the aggression of oral bacteria. Although some studies stated that TS increases the number of neutrophils, the first line of defense against bacterial infection, smokers have decreased activity of neutrophils including chemotaxis, phagocytosis, and adherence and capacity to produce cytokines. Furthermore, TS influences lymphocyte count and production of antibodies.

The study of the correlation between TS and PD could also improve the battle against peri- implantitis (94-101). In fact, in the last decades dental implants have had a great success for replacing missing teeth in partially or totally edentulous patients. Even if the main factor for implant dentistry success is the quality of bone of receiving sites, TS could be an important co-factor in developing peri-implantitis.

DISCUSSION

There is a lack of knowledge on the relationship between PDs and SDs, however, sufficient evidence has been collected to state that periodontal treatment could prevent SDs. There are several factors that can affect both TD and SDs, such as genetic factors (IL-6, IL-10, Vitamin D-receptor), environmental factors (smoking, diabetes, stress etc.), and impaired immune response. However PD is prevalent in the middle-aged population and can have a significant impact on oral health. Further studies are needed to establish a relationship between PD and systemic diseases.

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The use of laser in dentistry: a narrative review.

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Implant dentistry has emerged as a first line of treatment to replace missing teeth for both the edentulous and partially dentate patients. Implant dentistry is accompanied by the onset of peri-implantitis (PIM). PIM is characterized by the inflammatory destruction of the implant-supporting tissues, because of biofilm formation on the implant surface. A history of periodontitis, poor oral hygiene, and smoking are considered as risk factors for PIM. Occasionally PIM is associated with iatrogenic factors, that, only recently, have been acknowledged as direct cause of PIM, i.e.: non-parallel adjacent implants or the presence of a gap, between fixture and prosthetic components. The use both of traditional protocols of nonsurgical periodontal therapy and the laser seems to be an effective alternative treatment modality for PMI. By the application of laser-assisted non-surgical peri-implant therapy the periodontal pocket depth was reduced. The present article illustrates the nonsurgical management of one case, where failure to remove residual cement, from an implant-supported dental prosthesis, seemed to cause PMI.

The biological complications of restored dental implants and associated supra-structures share similarities with the biofilm infections of natural dentition (1). Cement-retained fixed implant-supported restorations involve the risk of excess cement, which can associate peri-implantitis (PMI) (2). Excess cement, retained in the peri-implant sulcus, despite careful clinical control, can become the basis of colonization by oral microorganisms. As a result of the biofilm formation, PMI may develop (3-5).

The success of dental implants depends on many factors, among which the diagnosis, clinical severity and treatment of peri-implant diseases play a key role (6). There is no reliable evidence indicating which could be the most effective intervention for treating PMI (7). This is not to say that currently used interventions are not effective. The outcome of nonsurgical treatment of PMI (NSPT) is unpredictable (8, 9), due to possible re- infection related to the inability to completely remove bacterial deposits from titanium implant surfaces, thus interfering with a new histological bone-to-implant contact (10).The primary objective of NSPT is the biofilm removal and decontamination to resolve the inflammatory lesion (11). Nonsurgical periodontics may be the treatment of choice in cases of peri-implant mucositis or if the patient has medical contraindications or refuses to consent to more appropriate treatment (8, 12).

It is always imperative to stress the importance of giving correct oral hygiene instructions to patients who are rehabilitated with a dental implant and with proper prosthetic constructions, that allow accessibility for oral hygiene around implants (13). A strict periodontal control offers predictable long-term results; nevertheless, patients with a history of periodontitis, who did not fully adhere to individually designed maintenance programs, presented a statistically significant higher number of sites that required additional surgical and/or antibiotic treatment (12).

Key words: oral medicine, oral surgery, oral biology, oral pathology

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Laser treatment may serve as an alternative or adjunctive treatment to conventional periodontal mechanical therapy of PMI (11, 13-19). Clinical application of lasers for the treatment of periodontal disease has continued to expand but remains controversial (20). Diode lasers have a bactericidal effect, due to a localized increase in temperature, *verified in vivo* by using DNA probes that detect periodontal pathogens (21). Threaded implants have different morphology compared to root surfaces; therefore debridement instruments might be different. Laser could be a valuable tool to detoxify implant surfaces. A significant bacteria reduction should justify a more satisfactory recovery (22). It is possible to point the diode laser insert towards the wall of the ulcerated pocket epithelium in order to kill some virulent periodontal pathogens. Vaporization of granulation tissue seems to result in a more favorable effect compare to solo instrumentation (18, 21). The diode laser detoxifies root and implant surfaces by inactivating bacterial endotoxins, as it is hemostatic and produces no smear layer (21). The thermal effect weakens calculus chemical adhesion to root and/or implant, facilitating its removal by curettes or ultrasonic devices (31-47).

Diode laser triggers fibroblast and osteoblast bio-stimulation (24-30), which in turn causes increased production of RNA messenger (48-56), leading to a significant collagen creation during periodontal tissue healing. The patient experienced no postoperative discomfort and he was able to comply with debridement, whereas home care results often more difficult after oral surgery. Any post-treatment discomfort affects patient compliance, so the patient feels uncomfortable performing the recommended home care protocols and might avoid correct plaque control, therefore impairing healing (57-63).

Important changes were also detected: bleeding, a marker of inflammation with a high prognostic value: reduced to values below 20%. Besides laser therapy, two other therapeutic interventions, manual application of a Silver-Chlorex gel, ultrasonic and manual scaling were used, all of these could have contributed to healing (64-79).

Anatase is one of the most common crystalline forms of TiO_2 and is normally produced by oxidation of titanium via thermal oxidation or anodization. This crystalline form shows photocatalytic activity when irradiated with UV-A light. This photocatalytic activity produces decomposition of several organic compounds. Recently, it has been demonstrated that the coating of the healing screws with a derivate of anatase (i.e., Bactercline) produced a lower quantity of bacteria on the surface of these screws (80-93). In a clinical trial, anatase coated implant was performed and no adverse effect on osteointegration was detected (94-101). A different device, a Silver-Chlorex gel, was used here to control bacterial activity on the implant surface as it has higher antibacterial activity and no side effect on oral mucosa and bone. It seems to be ideal in the treatment of PMI or in combination with other devices and instruments; however, it has been proven that laser alone cannot be resolute.

For many periodontal applications, laser has to be used as an additional tool, but does not replace conventional nonsurgical treatment, which remains necessary, and irreplaceable, as much as correct home care instructions and adequate patient compliance.

The absence of attached gingiva may have been a factor in the development of gingiva PMI. The issue is quite controversial. The prevention of cement extrusion during the restoration process beyond the restorative cement margins cannot be underestimated; however, this may be more difficult than it appears.

Traditional protocols of nonsurgical periodontal therapy, in conjunction with the use of 810 nm diode laser seems to be an effective alternative treatment modality for PMI, associated with iatrogenic factors, such as failure to remove residual cement, from implant-supported dental prosthesis. Other treatment options may successfully enhance resolution of the peri-implant soft and hard tissues, and bone regeneration as well as preserving periodontal health longitudinally. Nevertheless, correctly performed supportive periodontal therapy is a key factor in enhancing the long-term outcome of implant therapy. The prevention of cement extrusion, beyond the restorative cement margins, during the restoration process should be emphasized.

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An overview on periodontal disease and genetic polymorphism.

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Gene polymorphism and periodontal diseases seem to be related. Polymorphisms of genes could modulate the immune response and tissue homeostasis are the main causes of individual susceptibility to periodontal diseases. The aim of this study was to review gene polymorphisms in periodontal diseases. Evidence of association between periodontal diseases and gene polymorphisms was obtained. This data confirmed the role of gene polymorphism in susceptibility to periodontal diseases. The evidence that gene polymorphisms are also involved in gingivitis.

