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INDIVIDUALISING PERIODONTAL THERAPY NEED TO INDIVIDUALISE PERIODONTAL CARE

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ABSTRACT

The basis of individualised periodontal therapy and medicine is targeting treatment to a patient's specific needs on the basis of genetics, biomarkers, epigenetic, phenotypic, and socioeconomic or psychosocial determinants that distinguish an individual from others with similar clinical presentations. The clinical experimental gingivitis studies in dental students and the experimental periodontitis studies in dogs strongly supported the general concept that bacterial accumulations on the teeth predictably led to gingivitis and, if untreated, progressed to periodontitis. This led to the basic understanding of the concept of non specific and specific plaque hypothesis and the treatment aimed at eliminating microbial insults to gingival and sub gingival areas. But on the other hand this concept suggested that the severity of periodontitis was a simple function of the magnitude of bacterial accumulations and the time of exposure and all individuals are equally susceptible to periodontitis, and if treated according to the proven principles from the longitudinal studies patients should respond in a predictable manner. If those concepts are correct, there is no clear value to stratifying a patient's risk for developing periodontitis or responding predictably to therapy.

KEYWORDS: genetics, biomarkers, epigenetic, phenotypic, and socioeconomic.

The evidence that emerged from Sri Lanka over time indicated that despite extended exposure to substantial levels of bacteria and calculus on the teeth, only a small percentage of the population progressed to severe generalised periodontitis.[1] The second exception was that among patients treated and maintained appropriately for advanced periodontitis, approximately 20%-25% continued to have disease progression and lose teeth.[2] In some studies the disease progression during post-treatment maintenance care was associated with a small number of patient-level risk factors.[3] Thus, to treat chronic disease like periodontitis individualising the therapy can achieve better results in treating those percentage of patients who showed severe destruction and also those who were no responsive to therapy, So Leroy Hood's "P4 Medicine" has succinctly captured not only the overall vision of precision healthcare but emphasizes the critical role of prevention in precision medicine as an essential strategy for controlling chronic diseases.[4]

P4 medicine refers to programs that are:

1. Personalized. Identifying on which disease path an individual is traveling as they age.
2. Preventive. If one can intervene early at the predictive stage to modify the disease path there is an opportunity to extend the time until the individual develops sufficient disease severity and complications that there is compression of the individual's morbidity.
3. Participatory. Many chronic diseases require patient participation to manage the disease successfully. Both prevention and treatment of periodontitis have a participatory element that is substantial, if not deterministic.
4. Predictive. Identifying the disease path before an individual has developed a severe form of the disease or a major complication of the disease.

Individual's risk for periodontitis

The new era of precision medicine, often referred to as personalized, individualized, or stratified medicine, attempts to take advantage of molecular signatures or individual biomarkers combined with traditional risk factors to predict, more clearly, the course of one's disease or to guide choice of therapies. The chronic diseases often display disease heterogeneity,[5] meaning that different pathways can lead to the same clinical phenotype (ie, "many to one"), and also genetic heterogeneity, in which one node in a pathway may lead to multiple diseases (ie, "one to many").[6] The latter phenomenon is evident when the same drug (eg, a tumor necrosis factor alpha blocker) shows clinical value in treatment of multiple complex chronic diseases.

Identifying individual risk for periodontitis starts by explicitly defining the goal as follows[7]

1. Risk for this patient developing periodontitis?
2. Risk for this patient's periodontitis progressing to moderate to severe generalized periodontitis?

3. Risk for this patient having a less predictable response to standard periodontal therapies and maintenance care?
4. Risk for this patient's periodontitis having implications for systemic disease?

The next step after defining the risk factors of an individual is stratification of the subjects which can be either simple or complex.

Figure 1:

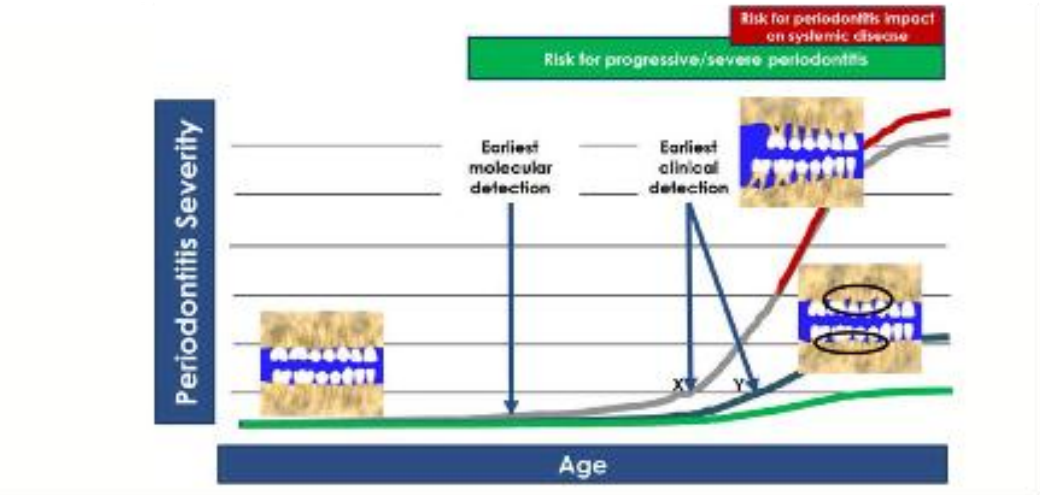


Figure 2:

As seen in the above figure 1, stratification of the patients can be done according to the risk factors they present and also the destruction of the periodontal tissues when they are observed in a clinical setup for the first time. Thus patients can be stratified as slight or mild periodontitis (represented by green dots and green line in the figures 1 and 2 respectively) Moderate periodontitis group which represents blue dots and constitute around 11% of the population, and severe periodontitis group with red dots and grey lines and red lines in the figure 1 and 2 respectively. even if the oral hygiene measures observed by the patients were not optimal, here in the green dots group are those patients likewise in the srilankan labourers study who belonged to the group of 80% group of subjects that showed less destruction or slight periodontal lesions.

