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Osteoblasts and insulin: an in vitro study

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To the Editor,

Insulin may stimulate osteoblast differentiation, which means the production of osteocalcin, the peptide that can stimulate pancreatic β cell proliferation and skeletal muscle insulin sensitivity (1-20).

Pre-osteoblasts show the isoform of the insulin receptor (IR) called IRA, while mature osteoblasts the insulin receptor called IRB. This feature makes sense that insulin is a fundamental molecule in osteoblast differentiation from stem cells. Furthermore, this process may have importance in producing the osteoblast peptide osteocalcin, a very important peptide for glucose metabolism. However, the direct effect of insulin on osteoblast differentiation is not completely clear.

Some authors (21-40) isolated stem cells from human exfoliated deciduous teeth (SHED). After isolation from deciduous teeth, cells showed the ability to form in vivo a substantial amount of bone. Therefore, dental pulp from exfoliated teeth could be a good source of postnatal stem cells. Dental pulp stem cells (DPSCs) can form complexes like pulp dentin consisting of a mineralized matrix with odontoblasts very similar to human dentin. The regeneration of a complete tooth is the objective of using 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 transition from a deciduous tooth to a

permanent one is a unique process in humans. The development and eruption of the permanent tooth are contemporary to the deciduous tooth's root resorption. This process starts at about 6 years of age and stops after 12. During this period, all the 20 deciduous teeth usually are replaced.

The dental pulp presents similar features to the gelatinous tissue of the umbilical cord and shares characteristics of primitive stem cells (41-60). 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 the dental pulp, and they can produce new dentin after mechanical or inflammatory stimuli (61-80). When the dental pulp is damaged, usually because of dental decay, quiescent dental pulp stem cells (DPSCs) are activated to produce reparative dentin. The new dentin, called tertiary dentine, presents the same primary and secondary dentine components but a different cytoarchitecture. Problems in mineralization are common in oral pathologies, and the role of stem cells in hard tissue formation has increased interest among researchers and dentists. However, the factors and signalling molecules that control the quiescence/activation and commitment to differentiation of human DPSCs are unknown.

Dental pulp stem cells (DPSCs) may be a source of differentiated cells inducing bone formation and controlled hydroxyapatite crystal growth. DPSCs

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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 (81-100). These DPSCs can self-expand and differentiate in pre-osteoblasts, producing in vitro autologous bone tissue.

The aim of our study is to investigate whether Total RNA extracted from stem cells using insulin can influence the differentiation of DPSCs in osteoblast and bone tissue. We propose a working model that explains the possible interactions between insulin and DPSCs 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 DPSC in cellular therapy and tissue regeneration

MATERIALS AND METHODS

DPSCs isolation

Following informed consent, dental germ pulp was extracted from third molars of healthy young subjects with a mean age of 18 years. Pulp was digested for 1 h at 37°C in a solution containing 3 mg/ml type 1 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 clarithromycin. 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 a 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 FACSscan. In addition, nonspecific mouse IgG was used as isotype control (Immunotech). Finally, live cells were gated tightly using forward, and side scatters to avoid nonspecific fluorescence from dead cells.

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 was 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 a control. Cells were treated for 24 and 48 hours.

RNA processing

GenElute™ 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 a 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 synthesized starting from 500 ng of each RNA sample (treated and controlled at 24 and 48 h) using SuperScript® VILOTM cDNA Synthesis 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 minutes and then inactivated at 85°C for 5 minutes.

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 KiCqStart™ Primers (Sigma Aldrich, Inc., St Louis, MO, USA), specific pre-designed 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

Flow cytometric analyses phenotypically characterized cell cultures. Cell preparations derived from dental pulp were homogenously CD105⁺, CD90⁺, CD34⁻, CD45⁻, CD14⁻, a typical mesenchymal stem cell surface antigen profile. In addition, DPSCs were treated with insulin at 100 ng/ml concentration for 24 and 48 h. Gene expression in treated DPSCs was compared with untreated cells (control) to check the effect of insulin on stem cell differentiation.