A normal periodontium provides the support for teeth attachment and function. It consists of several highly specialized tissues and anatomical components, including gingival with its junctional epithelium, periodontal ligament, cementum and alveolar bone. Periodontal disorders are extremely frequent in all populations although prevalence increase with poor oral hygiene and malnutrition (1). Gingivitis, the mildest form of periodontal disease, is a rapidly inducible and reversible inflammatory affection of the gingiva, mainly caused by accumulation of bacterial biofilm.

The combination of bacterial infection and persistent inflammatory response could be responsible for the progressive destruction of periodontal tissues characterizing chronic periodontitis (2-4). Gingivitis lesions do not necessarily progress to periodontitis. The proportion of gingival lesions converting to periodontitis and the factor promoting this conversion has not been well understood. However, longitudinal studies in humans indicate that gingivitis represents not only the precursor of periodontitis but also a clinically relevant risk factor for disease progression and tooth loss (5-7).

Several environmental and genetic susceptibility factors concur to the aetiology of periodontitis. Both the total amount of bacteria in the periodontal pockets as well as its specific composition can well differentiate healthy and periodontitis patients (8-10).

Specifically, bacterial species such as *Porphyromonas gingivalis, Treponema denticola*, and *Tannerella forsythia* were consistently found associated with periodontitis (11, 12). Additional recognized risk factors of periodontitis are tobacco smoking, alcohol consumption, race-ethnicity, socio-economic status and systemic conditions such as diabetes, osteoporosis, malnutrition and stress (13, 14). Familial aggregation studies suggested that genetic factors may be relevant in susceptibility to early onset of periodontitis (15), while relevance of genetic contribution to chronic periodontitis is still debated (16-20). Most of the associated studies that aimed to identify gene polymorphisms involved in periodontitis, focused on candidate genes selected for their role in immune response modulation and tissues degeneration (21-25).

Recently, genome-wide association analyses were carried out to identify novel genetic factors involved in periodontal disease (26-31); however, both approaches were not completely successful since confirmation studies often failed to replicate earlier results. Possible explanations could account for the

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conflicting results including genetic heterogeneity among population. Indeed, the contribution of a gene polymorphism could greatly differ in different populations because of a different genetic background, socio-economical status or because allele frequency variation based on population. On the other hand, the fairly small sample size of most of the published investigation, generating both false-positive and false-negative results, increased confusion and limited success rate in identifying genetic factors for periodontitis (32-36).

Previous investigations exploring genetic susceptibility factor of periodontitis provided conflicting data. This is not surprising since several interacting risk factors contribute to the aetiology of this complex disease (40-43). A number of investigations supported association with gene polymorphisms of inflammation modulators, however there is still no agreement regarding the genetic basis of periodontal diseases. Conflicting reports of genetic association may arise because of the different attributable risk level of a specific factor in different ethnicities as well as to the small sample size that may increase both false positive and false negative results of associated studies. Another source of variability could be related to the study design due to different studies focused on specific phenotypes such as aggressive periodontitis, chronic periodontitis or response to treatment (44-57). In such a complex scenario, every finding should be replicated through independent studies.

Previous studies of a sample of population reported evidence of association between periodontitis and IL6 polymorphisms, as well as suggestive association with IL10 and VDR polymorphisms. In this study we reported the results of a replication study performed on 750 Italian patients (58-65). These studies were aimed to test genetic association between IL6, IL10, and VDR polymorphisms and chronic periodontitis and investigated their role in gingivitis. The main finding was that an IL6 gene promoter variant influenced the risk of periodontitis in the Italian population. The variant C allele of rs1800795 (also named IL6 -174G>C) was confirmed to be more frequent in healthy patients than those with periodontitis [OR=0.47 (95% C.I. 0.27-0.82)] for homozygotes]. Interestingly, a similar level of association was observed for gingivitis patients [OR=0.36 (95% C.I. 0.21-0.64) for homozygotes].

The PSR system was used to evaluate periodontal disease in this investigation. This rapid and non-invasive measure of periodontal status is useful for case definition. However, it cannot be considered a comprehensive examination able to produce a precise diagnosis (66-79).

Il-6 is an important modulator of inflammatory response in periodontal tissues that could also activate osteoclasts and induce differentiation of B-cells acting synergistically with other factors like IL-1 and TNFa. In comparison to control group, a higher level of IL-6 was detected in crevicular fluid of periodontal disease group; specifically, IL-6 was significantly higher in aggressive and chronic periodontitis patients (80-93). Increased expression was found in gingivitis, but the difference was not statistically significant. Considering that the rs1800795(C) allele is generally associated with lower levels of IL6 (94-101), the data appear to agree with our results and with our data obtained through a Brazilian population sample. In this study the higher expression of IL6 positively correlated with clinical attachment loss and the rs1800795 CC genotype was more frequent in control group whereas the CC genotype that had an unusually higher frequency in a sample of German population, appeared associated with an elevated risk of developing periodontitis. Rs1800795 SNP tends to be quite polymorphic in Caucasians while Asian and African populations are almost monomorphic for the G allele.

Interestingly, the severity of gingivitis resulted associated with polymorphisms of IL6 gene in a Russian male population. These data appear to indicate that the rs1800795 in IL6 promoter could modulate IL-6 expression in periodontal tissues and carriers of the variant allele could be protected from periodontal diseases, including both gingivitis and chronic periodontitis. This information should be considered seriously in planning future studies. A control sample to investigate the role of IL6 in periodontitis should include only healthy individuals, as a mixed control sample which include healthy and gingivitis patients could significantly reduce the success of the study.

The rs1800795 SNP has been found to be associated to several diseases including heart disease, Kaposi's sarcoma, type-2 diabetes, stroke, obesity, Hodgkin's lymphoma, sudden infant death syndrome, cancer, endometriosis, and hypertension.

DISCUSSION

Regarding IL10 and VDR polymorphisms, the present study did not find any evidence of association with periodontal diseases. This result does not rule out a possible role of IL10 variant in periodontitis.

In conclusion, the present study confirmed the strong association between the IL6 polymorphism rs1800795 and periodontitis in Italian population that was found in two independent studies. Moreover, the same level of association was found for gingivitis. This data should be carefully considered when planning future studies or looking for possible diagnostic application.

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Osteoblasts and insulin: an overview

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Stem cells of dental pulp (SCDPs) have the ability to self-expand and differentiate in pre- osteoblasts. The aim of our study is to investigate whether insulin can influence differentiation of SCDPs in osteoblast and bone tissue. SCDPs were treated with insulin at the concentration of 100 ng/µl for 24 and 48 h. Gene expression in treated SCDPs was compared with untreated cells (control) in order to check the effect of insulin on stem cell differentiation. After 24 h, significant up-regulated genes (Fold change > 2) in SCDPs were the Bone Morphogenetic Proteins and their receptors. BMP results over-expressed after 48 h of treatment. Insulin was demonstrated to influence proliferation of SCDPs, differentiation and expansion in osteoblasts.

Some authors (1-15) isolated stem cells from human exfoliated deciduous teeth (HEDT). After isolation from deciduous teeth, cells showed the ability to form in vivo a substantial amount of bone. Dental pulp from exfoliated teeth could be a good source of postnatal stem cells.

