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RESEARCH IN CLINICAL PERIODONTOLOGY: CURRENT APPROACHES AND FUTURE PERSPECTIVE

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ABSTRACT

Research in periodontal science and practice have changed the understanding of periodontal diseases and have opened new, exciting prospects for its management. Newer approaches like tissue regeneration, microsurgery, LASER, precision medicine and many other are developed encompassing now a multitude of areas that were not addressed in the past. There is need for more clinical research in the present era of evidence based dentistry.

KEYWORDS: Research, microsurgery, nanomaterials.

INTRODUCTION

Current prevailing knowledge about the diagnosis and prevention of a disease is the result of continuous ongoing research in the respective field. A prospective approach towards research revolutionizes various aspects of clinical, epidemiological and molecular research and many mysteries. Over the years, the branch of Periodontology has witnessed various innovations and technologies which helps in better clinical management of the patients.[1,2] This paper attempts to analyze current approaches and future perspectives in periodontal research.

Research activities in various fields of periodontology

Numerous studies and modernizations have been done in every field of periodontology which has transformed the diagnosis and treatment planning.

PATHOGENESIS OF PERIODONTAL DISEASE

1. Host response

In the field of pathogenesis of periodontitis, the emphasis is mainly on the role of specific bacteria which initiates its progression. However, in a study done by Van dyke et al in 2019, evidence for a paradigm supporting the central role of inflammation is discussed rather than specific microbiota, in the early pathogenesis of periodontitis, and discussed whether controlling the inflammation can influence the character and composition of the periodontal infection.[3] In addition, with the rapid development of single cell technology, many newly identified immunocyte subsets and cytokines is identified, whose functions in periodontal tissue have not been determined.[4] Further investigations should be encouraged for periodontal-specific cytokine network and host immune response. A new unifying hypothesis called the "Inflammation-Mediated Polymicrobial-Emergence and Dysbiotic-Exacerbation" (IMPEDE) Model is designed by Van dyke et al in 2020, which demonstrates how inflammation can manifest within each classification stage as a principal driver of the clinical condition.[5]

Clinical evidence suggests number of neutrophils present, correlate positively with the severity of periodontitis. The "trained immunity" concept opens new avenues for investigation on the role of neutrophils in periodontitis, in the context of earlier systemic exposures.[6]

Recently, evidence suggests the relationship between periodontal disease and chronic obstructive pulmonary disease (COPD) (Takeuchi et al. 2019) as well as oral cancer (Shin et al. 2019).[7] Also, use of inflammasome regulators, for example, agents that target CARD-only proteins (COPs), pyrin domain (PYD)-only proteins (POPs), tripartite motif family proteins (TRIMs), which are normally inhibited in the healthy periodontium can offer a potential new therapeutic target in modulating the excessive inflammatory response.

DIAGNOSIS OF PERIODONTAL DISEASE

1. Probing system

Till date, five generation of probes are being used in periodontology. The first generation includes conventional probe, pressure sensitive probe as second generation, third generation as probe with controlled probing pressure and automated detection of the cement enamel junction. The fourth-generation probe which

includes sequential probe position within the gingival sulcus to provide a 3D image of the defect site is still under construction. Then is the fifth generation probe, which are designed to provide a 3D image and are being noninvasive. The Ultra Sonographic probe uses the ultrasonic wave to detect, image and map the upper boundary of the periodontal ligament to mark the periodontal disease. There are further research going on to provide even better tool for periodontal disease diagnosis which includes Optical Coherence Tomography (OCT) introduced by Huang et al in 1991 works on principle of coherence near infrared region. It includes the combination of capillaroscopy and optical fiber technology which could produce high-resolution imaging of the periodontal pocket microcirculation. Another technology is the Photoacoustic imaging which is a combination of the high contrast of optical imaging with the high resolution of ultrasound imaging. Diamond probe is another technology with additional benefit of measuring volatile sulfur content.[9]

2. Biomarkers

Various chair side kits available for detection of biomarkers for periodontal disease used are BANA, periodontal test, Periocheck, Perioscan, Evalusite, Prognostic, Biolise, Periogard, TOPAS. Furthermore, other devices and Biosensors like Carboxymethyldextran hydrogel sensor chip with immobilized monoclonal MMP-9 antibodies and Diagnostic chewing gums are being used which detect and measure chemical and biological reactions by generating signals when it comes in contact with the analyte. Nowadays technologies like lab-on-a-chip (LOC) which work on the principle of immunoassay are being used as point-of-care testing device to detect various biomarkers (MMP-8, IL-1b, and C-reactive protein) for periodontitis diagnosis. Recently, for rapid detection of periodontal pathogens a PCR chip has also been devised. This device can measure different bacterial strains in clinical sample.[9]