Genes related to ossification (BMP1, BMP2, BMP3, BMP4, BMP5, BMP6), osteoblast differentiation (BMPR1A, BMPR1B, BMPR2), bone mineralization (TGFβ1, TGFβ2, TGFβ3) and skeletal development (TGFβR1 and TGFβR2) 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 downregulated in treated DPSCs vs untreated DPSCs. Significantly up-regulated genes (Fold change > 2) were the Bone Morphogenetic Proteins BMP3 and BMP4. Significantly up-regulated genes were Bone Morphogenetic Protein receptor BMPR1A. After 48 h, insulin-induced the over-expression of bone-related gene BMP1.

DISCUSSION

In our study, BMP3 and BMP4 after 24h and BMP1 genes after 48h were up-regulated, inducing proliferation and differentiation of human MSCs. Our study confirms the assumption that insulin promotes markers of bone formation, providing support for the view that insulin influences the differentiation of DPSCs in an osteoblastic sense. Bone morphogenetic proteins (BMPs) have been shown to induce DPSCs to proliferate and then differentiate into osteoblastic cells. Insulin can modulate the expression of various osteogenic markers. Thus, the effects of insulin on DPSCs must be examined, considering their apparent maturity in terms of osteogenic potential. Previous studies showing that insulin promotes bone growth suggest that insulin facilitates differentiation as the cell population reaches a more mature, post-proliferative stage.

DPSCs showed differentiation profiles like those of bone differentiation (101-110), and this event makes them very interesting as a model to study osteogenesis. The 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 (111-129); thus, being able to obtain sorted cells quickly after collection and transplant them directly is an advantage that can lead to the easier application of bone-engineering protocols.

There is a considerable body of work showing osteogenic actions of insulin in cortical bone in several species. In our study, we demonstrated that insulin could increase DPSCs and influence the differentiation and proliferation of DPSCs in osteoblasts.

The extreme feasibility of managing dental pulp stem cells makes them ready to use in clinical trials on human patients. Autologous stem cells collected from the dental pulp of extracted wisdom teeth or from pulpectomy of teeth left *in situ* is a method that can be improved in clinical trials. Although dental pulp could play a fundamental role in all human tissues regeneration in the future, the main commitment is bone, and bone regeneration is the goal for these cells to find an immediate application.

Our study provides evidence that stem cells selected from human permanent dental pulp represent a population of postnatal stem cells that are able to extensively proliferate and differentiate into mesenchymal cells and mainly osteoblasts. Therefore, these cells constitute a large, ideal source of cells for tissue regeneration, tissue-based clinical therapies, and transplantation. Insulin has been demonstrated to influence this process in the production of DPSCs and differentiation and expansion in osteoblasts. Further studies are needed to explore this new way of creating bone tissue.

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Oral and general health: an inseparable pair

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Helicobacter pylori (HP) 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. The risk of developing gastric cancer is related to the different subtypes of HP and to the inflammatory response mediated by genetic factors (1-20).

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

It seems that HP infects the subject early in life and is transmitted from person to person. 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. HP reaches the stomach through oral ingestion, and because of its non-invasive nature, the stomach is the ultimate site of colonization. The evidence of oral transmission includes the high prevalence of HP in African children who are fed with food pre-masticated by the mother and in populations that exchange chopsticks (21-40).

In our study, we review the relationship between oral disease and HP and the role of the oral cavity as an extra-gastric reservoir of HP.

Periodontal disease and HP

Periodontal tissues include four defined structures that constitute the support of teeth: gingiva, cementum, alveolar bone, and the periodontal

ligament. Periodontal diseases are extremely prevalent worldwide, affecting roughly half of the adult population. Its prevalence is similar to HP diffusion in the world population. Gingivitis, the mildest form of periodontal disease, is a rapidly inducible and reversible inflammatory affection of gingiva, mainly caused by an accumulation of bacterial biofilm. The combination of bacterial infection and persistent inflammatory response can eventually induce the progressive destruction of the deeper periodontal tissues, a worse form of periodontal disease called periodontitis. Additional risk factors include genetic susceptibility, tobacco smoke, alcohol intake, and systemic conditions such as diabetes, osteoporosis, malnutrition and stress. Effective treatment of periodontal infections is important to reduce local inflammation and bacteremias. In addition, poor periodontal health appears to increase the risk of HP-induced gastric diseases.

The presence of HP 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 HP 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 HP infection (41-60).