Stem cells of dental pulp (SCDPs) can form complexes like pulp dentin consisting of mineralized matrix with odontoblasts very similar to human dentin. The regeneration of a complete tooth is the objective of the use of stem cells in dentistry to restore the loss of natural teeth. Some studies have indicated that cell-based strategies show promising potential for regenerating the whole tooth structure in rodents. Moreover, stem cell-based regeneration of human tooth structures has been achieved in immunocompromised mouse models.

The dental pulp presents similar features to the gelatinous tissue of the umbilical cord and share characteristics of primitive stem cells (16-23). Therefore, the ability to isolate a population of totipotent stem cells from the dental pulp of naturally exfoliated deciduous teeth, could provide a unique source of stem cells for future clinical applications.

It is well known that dental pulp is one of the sources of stem cells. In fact, in adults stem cells are present in dental pulp and they can produce new dentin after mechanical or inflammatory stimuli (24-32). SCDPs may be a source of differentiated cells inducing bone formation and controlled hydrossyapatite crystal growth. SCDPs have been isolated from teeth of subjects up to 30 years of age, and form sporadic dense nodules in vitro, but undergo mineralization and bone or dentin-like formation only when grafted in vivo (33-39). These SCDPs have the ability to self-expand and differentiate in pre-osteoblasts, producing in vitro autologous bone tissue.

The aim of our study is to investigate whether Total RNA was extracted from stem cells using the insulin can influence differentiation of SCDPs in osteoblast and bone tissue. We propose a working model that explains the possible interactions between insulin and SCDPs at the molecular level and describes the cellular consequences of these interactions. This model may be used to stimulate research on the clinical applications of SCDPs in cellular therapy and tissue regeneration

Key words: oral medicine, oral biology, oral pathology, oral surgery

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MATERIALS AND METHODS

SCDPs isolation

Pulp was digested for 1 h at 37°C in a solution containing 3 mg/ml type I collagenase and 4 mg/ml dispase in 4 ml phosphate-buffered saline (PBS) supplemented with 100 U/ml penicillin, 100 µg/ml streptomycin, and 500 µg/ml claritromycin. The solution was then filtered with 70 µm Falcon strainers (Sigma Aldrich, Inc., St Louis, MO, USA). Filtered cells were cultivated in α-MEM culture medium (Sigma Aldrich, Inc., St Louis, MO, USA) supplemented with 20% FCS, 100 µM 2P-ascorbic acid, 2 mM L-glutamine, 100 U/ml penicillin, 100 µg/ml streptomycin and placed in 75 ml flasks. Flasks were incubated at 37°C and 5% CO2 and the medium changed twice a week.

Flow cytometric analyses The purity of cell cultures was determined by analysis of different antigens after staining with fluorochrome (FITC- or PE-) conjugated mAbs anti-human CD14- FITC, CD14-PE, CD34-FITC, CD45-FITC, CD90- PE, CD105-PE (Immunotech, Marseille, France) and analyzed by FACScan. Nonspecific mouse IgG was used as isotype control (Immunotech). To avoid nonspecific fluorescence from dead cells, live cells were gated tightly using forward and side scatter.

Cell culture For the assay, DPSCs were collected and seeded at a density of 1x105 cells/ml into 9 cm2 (3ml) wells by using 0.1% trypsin, 0.02% EDTA in Ca++ - and Mg–free Eagle's buffer for cell release. One set of wells were added with Insulin (Sigma Aldrich, Inc., St Louis, MO, USA) at the concentration of 100 ng/ml. Another set of wells containing untreated cells was used as control. Cells were treated for 24 and 48 hours.

RNA processing

GenEluteTM Mammalian Total RNA Miniprep Kit (Sigma Aldrich, Inc., St Louis, MO, USA). Cells were lysed and homogenized in a lysis buffer. Then ethanol was added to the lysate to ensure the binding of RNA to the silica membrane of the GenElute Binding Column. After washing with specific buffer to remove contaminants, RNA was eluted in 50 µl of Elution solution. Total RNA was measured with a NanoDrop spectrophotometer (Thermo Scientific Inc., MA, USA). cDNA was synthetized starting from 500 ng of each RNA sample (treated and control, at 24 and 48 h) using SuperScript® VILOTM cDNA Syntesis Kit (Invitrogen, Carlsbad, CA, USA). The reaction mix contained 5X VILO Reaction Mix, 10X SuperScript Enzyme Mix, RNA (500 ng) and DEPC water in a final volume of 20 µl. The reaction was incubated at 42°C for 60 min and then inactivated at 85°C for 5 min.

Real time PCR

cDNA was amplified by real-time PCR using Power SYBR® Green PCR Master Mix (Applied Biosystems, Foster City, CA, USA) and the KiCqStartTM Primers (Sigma Aldrich, Inc., St Louis, MO, USA), specific predesigned primer pairs chosen for the investigated genes. Reactions were performed in a 20 µl volume using the ABI PRISM 7500 (Applied Biosystems, Foster City, CA, USA). Each reaction contained 10 µl 2X Power SYBR® Green PCR Master Mix (Applied Biosystems, Foster City, CA, USA), 400 nM concentration of each primer, and cDNA.

All experiments were performed including non-template controls to exclude reagent contamination. PCRs were performed with two biological replicates. The gene expression levels were normalized to the expression of the housekeeping gene GUSB and quantified as the fold changes relative to the expression of the untreated DPSCs. Quantification was made with the delta/delta calculation method (44-56).

RESULTS

Cell cultures were phenotypically characterized by flow cytometric analyses. Cell preparations derived from dental pulp were homogenously $CD105^{+}$which is a typical mesenchymal stem cell surface antigen profile. SCDPs were treated with insulin at the concentration of 100 ng/ml for 24 and 48 h. Gene expression in treated SCDPs was compared with untreated cells (control) in order to check the effect of insulin on stem cell differentiation.

Genes related to ossification (BMP), osteoblast differentiation (BMPR1), bone mineralization (TGFβ1) and skeletal development (TGFβR1) were investigated to study the potential effect of insulin in osteoblast differentiation and proliferation.

After 24 h of treatment many of the genes investigated were down-regulated in treated SCDPs *vs* untreated SCDPs. Significantly up-regulated genes (Fold change >2) were the Bone Morphogenetic

Proteins. Significantly up- regulated genes were Bone Morphogenetic Protein receptor. After 48 h, insulin induced the over-expression of bone related gene BMP.

DISCUSSION

Our study confirms the assumption that insulin promotes markers of bone formation, providing support of the view that insulin influences differentiation of SCDPs in an osteoblastic sense. Bone morphogenetic proteins have been shown to induce SCDPs to proliferate and then differentiate into osteoblastic cells. Insulin can modulate the expression of various osteogenic markers. Thus, the effects of insulin on SCDPs must be examined in light of their apparent maturity in terms of osteogenic potential. SCDPs showed differentiation profiles similar to those of bone differentiation (40-56) and this event makes them very interesting as a model to study the osteogenesis.

Dental pulp is a good source of stem cells that differentiate into osteoblasts, as well as other phenotypes, for hard tissue engineering. During life, bone tissue needs renewal, and dental pulp represents an additional source of mesenchymal cells to bone marrow. Selection and expansion of stem cells are complex procedures commonly used to obtain cells for potential therapy (57-80); thus, being able to obtain sorted cells quickly after collection and to transplant them directly is an advantage that can lead to easier application of bone-engineering protocols (81-115).

Insulin has been demonstrated to influence this process in production of SCDPs and differentiation and expansion in osteoblasts. Further studies are needed to explore this new way of creating bone tissue.