3. Epigenetics

Epigenetic mechanisms could be used for diagnosing inflammatory processes as it alters gene expression, producing either silencing or over-expression of molecular transcription. Multi-omics technologies are being used to tackle host-microbe interactions. Appropriate use of secondary metabolite software tools for analyzing the genome has resulted in the discovery of many novel antibiotics like gene inhibitors (oligonucleotides, siRNA), gene vaccines and gene substitutes.[10] Gene editing tools like Zinc finger nucleases (ZFNs), Transcription Activator Like Effector-based Nucleases (TALENS) and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR-Cas9)) is being used for controlling the release of growth factor to the defect site. For the diagnosis of biomarkers less invasive sources, such as gingival crevicular fluid could be used. In a study, it is found that the up-regulation of the miRNA has been associated to a decreasing number of cytokines such as TNFa and IL-B, as well as NF-kb. Well-designed randomized clinical trials are needed to assess the usefulness of these markers. Future studies should focus on those mechanisms that have shown stronger association with periodontitis.[11]

4. Precision medicine

It is obvious that patients with a diagnosis of some categories of periodontitis (eg, incipient, mild, moderate, severe) respond differently to the same treatment – meaning that current classifications of periodontal phenotypes do not contain patients who are homogeneous in their makeup. It has been suggested that a precision oral health approach would benefit the diagnosis and the treatment of periodontal disease as introduces the opportunity to use data-driven and biologically informed phenotypes in the its management. For example, in a recent metanalysis done by Munz et al in 2019, it was found that two loci were associated with periodontitis at a genome-wide significance level. They were located within the pseudogene MTND1P5 on chromosome 8 and intronic of the long intergenic noncoding RNA LOC107984137 on chromosome 16, downstream of the gene SHISA9. This study identified novel risk loci of periodontitis, adding to the genetic basis of aggressive periodontitis (AgP) and chronic periodontitis (CP).[12] Personalized medicine for periodontal diseases may soon involve utilization of saliva to develop subclinical profiles, identifying and measuring specific genotypes, phenotypes, putative pathogens, inflammatory markers and collagen-degradation biomarkers to make informed clinical decisions about disease susceptibility, site-specific risk and treatment interventions.[13] Discoveries in all of these areas can provide information leading to new treatments for various periodontal disease phenotypes that can then be used by dentists to practice precision dentistry.[14]

TREATMENT OF PERIODONTAL DISEASE

1. Tissue Engineering in Periodontology

Extensive research has led to the innovation of various scaffold designs and fabrication technologies with a focus on periodontal attachment and orientation. Various growth factors, signaling molecules and biomaterials are available for periodontal regeneration. The materials that seem to biomimetic the oral and periodontal regeneration are hydrogels, Nano fibrous scaffolds, Nano/micro spheres, and multiphase scaffolds. Unique bio-inspired injectable microsphere as an osteoimmunomodulatory scaffolding biomaterial was developed for alveolar bone regeneration.[15] Enamel matrix derivative (EMD) has gained popularity as a biological agent in periodontal regeneration. However, widespread clinical use still remains a challenge due to the complexities that are inherent to periodontal regeneration.[16] They cannot mimic the fine structures of the natural periodontal tissues, such as the different groups of PDL fibers, cellular and acellular cementum structure. Till date, no feasible and effective scaffolding systems regenerated functional Sharpey's fibers. Further research should be emphasized on the development on systems which can

simulate the complexities in periodontal regeneration and also including the restoration of horizontal alveolar bone loss and long-term stability of regenerated periodontal tissues.

In the future, better control of the local microenvironment for stem cell homing and accommodation will most likely render high levels of periodontal tissue regeneration a clinical reality, even for mature periodontal teeth.[17] Recently, bioengineered periodontal ligament called ligaplants provide better approach in implant placement.

2. Surgical techniques

Microsurgery is the new approach which is used to preserve a maximum amount of function and to improve patient comfort. The introduction of loupes, surgical microscope and recent video technology has revolutionized to increase visibility, minimize trauma and to enhance surgical results. Further, minimally invasive surgical approach is the new advancement of the outcome of usage of magnification. Cortellini and Tonetti in 2007 came with the concept of minimally invasive surgical technique and later introduced the concept of space provision for regeneration with the modified MIST 2009 (M-MIST). Also, videoscope assisted minimally invasive surgery (VMIS), Nonincised Papillae Surgical Approach (NIPSA), Vestibular Incision Subperiosteal Tunnel Access (VISTA) technique are few of the recent surgical approaches used.

3. Lasers

Various recent approaches for the use of lasers in periodontology include LANAP, Periolase laser MVP-7 basically an Nd: YAG which operates at a wavelength of 1064 nm was developed. The Waterlase Laser with a wavelength of 2.78μm which works on the principle of hydrophotonics. Also, dual wavelength soft tissue diode laser named Gemini 810 +980 diode laser for soft tissue laser surgery. Another laser system SiroLaser Blue has been introduced that works at three wavelengths that is at 970, 660 and 445nm.