The re-infection rate of HP is high, even after the standardized treatment regimen eradicating

Key words: Helicobacter pylori; oral cavity; periodontal disease; recurrent aphthous stomatitis

HP from gastric mucosa. The oral cavity and periodontal pockets have been hypothesized as one of the suggested mechanisms of re-infection and the possible re-colonization. Some studies have also reported that the condition of chronic infection related to periodontal disease may also favor colonization of periodontal pockets by HP (61-80).

However, the results are controversial. Different studies have found discrepant results, ranging from 0-100% positivity for HP in the oral cavity by polymerase chain reaction (PCR) methods (81-100). In addition, an 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, socio-economic level and differences in the accuracy of the methods used as well as the strain of bacteria (101-110).

HP was detected in different niches of the oral cavity: periodontal areas, mucosa and saliva. A high prevalence of HP was detected in the oral cavities of periodontitis patients. A positive link was observed between HP infection and periodontal disease, and an association was established between the supragingival colonization of HP and oral hygiene parameters, such as the presence of plaque and gingival bleeding (111-129).

The gastric infections caused by HP are treated with systemic therapy (antibiotics and proton pump inhibitors). The eradication of the infection reduces the risk of recurrence of gastric ulcers. 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 HP in dental plaque can persist after eradication therapy. Therefore, even if eradication therapy is successful, dental plaque might be a sanctuary for HP, leading to gastric recurrence. HP in dental plaque may represent a risk factor for gastrointestinal re-infection and ulcer relapse after antibiotic therapy. The periodontal pocket may be important as a natural reservoir for HP because it can provide microaerobic conditions.

The oral cavity of gingivitis or chronic periodontitis patients who are positive for HP in their stomachs can harbour HP after systemic eradication. Recently, a meta-analysis confirmed the close relationship between infection of HP in the oral cavity and the stomach. HP in the oral cavity is more difficult to eradicate than in the stomach and maybe a source of re-infection. One of the keys to success related to the eradication of HP is represented by oral hygiene and periodontal therapy. Some studies have suggested that periodontal disease may be related to an increased risk of gastritis and gastric ulcers. The persistence of inflammation factors due to periodontal disease and alteration of the gastrointestinal microbiome may be considered the associated cause of gastric diseases.

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

Recurrent aphthous stomatitis (RAS) and HP

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 grey 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 pre ulcerative 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 HP in RAS ulcers make this disease similar to gastritis and duodenal ulcers. Another important relationship between RAS and HP is the high incidence of anaemia in patients with RAS that may be caused by HP-positive stomach disease. In fact, antibiotic therapy and treatment of anaemia can reduce the frequency of RAS ulcer recurrence.

Oral cancer and HP

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 a 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 HP was considered a carcinogenic agent type 1 for stomach cancer by the International Agency for Research on Cancer, OMS/IARC, regarding the role of HP in the aetiology of squamous cell carcinoma, to date, no evidence is available.

CONCLUSION

There is evidence of the relationship between oral and HP-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 HP and that periodontal therapy associated with systemic therapy may better eradicate HP from the mucosa of all gastro-enteric tract, reducing the relapse of HP infection. Prospective cohort studies are needed to reveal the bacterial action in the oral cavity.

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The use of laser in dentistry: an in vivo study

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The biological complications of restored dental implants and associated supra-structures share similarities with the biofilm infections of natural dentition. Cement-retained fixed implant- supported restorations involve the risk of excess cement, which can associate peri-implantitis (1-20). Excess cement, retained in the peri-implant sulcus, despite careful clinical control, can become the basis of colonisation by oral microorganisms. As a result of the biofilm formation, peri-mucositis, or peri-implantitis may develop (21-40).

CASE REPORT

A 57-year-old man in good general health who presented with a main complaint of pain and swelling at a maxillary right implant site was referred by his dental practitioner to our periodontal department for consultation. Clinical examination revealed 9 mm probing depth (PD) and bleeding on probing BoP with suppuration, buccally, and 8 mm PD, BoP positive palate distal, bucco- mesial, associated with a purulent exudate. On a periapical radiograph, an extensive radiopaque area is visible distally to the most posterior maxillary right implant. A significant bone loss is visible around both implants. Either calculus deposit or residual cement could be suspected for the radiopaque mass detected on the X-ray. The patient did not take any medication and did not smoke. No occlusal trauma or parafunctional habits were detected. In the presence of such a deep pocket, a surgical approach is

more indicated. However, non-surgical management is the initial treatment modality.