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Bone regeneration in dentistry: an overview

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Reconstructive surgery (RS) is necessary before implant placement to regenerate bone defects. Success rate of implants is related to RS and to the correct position of implants in residual crest. The most popular surgical procedures of RS are bone grafts, guided bone regeneration. Bone graft is the gold standard technique to achieve RS of edentulous crests. RS is a surgical technique that uses barrier membranes to promote osteoblast cells proliferation. RS is often combined with bone grafting procedures. Sinus floor elevation procedures are elective treatments when there is insufficient bone height for implant insertion in maxilla. Bone osteogenesis distraction is the process of RS between two bone segments in response to tensile stress. The aim of this short review is to analyze the different methods of RS: bone grafts, guided bone regeneration, maxillary sinus floor elevation, and bone osteogenesis distraction.

Long-term success rate of implants inserted in atrophic maxilla is ensured through sufficient bone volume in edentulous sites (1). Reconstructive surgery (RS) is necessary before implant placement to regenerate bone defects caused by atrophy, dental trauma, extractions or periodontal disease (2, 3). SRI is related to the correct position and angulation of implants in residual crest, so RS, in height and thickness, can allow predictable results (4). Bone grafts are the gold standard technique to achieve RS of edentulous crests and to obtain appropriate bone volume and morphology (5-8).

The aim of this short review is to analyze the different methods to increase bone in atrophic maxilla. The most popular surgical procedures of RS are: bone grafts, guided bone regeneration (GBR), maxillary sinus floor elevation (SFE), and bone osteogenesis distraction (BOD).

Augmentation of bony defects

The goal of RS is to provide a baSuppl for ideal implant placement and to support soft tissue for optimal esthetics. Through the years, multiple procedures and augmentation materials have emerged to allow RS. RS is done either in conjunction with the implant placement (one phase approach) or during a surgical intervention prior to implant placement (two phases approach). The two phases approach is the preferred treatment in situations with severe bone atrophy when the success rate of implants inserted in a prosthetically desired position is unachievable. The RS procedures used in implant dentistry includes graft reconstruction, guided bone regeneration (GBR), maxillary sinus floor elevation (SFE), and bone osteogenesis distraction (BOD).

Graft Reconstruction

The RS of the edentulous crests with bone grafts is considered as the best surgical technique to place implants in a prosthetically guided position. Currently in dental practice, either autogenous graft (removed from intraoral or extra oral sites) and/or allograft (allogenic, homologous homograft) are used. In our review, only autogenous grafts are included to simplify the description.

The physiology of RS healing is analogue

Key words: bone defects regeneration, reconstructive surgery, RS, bone grafts, oral medicine, oral biology, oral surgery, oral pathology

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to primary/secondary healing. Bone grafts are integrated into native bone with three different processes: osteogenesis, osteoinduction and osteoconduction. Osteogenesis is the formation of new bone from osteocompetent cells and is the only process where the graft itself can induce RS. Osteoinduction induces RS from the differentiation and stimulation of mesenchymal cells by the bone-inductive proteins. Osteoconduction is the formation of RS along a scaffold from osteocompetent cells of the recipient site (9-15).

Onlay bone graft indications

The bone grafts are used to increase the native bone in the vertical and horizontal direction. Vertical RS by means of block grafts is indicated when the height of the residual crest is less than 5 mm (Cawood and Howell class IV, V and VI) (16-22). Horizontal RS is recommended when the width of the alveolar ridge is less than 4 mm or less than 5 mm in aesthetic areas with high labial line. Some authors established the following exclusion criteria for RS: smoking more than 10 cigarettes per day; severe renal or hepatic disease; history of head and neck radio-therapy; preview treatment with chemotherapy; uncontrolled diabetes; untreated periodontal disease; diseases of the oral mucosa (such as lichen planus); poor oral hygiene; non- collaborating patient; any other pathological situation that contraindicates oral surgery. In all studies, RS with grafts was performed in both men and women and age range of patients was from 18- to 76-years- old (26-35).

Graft success and resorption

Survival rate for RS were based on success criteria such as absence of infection of the graft site, absence of exposition of bone graft, incorporation of the graft into native bone, absence of radiolucent areas, bleeding of the grafted bone when removing the fixation screws and sufficient bone to place the dental implants (36-47). Different resorptions are related to grafts of different origins (48-54). Homografts and fresh frozen bone are the gold standard to obtain the maximum of millimeters gained. The percentage of bony survival after 10 months for the calvarial graft was 83%, whereas for the iliac it was only 61%. The iliac crest graft lost most of the RS height in the first 6 months, but the bone reduced to almost 0% as the process advanced. The calvarial graft had a low resorption rate at the beginning of the study but showed a difference of only 10% compared with iliac after 30 months. Regarding healing time, in most of the studies implants were inserted after 4-6 months (55-67) or 6 months after BA with bone grafts

Guided Bone Regeneration (GBR)

Guided bone regeneration (GBR) for RS is a surgical technique that uses barrier membranes to promote osteoblast cells proliferation and exclude other cells such as epithelium and connective tissue cells. GBR is often combined with bone grafting procedures.

Initially, barrier membranes (BM) were made from polytetrafluoroethylene (PTFE). BM was later reinforced with fluorinated ethylene propylene (ePTFE) for rigidity and they were non-riabsorbable (NRBM). Subsequently, it was observed that NRBM showed disadvantages such as a rough surface favoring bacterial adhesion and a second surgical procedure to remove them. To avoid these disadvantages, a high-density polytetrafluoroethylene (dPTFE) was adjusted to NRBM and a smooth surface of these new NRBM facilitated the removal of the membrane. The requirement of second surgical procedure for the removal of NRBM led to the introduction of bioresorbable barrier membranes (RBM). The advantages of RBM compared to NRBM were as follows: improved soft tissue healing, incorporation of the membranes by the host tissues (depending on material properties), and quick resorption in case of exposure, eliminating bacterial contamination. The RBM are classified in two groups: aliphatic polyesters and collagen. Today, a lot of RBM are commercially available including collagen, freeze-dried fascia *lata*, freeze-dried *dura mater* allografts, polyglactin-acid, polylactic acid, polyglycolic acid, polyorthoester, polyurethane, polyhydroxybutyrate, etc. (68-75), however, the relative amount of bone formation using RBM was less favorable than NRBM. RBM are not capable of maintaining adequate space unless the defect morphology is minimal and favorable because they lose their mechanical strength soon

after implantation in the tissues and need support. Although RBM provide more bone regeneration, NRBM should be the material of choice for GBR to avoid dehiscence of soft tissues.

RS using GBR can be performed at the same time of implant placement (one-phase procedure) or prior to implant placement (two-phase procedure). The two-phase surgical procedure is preferable when maxilla is severely atrophic, and it is difficult to insert implant in the correct position.

Sinus floor elevation

Sinus Floor Elevation (SFE) procedures are elective treatments in case of insufficient bone height for implant insertion in maxilla. SFE for implant insertion in maxilla in adjunction with autologous bone was described with long-term follow-up (76-84). From those initial investigations, many techniques have become available to the implantologists. There are currently two techniques considered as the most predictable for vertical BA of posterior maxilla in adjunction with SFE: lateral window technique and sinus intrusion osteotomy technique (85-98).

One of the most frequent reasons for failure during the SFE operation is connected to the possibility of a rupture of the Schneiderian membrane, which, if lacerated, cannot perform the function of graft containment. To reduce the incidence of complications of SFE it is necessary to cut the hard tissue with extreme accuracy and as little trauma as possible, while saving the soft tissue.