4. Vaccine

In the 20th century, the periodontal vaccine came into the picture with Vancott's vaccine and Inava endocarp vaccine. There are still researches going on to find an antigenic component from various organisms to decrease the load of subgingival microflora. Huang et al. in his study in 2018 used cell-free protein synthesis (CFPS) to produce vaccinable targets suitable for testing in a P. gingivalis-induced murine oral bone loss model.

5. Probiotics

Zupancic et al. in their study incorporated autochthonous bacteria a potential probiotic into nanofibers for local treatment which offers a promising look out for the inhibition of periodontal pathogens with the restoration of the healthy oral microbiota. Also, Golfre et al. used Lactobacillus reuteri Prodentis as a probiotic to treat patients with peri-implant mucositis or periimplantitis and significant improvement was noted.

6. Host modulation therapy

Immunoglobulin Y, gingipains are recommended to be an effective immunotherapeutic agent in the treatment of periodontitis. In addition, more research is required to make treatment response more predictable and to enhance periodontal stability. The clinician can be benefited by both established treatment strategies and with new systemic and local drug treatment by host modulation in high-risk groups.[18]

7. Herbal medicine

Herbal medicine is proving to be potential effective competitor to modern medication as an adjunct to scaling and root planning procedures. However more evidence number of clinical trials are required to further establish herbal medication as a reliable treatment modality for periodontal therapies. The most common herbs used are Curcumin, Babul, Neem, Green tea, lemongrass, Tulsi, Aloe-vera and many more. There number of clinical trials to ascertain effectiveness and safety of traditional herbal medications are relatively less in number. The effects of chemically modified curcumin-2.24 were recently associated with decreased activation/phosphorylation of nuclear factor kappa-light-chain-enhancer of activated B cells, which regulates transcription of a number of gene products associated with inflammatory diseases.

8. 3 D printing

Rapid Prototyping (RP) technique has revolutionized the treatment procedure in periodontology as it quickly and automatically constructs three-dimensional (3D) models of a final product or a part of a whole using 3D-printers. Scaffolds printed using this technique shows predictable outcome for bone and periodontal repair and regeneration. Also, Implant placement using 3D printing surgical template increases the accuracy, reduces deviation in position, incidence of complications, surgical time, postoperative pain, and swelling. Although the use of 3D printing is of prime focus for periodontist, documented literature is limited to preclinical studies, case reports, and few clinical trials. Future implications need more good quality randomized control trials.[19] Many research groups are focusing on the development of printable materials for dental reconstructions, such as zirconium dioxide (ZrO2). RP will most likely offer low-cost production and highly customized solutions in various fields of dental medicine that can be tailored to suit the specific needs of each patient.[20]

9. Nanomaterials

Nanomaterials like Bioactive glass, carbon nanomaterials, Titanium nanotubes coated dental implants, nanoceramics for bone regeneration; Nano biomaterials being used for the preparation of scaffolds for regeneration of periodontium; metallic nanoparticles in the form of toothpaste and mouth rinses for control of

oral biofilm and nanoparticles for local drug delivery, Nanorobots for oral analgesia, drug delivery etc. Research is being carried out in the field of nanotechnology for producing better and even modified products for periodontal regeneration with the elimination of side effects and increasing the biocompatibility of the product.

10. Newer drugs

Resolvin is the new drug to resolve inflammation in periodontal tissue. Various other new drugs like TNF-α inhibitors such as Adalimumab, Golimumab; anti-cytokine. agent like Anakinra, AMG714, Tocilizumab; and RANK/RANKL inhibitor like Denosumab and antibiotic named amixicile, are developed and are being tested in animal model.

11. Other advancements

- Photodynamic therapy also aids to provide significant results when used as an adjunct to the scaling and root planning procedure. In a recent study, the use of toluidine blue O and methylene blue photosensitizer and 633nm He/Ne Laser light has found to be effective in reducing bacterial load.
- Various studies have been done where ozone is used as an adjunctive therapy in chronic periodontitis patients and has offered favorable results.
- In halitosis diagnosis, Biomimetic Olfactory Sensors have been introduced that combine nanoelectronics technology and olfactory receptors themselves as a source of capturing elements for biosensing.[21]
- Developments should be encouraged in the development of dental CAD/ CAM systems.

CONCLUSION

Various new methods and approaches in research have evolved to become more precise and efficient in the treatment procedures. Fields like genetics, precision dentistry, advanced tools like 3D printing need to be addressed and encouragement should be made for use in clinical practice and get benefitted. There is a need to conduct multicentred randomized controlled studies and systematic reviews because we are in an era of evidence based dentistry. More basic science and clinical research is needed to have a better understanding of the biological mechanisms, the long-term effects, and the utilization of the proper carrier and ideal concentration of biomaterials used for periodontal regeneration.

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