The patient was scheduled for causal therapy to treat the inflammatory lesion by removing the bacterial biofilm and alleviating pain via the use of a diode 980 nm laser (Fibre: 0.300 mm; Power: 2.5 W, Modality: pulsed (pw) ton = 30 μ s, toff = 70 μ s; mean, 0.7 W; 10 kHz; with a Fluence of 120 J/cm², for the total energy of 20,000 mJ, at a frequency of 10 Hz. (Wiser, Doctor Smile, Lambda S.p.A. Vi, Italy). The treatment in each site takes 30 sec, preceded and followed by Hydrogen peroxide 3% or 10 Volumes irrigation. The same procedure is replicated in each pocket 3 times.

After insertion of the optical fibre (0.3 mm) into the peri-implant sulcus, 1 mm from the most apical portion of the pocket, the diode insert was moved in an apico-coronal and mesio-distal direction for 30 sec at each inflamed implant site. Non-surgical periodontal instrumentation was performed by hand, utilising a titan curette and piezoelectric ultrasonic device with plastic fused to a metal insert, as needed. Finally, a Silver-Chlorex Gel containing 0.2% Chlorhexidine and 0.005% Silver cations supported anionic silica particles was delivered into the pocket with a disposable syringe and a blunt needle. At the end of the prophylaxis appointment, a cotton pellet soaked in the same gel was applied.

The same diode laser 980 nm was used with a specific handpiece for biostimulation, with an output lens of about 1 cm in diameter, characterised by a defocalized

Key words: iatrogenic periodontal damage, non-surgical periodontal treatment, peri-implantitis, prosthodontic residual cement

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beam, at a power of 0.7 Watt, in continuous-wave (cw), for 60 sec in duplicate, at each site for a total of 3600 seconds, producing a fluence 1 J/cm², equivalent to 6.000 mJ, with a frequency of 20 Hz. The handpiece was kept perpendicular to the gingival tissue and, in slow motion, in contact with the mucous membrane, drawing small circles. These procedures were repeated the next day. The area was checked for plaque removal and home care evaluation for the first month on a weekly basis and followed by routine supportive periodontal therapy with a periodicity of 3 months. The diode laser was used if signs of inflammation were detected and to prevent peri-implant disease recurrence at the 6th month recall appointment. The entire oral cavity was treated as needed. At a subsequent appointment, the peri-implant tissue appeared to be significantly less inflamed, and the patient referred that all symptoms were regressed. Periodontal indices were documented, and intraoral periapical radiographs were carried out at the 6-month and 1-year follow-up appointments.

RESULTS

Satisfactory results were obtained by the application of laser-assisted non-surgical peri-implant therapy. Periodontal pocket depth was reduced from 9 to 3 mm probing depth with no bleeding on probing. Intraoral periapical radiographs, taken at 6 months and 1-year post-non-surgical treatment, provided evidence of some improvement in the bone level.

In the second X-ray, six months after the initial one, taken to evaluate the effective removal of residual cement, the calcified deposits were no longer present, indicating the non-surgical periodontal instrumentation had proven effective. It also seemed that the quality of bone support had improved, even after such a short period of time.

The reduction of periodontal pockets is probably due to re-epithelialisation, with the formation of a long junctional epithelial attachment (42-60).

DISCUSSION

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. There is no reliable evidence indicating which could be the most effective intervention for treating peri-implantitis (61-80). This is not to say that currently used interventions are not effective. The outcome of non-surgical treatment of peri-implantitis (NSPT) is unpredictable 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. The primary objective of NSPT is biofilm removal and decontamination to resolve the inflammatory lesion (81-100). Non-surgical 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 (101-110).

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 allows accessibility for oral hygiene around implants. 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 significantly higher number of sites that required additional surgical and/or antibiotic treatment (111-129).