The precision of pre-operation measures obtained through endoral X-rays, dental-scans, and cone-beam CT during SFE, allows us to approach and cut the sinus cortical floor delicately. Recently, it has been described a new SFE technique named "Hydraulic sinus lift technique" (99-101). The sinus lift techniques, through the crestal approach, are widely used today in clinical practice to manage bone atrophy of the lateral- posterior sectors of the maxilla for implant purposes. The indication of these techniques has progressively increased over the years because of the lower morbidity compared to the techniques that adopt the lateral approach. In addition, the recent development of computer-guided surgery, allows planning the operation of SFE, decreasing the risk of failures.

The cortical of the maxillary sinus is reduced using calibrated burs and a profiler to obtain a hole that enables both access to the maxillary sinus and subsequently, the lifting of the sinus. Each stage of the operation is monitored, and all the devices used pass through a custom-made template, which acts as a surgical guide. The fluid- dynamic technique is characterized by the hydraulic detachment of the mucosa and simultaneous filling of the sub-Schneiderian space, with a graft material of paste-like consistency. The sinus is filled using a fluid biomaterial distributed through a dispenser, which was created specifically for this technique. Once the Schneiderian membrane is detached and elevated and the graft materials distributed, the implants can be inserted in maxilla. Due to the reduction in trauma and less invasiveness of the process, this technique could be a valid alternative to the others known and carried out to date. Work time is reduced to less than 3 min in the cortical thinning operation and percussive trauma is avoided.

Bone osteogenesis distraction

Bone osteogenesis distraction (BOD) is the process of bone generation between two bone segments in response to tensile stress. The biological processes of BOD are the results of three distinctive stages such as latency stage (initial post- surgical healing period of osteotomy site), distraction stage (gradual and incremental bone separation at the rate of 1 mm/day) and consolidation stage (bone regeneration at distracted site).

BOD is recommended when it is necessary to achieve a vertical augmentation of 6-7 mm of the ridge. BOD is indicated when the edentulous zone has lost three or more teeth. In case of severe atrophic maxilla, a RS is initially performed and subsequently BOD technique is used after 4 months of healing period. In moderate horizontal atrophy situations, the BOD is performed first, followed by a RS. If secondary grafting is not necessary due to mild atrophy, implants are usually placed at the time of distractor removal, minimizing the resorption.

SRI of implants placed in distracted areas are consistent with implants in native bone. Despite

the greater predictability and SRI (98.9 %) of BOD, many complication were reported: tilting of the segments, change of the distraction vector, occlusal interferences and fracture of basal bone or the transport segment, breakage of the distractor and severe mechanical problems.

DISCUSSION

Maxilla and mandible present different characteristics regarding functionality, physiology, and bone density. These differences define different prosthetic RS methodologies for the implant insertion. The correct application of RS techniques, the correct patient selection and use of the most suitable filling materials, allow a long-term SRI in the treatment of atrophic maxilla.

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Protozoa and oral health: a systematic review

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Gingivitis and periodontitis (GP) are the main diseases of the oral cavity. The ethiology of GP have never been completely understood, however, loss of balance between the host immune system and the microbial virulence of GP pathogens may be considered the trigger of GP. In fact, the immune system, activated by microbiological agents, attacks the host and not the biofilm bacteria, causing the destruction of periodontal tissue, alveolar bone, and loss of teeth. Parasites may play an important role in the pathology of GP. The first studied and the most common parasite in the oral cavity is Entamoeba gingivalis. A possible link between E. gingivalis and GP has never been demonstrated completely, however E. gingivalis is infrequently found in people without GP. In addition, there is evidence that E. gingivalis could favour the onset and progression of GP. In conclusion, we can assert that E. gingivalis and GP may be correlated. This relationship can open new therapeutical approaches for treating GP, particularly in cases refractory to therapy.

Gingivitis and periodontitis (GP) are the most prevalent diseases of the oral cavity and manifest with the classical symptom triad: tooth mobility, foetor ex ore, and gingival bleeding. GP is characterized by loss of connective tissue attachment to the tooth, and pathological migration of the junctional epithelium apically, which leads to pocket formation, tooth mobility, and finally tooth loss. There are different types of GP, but the most common is chronic periodontitis. The pathogenesis of GP is multifactorial, and bacteria have a prominent role (1-5). There is ample evidence supporting the microbial aetiology of GP. Smoking, alcohol consumption, and systemic conditions such as diabetes, osteoporosis, malnutrition, and stress are considered relevant risk factors. Recently, it was observed that GP appears to increase the risk of cardiovascular disease, pulmonary disease, preterm and low birth weight.

Pathology of GP

In the oral cavity, bacteria are structured as dense aggregates, attached to enamel surface, called biofilms (6-12). Under certain conditions, biofilm could alter its composition and may cause disease (13-22). Dental plaque and microflora colonizing gingival pockets can promote inflammation of the adjacent host gingival tissues. The epithelial cells of gingival sulcus are the first line of defense against the plaque bacteria (23-27).

Dental plaque is structured as a complex polymicrobial biofilm (28-35). In the progression of GP, this biofilm changes from Gram-positive facultative anaerobes to Gram-negative anaerobic bacteria (36-42). The accumulation of dental plaque causes inflammation in the adjacent gingival sulcus extending biofilm in the deepest part of sulcus itself, creating a deeper pocket and favouring the growth of *anaerobes*, such as *Spirochetes* and *Bacteriodetes* (43-52).

Innate immune responses in periodontal tissues are stimulated by Gram-negative periodontal bacteria, among which the most aggressive have been identified as the "red complex" group:

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Porphyromonas gingivalis, *Tannerella forsythia*, and *Treponema denticola*. These microbes are highly virulent and neutralize host defences, causing GP. However, only a limited number of individuals with red complex species develops GP, suggesting a complex multifactorial aetiology of this disease, involving loss of balance between bacteria virulence and the innate immune system.

Loss of balance between the host immune system and the microbial virulence may be considered the trigger of GP. In GP, the persistently activated immune system, triggered by microbiological agents, damages the host tissues with little effect on the biofilm bacteria, causing a progressive destruction of periodontal tissue, alveolar bone, and teeth loss. This process is related to the severity of GP, modulating responses of immunity to oral biofilm, leading to dysregulation of innate immunity (53-62). It is also known that immune dysregulation is associated not only with GP, but also with other numerous systemic diseases such as cardiovascular disease, obesity, pulmonary disease, etc. In fact, the interactions between microbial virulence factors and the immune system, have been largely investigated regarding the aetiology of GP.

Recent genetic and molecular studies have described the relationship between bacterial virulence and host immune response and the pathways involved in GP progression (63-69).

A possible link between protozoa and GP

Protozoa could play an important role in the pathology of GP. The first studied and the most common parasite in the oral cavity is *E. gingivalis*. Some authors detected *E. gingivalis* in periodontal pockets, but not in healthy sites (70-75). Basing on the idea that *E. gingivalis* was involved in the pathogenesis of GP, they tried a new protocol based on oxygen peroxide and metronidazole that, even recently, demonstrated to be effective (76-80). This idea was firstly contrasted for difficulties in molecular identification of the parasite.

Recently, an *in vitro* experiment explained a host-protozoa relationship. Human cell line cultures were challenged with putative pathogenic GP bacteria in the planktonic state, i.e., a cell suspension in growth media or buffered solutions, evidencing that *in vitro* experiments are far disconnected from *in vivo* conditions. In fact, *in vitro* studies do not reflect the challenge to host cells by multi-species biofilms. Biofilm eradication is difficult, because they are highly resistant to antimicrobial agents and the host immune response (81-86). Biofilms are involved in the pathogenesis of many inflammatory diseases, such as GP, as well as in urinary catheters and tracheal tube colonization (87-91).