Laser treatment may serve as an alternative or adjunctive treatment to conventional periodontal mechanical therapy of peri-implantitis. The clinical application of lasers for the treatment of periodontal disease has continued to expand but remains controversial. Diode lasers have a bactericidal effect due to a localised increase in temperature, *verified in vivo* by using DNA probes that detect periodontal pathogens. Threaded implants have different morphology compared to root surfaces; therefore, debridement instruments might be different. A laser could be a valuable tool to detoxify implant surfaces. A significant bacteria reduction should justify a more satisfactory recovery. It is possible to point the diode laser insert towards the wall of the ulcerated pocket epithelium to kill some virulent periodontal pathogens. Vaporisation of granulation tissue seems

to result in a more favorable effect compared to solo instrumentation. The diode laser detoxifies root and implant surfaces by inactivating bacterial endotoxins, as it is hemostatic and produces no smear layer. The thermal effect weakens calculus chemical adhesion to root and/or implant, facilitating its removal by curettes or ultrasonic devices. Diode laser triggers fibroblast and osteoblast bio-stimulation (24), which in turn causes increased production of RNA messenger, 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.

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.

Anatase is one of the most common crystalline forms of TiO_2 and is normally produced by oxidation of titanium via thermal oxidation or anodisation. 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 coating of healing screws with a derivate of anatase (i.e., Bactercline) produced a lower quantity of bacteria on the surface of these screws. Then in a clinical trial, anatase coated implant was performed and no adverse effect on osseointegration was detected. Here a different device, a Silver-Chlorex gel, was used to control bacterial activity on the implant surface. It has higher antibacterial activity and no side effect on oral mucosa and bone. It seems to be ideal to be used in the treating of peri-implantitis or in combination with other devices and instruments.

It is therefore impossible to isolate one modality more effective than the others. However, it has been proven that laser alone cannot be resolute. Laser for

many periodontal applications must be used as an additional tool, but it does not replace conventional non-surgical 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 peri-implantitis. 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 non-surgical periodontal therapy, in conjunction with the use of 810 nm diode laser seems to be an effective alternative treatment modality for peri-implantitis, 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 emphasised.

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Periodontal disease and smoking: the role of dentist

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To the Editor,

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 disease (PD) 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 PD and systemic diseases (SDs), PD 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 disease' (PD) is generally used to describe diseases affecting the gums and tooth support tissues, causing damage to the connective tissue and alveolar bone (1-20). PD is 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. 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 (21-40). The pathological mechanisms by which PD 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 species called "red complex": *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*. The aim of this study is to explore the relationship between PD and respiratory diseases and smoking.

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 defense mechanisms to reach the lower respiratory airways. The immune defense mechanisms are so efficient, that the lower respiratory airways are sterile, despite the upper airway bacterial load being huge.

Key words: chronic periodontitis, periodontal therapy, smoking

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Pulmonary tract infected by oral biofilm pathogenic bacteria can occur when the immune system defense is decreased, and the pathogens are particularly virulent (41-60). The pathogens can enter via inhalation, but the most accepted hypothesis is that infection of the lung mucosa 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 by another study 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 reported that periodontal enzymes may cause the loss of fibronectin from the epithelial cell surface, uncovering mucosal surface receptors for respiratory pathogen adhesions, and favouring a better adhesion of periodontal pathogens to respiratory mucosa.

Oral pathogens may stimulate the oral mucosa cells to release cytokines, such as interleukin (IL)-1 α , IL-1 β , IL-6, IL-8, and TNF- α . Inflammatory cells may be recruited to the lower respiratory airways by oral tissue cytokines. These inflammatory cells damage the epithelium, making it more susceptible to colonization by respiratory pathogens (61-80).

Smoking and periodontal disease

There are many studies evidencing that TS increases PD progression and slows healing after periodontal therapy. 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 (81-100). 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 (101-110).

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. 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 (111-129).

There is a lack of knowledge on the relationship between PD 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-age 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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Periodontal disease and cardiovascular diseases: a two-way relationship

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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 disease (PD) 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 PD and systemic diseases (SDs), PD 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 disease’ (PD) is generally used to describe diseases affecting the gums and tooth support tissues, causing damage to the connective tissue and alveolar bone (1-20). PD is 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. 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 (21-40). The pathological mechanisms by which PD 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 species called “red complex”: *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*. The aim of this study is to explore the relationship between PD, 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

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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 (41-60).