E. gingivalis is one of seven *Entamoeba* species that infect humans, including *E. histolytica*, which causes amoebic dysentery and amoebic liver abscesses. Both parasites are detected in cytologic and histopathologic analysis. Distinguishing the two species is very important for therapeutic purposes: *E. gingivalis* infection is treated with doses of metronidazole, whereas *E. histolytica* is sensitive to antibiotics such as paromicyn which is used to eradicate cysts from the intestinal lumen. *E. gingivalis* may be detected in the mouth and pharynx; it is a commensal and is characteristic in patients with partial or total edentulism, poor oral health, and in immunodepressed patients (positive HIV and AIDS patients.

New therapeutic approaches for GP

The oral microbiota is constituted by a large number of bacteria species that form a biofilm. The biofilm includes both saprophytes and potentially pathogenic species. It is well understood that most destructive types of periodontal diseases occur due to the presence of pathogenic microorganisms colonizing the subgingival area and the suppression or eradication of these microbes results in improvement in periodontal health. The oral cavity is suitable for invasion of many microorganisms. *E. gingivalis* is considered an oral commensal, but demonstrates a pathogenic potential associated with GP, in particular in immunocompromised individuals.

A causative link between *E. gingivalis* and GP has never been demonstrated; however, *E. gingivalis* is infrequently found in people without GP. In addition, there is evidence that *E. gingivalis* could favour the onset and progression of GP.

DISCUSSION

The controversial results observed, in particular

in patients negative for clinical symptoms and positive for *E. gingivalis*, could be explained by a better understanding of the interactions between this protozoa and immune response. However, we can assert that *E. gingivalis* and GP are correlated. This relationship can open new therapeutical approaches for treating PD, particularly in those cases refractory to therapy. In fact, GP treatment has the aim of reducing oral infection, and preventing progression of the disease. GP non-surgical therapy with scaling and root planing associated with a high level of domestic oral hygiene, can prevent the onset of the disease and allow for the correct maintenance of oral health. Good oral hygiene aims to control bacterial plaque, but when the patient's attention to oral hygiene decreases, it is possible to experience a recurrence of the disease. In addition, GP has periods of remission and exacerbation, therefore a control of oral microbiota may be reached by the administration of anti-parasitic drugs. The study of correlation between GP and *E. gingivalis* could also improve the battle against peri-implantitis (92-95).

Dental implants have had a great success in the last decades for replacing missing teeth in partially or totally edentulous patients. Even if the main factor for the success of implant dentistry is the quality of bone of the receiving sites (96-101), the bacteria and protozoa of periodontal disease also cause peri-implantitis.

GP is one of the most prevalent diseases in the world, and *E. gingivalis* is common in humans, therefore an anti-parasitic treatment may represent a new frontier in periodontal treatment.

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Oral and general health: an inseparable pair

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***Helicobacter pylori bacteria* (HPB) is one of the most common gastric infections in the world. It seems that HPB infects the subject early in life and is transmitted from person to person. The oral cavity could be a reservoir of HPB participating in infection transmission. HPB and recurrent aphthous stomatitis (RAS) show similar clinical and histological findings, and the discovery of HPB in RAS ulcers support the idea of a correlation between the two diseases. Another important relationship between RAS and HPB is the high incidence of anemia in patients with RAS that may be caused by HPB. In fact, antibiotic therapy and treatment of anemia can reduce the frequency of RAS ulcer recurrence. HPB is considered a carcinogenic agent type 1 of the stomach. In conclusion, the oral cavity is an extra-gastric reservoir of HPB and periodontal therapy associated with systemic therapy can better eradicate HPB from the mucosa of all gastro-enteric tract. Prospective cohort studies are needed to demonstrate the bacterial action in the oral cavity.**

Helicobacter pylori bacteria (HPB) is one of the most common gastric infections in the world, affecting about half the world's population and is the principal cause of adenocarcinoma of the distal stomach (1). The risk of developing gastric cancer is related to the different subtypes of HP and to the inflammatory response mediated by genetic factors (2).

HPB presents two different microbiological forms, spiral and coccoid. The spiral form is virulent, whilst the coccoid form may be a dead form of HPB, and its role in transmission of infection is not clear (3).

It seems that HPB infects the subject early in life and is transmitted from person to person (4). The transmission of the bacterium is related to crowded living associated with low socio-economic conditions and intra-familial clustering. However, the exact manner of transmission is not yet known (5). HPB reaches the stomach through oral ingestion, and because of its non-invasive nature, the stomach is the ultimate site of colonization (6). The evidence of oral transmission includes the high prevalence of HPB in African children who are fed with food pre- masticated by the mother (7), and in populations that exchange chopsticks (8). In our study, we review the relationship between oral disease and HPB and the role of the oral cavity as an extra-gastric reservoir of HPB.

Periodontal disease and HPB

The presence of HPB in the oral cavity was discovered for the first time in 1989 when the bacterium was cultured from dental plaque of a patient with gastritis associated with HP infection. Recently, it has been debated whether the oral cavity is a reservoir of HPB bacteria participating in infection transmission, or representing a nidus of re-infection after eradication of the bacterium. In particular, some studies evaluated the effect of periodontal therapy on HPB infection (9-12); however, the results are controversial. Different studies have found discrepant results, ranging from 0-100% positivity for HPB in the oral cavity by polymerase chain reaction (PCR) methods (13-16).

Key words: Systemic diseases, oral cavity, periodontal disease, oral biology

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In addition, inconsistent correlation between HP positivity in the oral mucosa and in the stomach has been found. Many factors likely account for this variability, including the genetic background of the study population, cultural habits, socioeconomic level, and differences in the accuracy of the methods used as well as the strain of bacteria (17).

HPB was detected in different niches of the oral cavity: periodontal areas, mucosa and saliva. High prevalence of HPB was detected in the oral cavities of periodontitis patients (18-20). A positive link was observed between HP infection and periodontal disease, and an association was established between the supragingival colonization of HPB and oral hygiene parameters, such as the presence of plaque and gingival bleeding (21-23).

The gastric infections caused by HPB are treated with systemic therapy (antibiotics and proton pump inhibitors). The eradication of the infection reduces the risk of recurrence of gastric ulcers (24-26). However, relapse is always possible. In view of the difficulties in eradicating the bacteria in the stomach, it is essential to identify potential reservoirs of the bacteria that could be responsible for the refractoriness to therapy.

It has been shown that HP of the oral cavity is associated with recurrent gastric infection. Oral colonization of HPB in dental plaque can persist after eradication therapy. Therefore, even if eradication therapy is successful, dental plaque might be a sanctuary for HPB, leading to gastric recurrence (27-40). HPB in dental plaque may represent a risk factor for gastrointestinal reinfection and ulcer relapse after antibiotic therapy. The periodontal pocket may be important as a natural reservoir for HPB because it can provide microaerobic conditions (41-50). Oral cavity of gingivitis or chronic periodontitis patients who are positive for HPB in their stomachs can harbor HP after systemic eradication. Recently, a meta-analysis confirmed the close relation between infection of HP in the oral cavity and the stomach. HPB in the oral cavity is more difficult to eradicate than in the stomach and may be a source of re-infection (50-63). One of the keys to success related to the eradication of HPB is represented by oral hygiene and periodontal therapy (64-71).

Some studies have suggested that periodontal disease may be related to an increased risk of gastritis and gastric ulcers. Persistence of inflammation factors due to periodontal disease and alteration of gastrointestinal microbiome may be considered the associated cause of gastric diseases (72-86).

Despite an association between HPB and periodontal disease has not been demonstrated, the effectiveness of periodontal therapy on the elimination of HPB is clinically relevant even if not well documented.

Recurrent aphthous stomatitis (RAS) and HPB

Recurrent aphthous stomatitis (RAS) is a common condition that is characterized by multiple recurrent small, round, or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or gray floor, with a wide range of reported prevalences from 5 to 50% in different populations. These ulcers appear on the non-keratinized (or less keratinized) oral mucosal tissues, and usually regress spontaneously within 14 days.

The onset of these ulcers is usually during childhood, and they tend to diminish in frequency and severity with age. The frequent aphthous ulcers can increase the severity of patient discomfort and cause functional complications, including associated difficulties in speaking, brushing teeth and eating. The aetiology of aphthous lesions is still not clear. The histopathological changes in the preulcerative stage include infiltration of the epithelium by mononuclear (lymphocytic) cells; oedema develops, followed by keratinocyte vacuolization and localized vasculitis, causing localized swelling that ulcerates and is infiltrated by neutrophils, lymphocytes, and plasma cells before the healing phase and regeneration of the epithelium. These clinical and histological findings and the discovery of HPB in RAS ulcers make this disease similar to gastritis and duodenal ulcers (87-93).

Another important relationship between RAS and HPB is the high incidence of anemia in patients with RAS that may be caused by HPB-positive stomach disease. In fact, antibiotic therapy and treatment of anemia can reduce the frequency of RAS ulcer recurrence.

Oral cancer and HPB

Oral cancer is the sixth most common cancer in the world, with approximately 350,000 deaths and 650,000 new diagnoses per year. It is estimated that more new cases will be diagnosed in developing countries. Risk factors for the development of oral cancer are many. Smoking: cigarette, cigar, or pipe smokers are six times more likely than non-smokers to develop oral cancers. Alcohol consumption: oral cancers are about six times more common in drinkers than in non-drinkers. Excessive sun exposure, especially at a young age, and family history of cancer are considered risk factors. Human papillomavirus (HPV): certain HPV strains are etiologic risk factors for oropharyngeal squamous cell carcinoma (OSCC). Even if HPB was considered a carcinogenic agent type 1 for stomach cancer by the International Agency for Research on Cancer, OMS/IARC, regarding the role of H.P in the etiology of squamous cell carcinoma, to date no evidence is available (94-101).

DISCUSSION

There is evidence of relationship between oral and HPB-related gastric diseases, in particular periodontitis, peri-implantitis, RAS and oral cancer. Both infections have in common their great diffusion in the world population. It is well known that the oral cavity is an extra-gastric reservoir of HPB and that periodontal therapy associated with systemic therapy may better eradicate HP from the mucosa of all gastro-enteric tract, reducing the relapse of HPB infection. Prospective cohort studies are needed to reveal the bacterial action in the oral cavity.

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Titanium and implantology: a review in dentistry

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Implant dentistry has become a popular restorative option in clinical practice. Titanium and titanium alloys (TTA) are the gold standard for endo-osseus dental implants production, thanks to their biocompatibility, resistance to corrosion and mechanical properties. The characteristics of the TTA implant surface seem to be particularly relevant in the early phase of osseointegration. Furthermore, the microstructure of implant surface can largely influence the bone remodelling at the level of the bone-implant surface. Recently, research has stated on the long-term of both survival and success rates of osseointegrated implants and mainly on biomechanical aspects, such as load distribution and biochemical and histological processes at the bone-implant interface. This short review reports recent knowledge on chemical and mechanical properties, biological aspects, innovations in preventing peri-implantitis, describing clinical applications and recent improvements of TTA dental implants. In addition, it highlights current knowledge about a new implant coating that has been demonstrated to reduce the number of initially adhering bacteria and peri-implantitis.

Titanium and titanium alloys characteristics

The characteristics of the titanium and titanium alloys (TTA) implant surface seem to be particularly relevant in the early phase of osseointegration, furthermore implant microstructure influences the bone remodelling at level of the bone-implant surface (1-10).

Recent studies have reported higher bone- to-implant contact (BIC) percentages in rougher TTA implant surfaces (TTAIS) than in machined surfaces (11). Irregular morphologies of TTAIS allow significantly higher levels of cellular attachment in osteoblast-like cells and may play a crucial role in biomolecular adsorption and cell adhesion to the TTAIS as well as in osteoblast cells maturation (12). In fact, the success of TTAIS is highly related to the surface properties of the implant materials that influence molecular interactions, cellular response and thereby, bone regeneration. Mesenchymal stem cell involvement, cell-cell communication at the bone-TTAIS and in particular interactions between the surface oxide and the biological host, are the underlying mechanisms of osseointegration (13-16).

Improved biological host response (e.g. increased cell proliferation and cell activities, higher mRNA expression for osteoblast markers and enhancement in matrix mineralization) has been reported as an effect of interaction with TTAIS (17-19). Moreover, it was reported that different microtopography of TTAIS may induce mesenchymal stem cell (MSCs) differentiation at a more accelerated rate, compared to similar material with a smooth surface (19). To achieve osseointegration of TTAIS, rougher surfaces seemed to improve the de novo bone formation due to the early surface adhesion of non- collagenous proteins such as osteopontin and bone sialoprotein (20). Subsequently, calcium phosphate nucleation at the calcium binding sites on these proteins continues

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the process of osseointegration of TTAIS, which is completed by crystal growth and collagen production with mineralization (21, 22).

Different studies on the TTAIS micromorphology are difficult to compare due to the variability of surface treatment methods, sources of cells and the experimental methods. TTAIS of oral implants have been modified to play an important role for cellular reactions, tissue healing and implant stability (24,25). Different methods such as machining, air-abrasion, acid etching, and electrochemical oxidation and laser treatment were applied to model TTAIS at various dimensions.

TTAIS corrosion can occur if titanium is put in contact with anoxic acid media, with a complete dissolution of anodic oxide (26,27). To overcome these problems, typically the TTAIS are air-abraded with aluminium trioxide particles (27). Blasted TTAIS demonstrated better bone integration than turned/ machined implants. In addition, blasted TTAIS are also etched in some types of implants. In contrast to animal studies, clinical studies didn't find any advantages with blasted TTAIS when compared with turned implants (28).

Biological aspects

Bone regeneration around oral TTAIS is a process that comprises inflammation, regeneration and remodelling with possible overlap of all these phases. TTAIS influence bone healing at cellular and molecular level. In fact, the implant itself acts as an osteoconductive substrate decreasing the size of the defect bridged by new tissues. The TTAIS influences the initial sequences of protein adsorption, platelet adhesion, haemostasis, inflammation and osteogenic cell response (29). Further studies should define physic-chemical properties of the TTAIS interacting with cellular pheno- and genotypes, so as the molecular mechanism with which the cells are recruited and become adherent to the surface. Moreover, the cell-cell communication during the early phase of osseointegration of TTAIS requires better understanding (29).

Immunohistochemistry and SEM analysis show gene expression of cells adherent to TTAIS during the first hours and days after implantation (30,31) with higher expression of monocyte chemo attractant protein-1 (MCP-1) coupled with higher expression of pro-inflammatory cytokines TNF-a (3 h and 1 day after implantation) and IL-1b (1 day and 6 days after implantation) at machined TTAIS. On the other hand, the expression of the chemokine receptor CXCR4, a receptor for stromal derived factor-1a (SDF-1a), was highly expressed at oxidized surfaces of TIS as early as 12 h after implantation. Coexistence of monocytes/ macrophages and mesenchymal stem cells (MSCs) at the interfacial region with predominance of MSCs at the oxidized TTAIS has been identified. It has been also shown that early peak expression of SDF-1a during the first day after surgery was associated with the highest MSCs at the TTAIS level. The role of SDF-1a/CXCR4 chemotactic axis in mediating the recruitment of progenitor cells is of current research interest to reveal the mesenchymal cell recruitment to different sites of osseointegration (31).