After eliminating other risk factors, some studies indicate that severe PD is associated with an increased risk of CVD ranging from 25% to 90%; 8.91% of patients with CVD are also affected by PD, which can be mild or severe, while 66% of subjects who have CVD also manifest PD. This data must be explained also by the fact that CVD and PD share similar risk factors such as smoking, diabetes mellitus, obesity, and hypertension. In literature some studies demonstrated a mild-moderate association between CVD and PD (61-80).

In one study, Ziegler et al. demonstrated that the depth of pathological periodontal pockets is related to diastolic blood pressure in obese adolescents. This association was unaffected by other risk markers for cardiovascular events or periodontal disease. In addition, Kumar reported that a persistent infection, such as chronic periodontitis, may influence changes at systemic levels of high-sensitivity C-reactive protein (HsCRP), LDL and HDL, which potentially have an impact on inflammation-associated atherosclerotic processes, such as CVD.

Another study affirmed that PD has a significant relationship as a risk factor in people aged over 40 years, who had coronary artery disease proved by coronary angiography. Another clinical trial provided new evidence regarding the positive effect of periodontal treatment on risk markers for recurrence of cardiovascular events in stable coronary artery disease patients. 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 (81-100).

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. As in the latter study

cited, Thomopoulos stated that from the clinical point of view, advising periodontal prevention or treatment targeting on the prevention of CVD is unjustified (111-129). By contrast, oral hygiene including periodontal health might contribute to the overall well-being and healthy lifestyle which may, at least partially, contribute to cardiovascular prevention.

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 defense mechanisms to reach the lower respiratory airways. The immune defense mechanisms are so efficient, that the lower respiratory airways are sterile, despite the upper airway bacterial load being huge. Pulmonary tract infected by oral biofilm pathogenic bacteria can occur when the immune system defense 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 by another study 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 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.

Oral pathogens may stimulate the oral mucosa cells to release cytokines, such as interleukin (IL)-1 α , IL-1 β , IL-6, IL-8, and TNF- α . Inflammatory cells may be recruited to the lower respiratory airways by oral tissue cytokines. These inflammatory cells damage the epithelium, making it more susceptible to colonization by respiratory pathogens.

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Diabetes and oral health: an old relationship

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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 disease (PD) 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 PD and systemic diseases (SDs), PD 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 disease' (PD) is generally used to describe diseases affecting the gums and tooth support tissues, causing damage to the connective tissue and alveolar bone (1-20). PD is 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. 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 (21-40). The pathological mechanisms by which PD 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 species called "red complex": *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*. The aim of this study is to explore the relationship between PD, 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

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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 (41-60).

After eliminating other risk factors, some studies indicate that severe PD is associated with an increased risk of CVD ranging from 25% to 90%; 8.91% of patients with CVD are also affected by PD, which can be mild or severe, while 66% of subjects who have CVD also manifest PD. This data must be explained also by the fact that CVD and PD share similar risk factors such as smoking, diabetes mellitus, obesity, and hypertension. In literature some studies demonstrated a mild-moderate association between CVD and PD (61-80).

In one study, Ziegler et al. demonstrated that the depth of pathological periodontal pockets is related to diastolic blood pressure in obese adolescents. This association was unaffected by other risk markers for cardiovascular events or periodontal disease. In addition, Kumar reported that a persistent infection, such as chronic periodontitis, may influence changes at systemic levels of high-sensitivity C-reactive protein (HsCRP), LDL and HDL, which potentially have an impact on inflammation-associated atherosclerotic processes, such as CVD.

Another study affirmed that PD has a significant relationship as a risk factor in people aged over 40 years, who had coronary artery disease proved by coronary angiography. Another clinical trial provided new evidence regarding the positive effect of periodontal treatment on risk markers for recurrence of cardiovascular events in stable coronary artery disease patients. 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 (81-100).

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. As in the latter study cited, Thomopoulos stated that from the clinical point of view, advising periodontal prevention or treatment targeting on the prevention of CVD is unjustified. By contrast, oral hygiene including periodontal health might contribute to the overall well-being and healthy lifestyle which may, at least partially, contribute to cardiovascular prevention.