Cell attachment to the TTAIS is one of the critical first steps in the cell response to a biomaterial. The cellular attachment to TTAIS is mediated through a protein-rich layer through adhesion receptors including the integrins. Osteoblasts-like cells near TTAIS revealed up regulation of integrin b1 during the 24 h of osseointegration (30).

Inflammation at the bone-TTAIS has not received much attention as that given to the soft tissue-TTAIS. Histological studies in bone revealed that macrophages and multinucleated cells are present in machined TIS (32) as well as HA-coated TTAIS (33) during the early stage after implantation. These cells are known to express a wide range of pro-inflammatory and anti-inflammatory cytokines, growth and differentiation factors and chemotactic mediators. Major pro-inflammatory cytokine, TNF-a, was unregulated after 3 hours at the machined TTAIS compared with oxidized TIS (30). Higher expression was also observed after 1 day. Down regulatory effect was observed on the expression of IL-6 at TIS blasted with TiO_2 particles and subsequently treated with hydrofluoric acid (34).

Many cell types, including osteoblasts, can express these cytokines and growth factors, so it is important to define which cell type is responsible for these changes in gene expression. For instance, the expression of IGF-1 was also up regulated at TTAIS

level during the eight-week evaluation period. *In vitro* studies have demonstrated that monocyte cell line expressed BMP-2 (35) that contributed principally to the osteogenic differentiation. However, *in vivo* data are not available showing the expression of BMP-2 from monocytes at TTAIS level. Research based on antibody-labelling strategies such as immunohistochemistry and fluorescence assisted cell sorting are suggested to verify these findings (36).

The regulation of gene expression at TTAIS clinically is a complex phenomenon. The TTAIS properties possibly influence the gene expression by affecting transcription factor, such as RUNX2, in the differentiation of mesenchymal cells towards the osteoblastic lineage. This factor has also been shown to contribute to the osteoclastic differentiation (37). The higher expression of osteoblast markers alkaline phosphatase (ALP) and osteocalcin (OC) and osteoclast marker cathepsin K (CATK) was similar to a higher expression of RUNX2 at the oxized TIS compared with machined ones after 3 days of osseointegration (31). Similar results were demonstrated for acid etching TIS in comparison to surfaces without acid etching.

Although all these studies suggest influence of the different TTAIS properties on the expression of critical switching factors, it is still not clear in which way and which specific surface properties contribute to such effects. Recent studies on early osseointegration of TTAIS (hours-days) have demonstrated that the upregulation of genes responsible for bone formation ALP and OC was coupled with up regulation of genes expressed by osteoclasts, indicating that the bone remodelling phase is triggered much earlier than what has previously been assumed (31).

Osteogenic cells and osteoclasts show a strictly cross talk between each other. For instance, the surface receptor RANK on osteoclasts recognizes and binds to osteoblast membrane-associated factor (RANKL) during the osteoclastic differentiation from the monocytic lineage (37). In fact, bone remodeling begins during the first days after osseointegration and continues over time. Further studies on gene expression of osteoblasts in relation to properties of the TIS are desirable to establish possible changes at implant-bone interface. Other studies showed that different titanium surfaces led to osteoblasts recruitment, maturation, and differentiation, thus promoting osseointegration at the tissue□implant interface (1). In addiction these studies demonstrated that titanium nanotubes could lead to osteoblast differentiation and extracellular matrix deposition and mineralization in dental pulp stem cells by the activation of osteoblast related genes SPP1, FOSL1 and RUNX2 (9, 38-44).

Peri-implantitis

Peri-implantitis can happen with high frequencies in patients affected by periodontal diseases (8, 11, 45-63) (64-67, 68), after cancer resection (69) and in some syndromic diseases (70).

Peri-implantitis is caused by the formation of a biofilm at TTAIS level and by compromised immune ability at the bone-TTAIS. The biocompatibility of TTAIS can be attributed to a surface protein layer formed under physiological conditions (71).

This protein layer makes the TTAIS suitable for bacterial colonization and biofilm formation. Biofilms are defined as a microbial derived sessile community characterized by cells irreversibly attached to a substratum, interface or to each other, embedded in a matrix of extracellular polymeric substances that they have produced, and exhibiting an altered phenotype with respect to growth rate and gene transcription (72). The role that biofilm plays at TTAIS level in developing peri- implantitis is well documented (73, 74). The biofilm protects adherent bacteria from the host defence system and bactericidal agents via several proposed mechanisms (75).

The host immunity ability on the TTAIS is consequently impaired. The time immediately after surgery is the most favourable for developing infection at TIS level, in fact the local defence system is severely disturbed by the surgical trauma. Even after osseointegration the small number of blood vessels at TIS level compromises local immunity (76). The reduced defence mechanism facilitates biofilm formation and infection may occur. Even if different aseptic protocols have been proposed to reduce bacterial leakage at TIS level, there is still

evidence that bacterial invasion usually occurs after surgery (77). Bacterial contamination can also arise from haematogenous sources later (78).

The nanostructured surface of biocompatible materials strongly influences the adhesion and proliferation of biofilm at TTAIS level. The observation of this phenomenon has led to an increased effort to develop new strategies to prevent bacterial leakage and biofilm formation, primarily through nano engineering of TTAIS. Bacterial species Staphylococcus aureus and Escherichia coli interaction with nanostructured TIS showed an increase in adhesion and biofilm formation with increasing nano scale morphological properties (72, 73, 78).

As previously stated, bacterial adherence to implants is considered to be an important event in the pathogenesis of bacterial infections. In fact, this infection process is a first stage of peri-implant mucositis and peri-implantitis, and a positive correlation has been found between oral hygiene and marginal bone loss around implants in the edentulous mandible. Surface properties of trans gingival implant components are important determinants in bacterial adhesion. In addition, coating characteristics of dental implants such as composition and topography regulate cell response during implant healing. In fact, the characteristics of the implant surface seem to be particularly relevant in the early phase of peri-implant bone healing, and the bone tissue microstructure is mainly related to the remodeling processes at level of the bone- TTAIS.

The modification of the surfaces or the use of different materials has been shown to play a relevant role in the bacterial adhesion to implant surfaces (74,79). Bacterial adherence to implants is considered an important event in the pathogenesis of bacterial infections and the infectious process can be viewed as a stepwise process in which the bacteria must first adhere to an implant surface. The failure of adhesion would result in their being swept away in the fluids, which constantly bathe the tissue surface. Surface properties of trans gingival implant components are important determinants in bacterial adhesion. The study of correlation between TTAIS and periodontal disease could improve also the battle against peri-implantitis (55, 57, 75, 80-84). In fact, dental implants had a great success in the last decades for replacing missing teeth in partially or totally edentulous patients (85-94). Even if the main factor for implant dentistry success is the quality of bone of receiving sites, TTAIS could be an important co-factor in developing peri-implantitis (95-101).

CONCLUSIONS

Titanium AND TITANIUM ALLOYS, based on its physical, chemical and biological properties, appears to be especially suitable for dental implants and prostheses. For the production of dental implants, titanium and its alloys have become well accepted and can be considered the golden standard. Surface activation or tuning of titanium surfaces certainly will improve biological integrity in compromised situations, increasing clinical service of implant therapies even further. Titanium chemical and mechanical characteristics, however, have limited usefulness in fixed and removable prostheses in dentistry. For crown and bridge prostheses, dentists can consider titanium and its alloys as a viable options to more traditional noble and base metal alloys, but careful selection of processing methods and laboratory skill is necessary to ensure the therapy success.

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