Diabetes mellitus and periodontal disease

The direct correlation between diabetes mellitus (DM) and PD 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 PD. In diabetic patients, proteins become glycated to form advanced glycation end products (AGE) (101-110). 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. This phenomenon reduces osteoblastic differentiation and extracellular collagen matrix production. 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 PD 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 PD. Furthermore, DM slows the healing of tissues. This phenomenon can be explained by increased apoptosis of fibroblasts. Periodontal tissue is mainly formed by fibroblasts, whereby PD is particularly aggressive in these patients. Alteration of immune functions, such as phagocytosis and chemotaxis of neutrophils, may

predispose to the most severe manifestations of PD.

Patients with DM have an impaired immune response. Many studies have shown that these subjects have a higher incidence and more aggressive forms of PD. DM causes vascular changes in periodontal tissue (microangiopathy), hypofunction granulocyte, changes in the oral microflora and, as mentioned before, changes in collagen of periodontal tissue and alveolar bone (111-129). All these studies demonstrated changes at periodontal tissue level, but do not give information regarding the relationship between DM and PD in general. Latest researches suggest important changes at the cellular and molecular level with changes in systemic physiology. These changes provide alterations of immune cell phenotype and increase of serum proinflammatory cytokine/ lipid.

Recent studies have demonstrated that PD can produce these same alterations and, if in association with DM, they are exacerbated. As previously mentioned, the receptors of AGE (RAGE) are over-expressed on the surface of smooth muscle cells, endothelial cells, neurons, macrophages, and monocytes in DM. The binding between AGE and RAGE, may lead to alterations including endothelial surface changes, vascular permeability, adhesion molecules, and migration and activation of monocytes. So far, we have described a glucocentric view of DM. Recently, new knowledge has shifted the spotlight onto a lipocentric vision. Obesity is related to insulin resistance and worsens clinical manifestations of DM and PD. It was discovered that adipocytes are not only fat storage cells, but also produce enzymes called adipokines. These adipokines modulate levels of insulin and insulin sensitivity in DM patients.

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An overview on periodontal disease and genetic polymorphism

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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 (1-20). 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. 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.

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 (21-40).

Specifically, bacterial species such as *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* were consistently found

associated with periodontitis. 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. Familial aggregation studies suggested that genetic factors may be relevant in susceptibility to early onset of periodontitis, while relevance of genetic contribution to chronic periodontitis is still debated (41-60). 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. Recently, genome-wide association analyses were carried out to identify novel genetic factors involved in periodontal disease (61-80).

However, both approaches were not completely successful since confirmation studies often failed to replicate earlier results. Possible explanations could account for the 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-economic status or because allele frequency variation based on population. On the other hand, the 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 (81-100).

This study involved 750 Italian patients and was

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aimed to verify whether Interleukin-6 (IL6), Interleukin-10 (IL10) and Vitamin D Receptor (VDR) gene polymorphisms were susceptibility factors of periodontal disease. The study attempted to replicate previous data obtained with an independent sample of the same population, where single nucleotide polymorphisms (SNPs) of IL6 and IL10 were found to increase the risk of developing periodontitis in Italians. The present study also explored the role of polymorphisms in gingivitis. Polymorphisms of IL6 and IL10 were found associated to periodontal disease in various populations.

MATERIALS AND METHODS

Sampling and genotyping

A total of 750 patients participated in the study. Patients were randomly selected over a period of 12 months according to the following criteria: a 20-year-old age limit; all individuals had to have good general health. Exclusion criteria included diabetes, hypertension, rheumatoid arthritis, depression-anxiety, and obesity as well as heavy exposure to risk factors such as alcohol consumption and smoking. Patients had not had periodontal treatment in the previous 2 months.

Case definition was performed according to the Periodontal Screening and Recording (PSR) system. Gingival bleeding and pocket probing depth were monitored by a specific WHO probe and scored using the basic method indicated by the WHO oral health survey. Basically, the mouth was divided into sextants for the PSR examination. The probe examines each tooth circumferentially in the examined sextant. The clinician only observed the position of the color-coded reference marking in relation to the gingival margin and the presence of furcation invasion, mobility, mucogingival problems or recession. Only the highest code obtained was recorded for each sextant in the mouth.

The American Dental Association and the American Academy of Periodontology suggest that all routine dental examinations include a screening examination using PSR to identify patients who need a comprehensive periodontal assessment. The results of this screening examination are used to separate patients into two broad categories: those who have periodontal health or gingivitis, and those who have periodontitis. These two categories were the main

subject of the investigation, the control group of patients with low PSR in all sextants (PSR code 0, 1 or 2), and a second group of patients with evidence of periodontitis in one or more sextants (code 3, 4 or *). In addition, healthy patients with no periodontal disease (code 0) were compared to patients with plaque-associated gingivitis (code 1 or 2).

The study was approved by the Ethics Committee and written informed consent was obtained from enrolled individuals. After the removal of supragingival biofilm, a sample of the periodontal pocket microbiota was taken from a single site using sterile paper probes, among sites having the highest score, or randomly in the case of healthy patients. Specimens were processed to extract and purify DNA through a silica spin-column (Sigma-Aldrich, St. Louis, MO, USA).

The following polymorphisms were investigated: the XR_108749.1:n.50-321G >C (rs1800795) at IL6 locus, the NG_012088.1:g.3943A >G (rs1800896) and NG_012088.1:g.4433A >C (rs1800872) at IL10 locus, and the NM_000376.2:c.1056T >C (rs731236) at VDR locus. Single nucleotide polymorphisms (SNP) were selected to replicate results obtained in a previous investigation on the same population (PMID: 23814583). Genotyping were performed using ABI PRISM 7500 Sequence Detection System and TaqMan chemistry according to manufacturer's protocols (Life Technologies). Genotypes were scored by researchers in a blind system with no information about the clinical data associated with samples.

Statistical analysis

The distribution of genotypes in patient and control groups was tested for deviations from the Hardy-Weinberg equilibrium using Pearson's χ^2 test. Genetic association was investigated by both allelic and genotypic tests with a likelihood ratio approach using Unphased software v3.1.5 within a Windows Vista operative system. Odds Ratios (ORs) were calculated to evaluate the level of association of the rare allele carriers as well as heterozygote and homozygote individuals. Haplotype association was evaluated for IL10. A global test of association was performed which tested whether any haplotype was associated with the disease. A specific association test for each haplotype was also performed. Logistic regression analysis was performed to evaluate association levels corrected by patients' age and gender covariates.

RESULTS

Of the 750 patients, 215 were diagnosed as healthy, 250 affected by gingivitis, and 285 affected by periodontitis. Mean age was similar for control and gingivitis patients, 48 years (SD=15) and 47 (SD=15) respectively, while it was higher for periodontitis patients 56 (SD=13), P value>0.001. A total of 2892 genotypes were obtained at four polymorphic loci. Genotyping success rate was 99% for rs1800795 and rs1800872 and 94% for rs1800896 and rs731236. Genotype frequency distribution of all polymorphisms in both groups agreed with the Hardy-Weinberg equilibrium law.

A significant difference between control and periodontal disease groups was observed for the IL6 polymorphism rs1800795 while the variant allele C was less frequent in both gingivitis and periodontitis patients (P value 0.008 and 0.0009 respectively). Homozygous individuals with variant allele at IL6 polymorphisms appeared less susceptible to both gingivitis OR=0.47 [95% confidence interval (C.I.) 0.27-0.82] and periodontitis OR=0.36 (95% C.I. 0.21-0.64). No evidence of association between periodontal diseases and IL10 or VDR polymorphisms was obtained.

Since both median age and gender ratio differed in periodontitis group, logistic regression analysis was used to calculate the level of association with IL6 polymorphisms considering these covariates. The corrected OR were 0.76 (95% C.I. 0.51-1.2) and 0.32 (95% C.I. 0.18-0.59) for heterozygous and homozygous patients, respectively. Haplotypes analysis of IL10 polymorphisms did not show any evidence of association with gingivitis (global P value=0.26) nor periodontitis (global P value=0.41).

DISCUSSION

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 (101-110). Several 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. In such a complex scenario, every finding should be replicated through an independent study.

A previous study of a sample of Italian ancestry 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 with 750 Italian patients. The study was 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. Nonetheless, PSR demonstrated a high predictive potential compared to current periodontal disease definitions as outlined by the 1999 International Workshop Classification of Periodontal disease.

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 TNF α (PMID: 9655045). 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. 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, 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 (111-129).

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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