Thus these group of patients can be stratified into the green group but the challenge still exists as specialists, is to identify subsets of patients in this group who overtime respond differently to bacterial challenge and either express more severe periodontitis or do not respond predictably to standard clinical approaches to periodontitis prevention and treatment. As seen in the figure 2 the clinical presentation of all the groups of patients would be same as the age progress which is represented in X axis but at certain time in their age different groups of patients will develop destructive periodontal disease of various degrees. So, we can also enrol these patients for a regular preventive dental care program. As explained by Axelsson et al[8] that the assumption of all periodontitis lesions are entirely due to the presence or exposure to sunbgingival bacterial load over time. The treatment approach generally used in such situations after detection of early periodontitis involves repeated prophylaxis with scaling and root planing as indicated in the isolated sites. Such approaches may be augmented with targeted interproximal oral hygiene instructions and local delivery of antimicrobials. Although this approach might heal the periodontal

lesions and might keep the active disease at bay, but in certain group of patients this "all for one" approach could lead to false assumptions of treatment. The current standard in most dental offices throughout the world is that scaling and root planing management of mild periodontitis rarely has a follow-up visit to assess response of the patient. But, individualising periodontal therapy involves a very strict maintenance phase after stratification of patients and will be carried out according to which stage of periodontitis the patients will fall under.

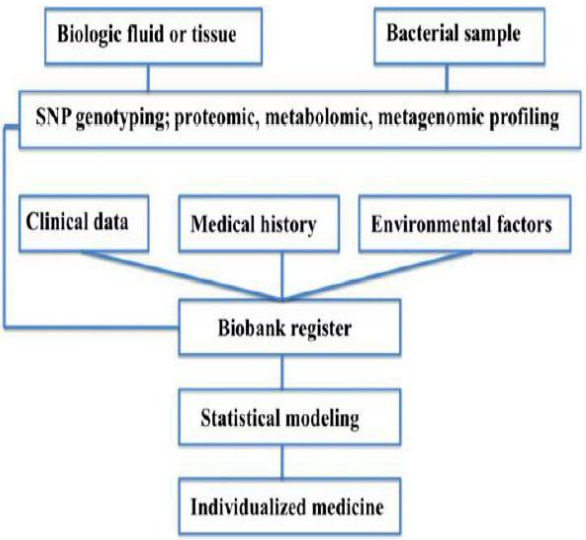
Identifying the disease path before an individual has developed a severe form of the disease or a major complication of the disease.

As seen earlier this is the P4 question that needs to be addressed at the stage of detection of mild periodontitis which in the figure 2 represents blue line, and at what stage that the patients would take the path of grey curve where in the destruction of the periodontal tissues assume a more rapid one leading to complications involving tooth loss. Now it makes sense for us to alter our current approach to primary periodontitis prevention and treatment of mild disease as explained by Paulander J et al above, only if we can do 2 things: (i) use tools which reliably increase the probability that we can identify an individual patient who is more likely to be on the gray path than the blue path; and (ii) obtain evidence that a different approach to prevention or early treatment would make a difference to the individuals on the gray path in terms of reducing the severity and complications of periodontitis.

To answer the above questions inorder to deliver the personalised therapy grouping the patients who are presenting with risk factors like smoking, Diabetes, stress smoking and genetic variations or SNPs is the first step. Identification of systemic disease and treating both the systemic and periodontal disease is the key, important aspect in treating the patients of this group is employing methods like host modulation therapy and antimicrobials like local drug delivery as an adjunct to reduction of microbial insults by more traditional methods.

Smoking (tobacco) is also a risk factor that needs to be controlled in treating a patient with periodontal destruction so, identification of the risk factor and controlling them effectively with proper cessation measures will be important. Also, use of FDA approved host modulation therapy has been shown as effective therapy in treating these patients as shown in studies by preshaw et al.[10] Genetic variations for chronic and aggressive periodontitis showing mutations or variations in single gene or a cluster gene have been identified and studied using independent case control, cohort studies or Genome Wide Association Study (GWAS). The difference between GWAS study and other association studies till date is that the association studies are formulated entirely on the basis of biologic plausibility and have less weightage on evidence. most of the association and linkage analysis studies for genetic variation showed changes in the IL-1 and IL-B, TNF-alpha, vitamin D receptor, TLR CD-14 receptors coding genes as a major risk factor, MMP-1 gene, also studies showing FcG receptor for the neutrophil and macrophages have also shown certain variations. But in GWAS more than 322,825 SNP genetic markers were evaluated for association as risk factors of aggressive periodontitis[11] statistical testing was done in sequence for three independent sets of samples with a total of 438 cases and 1320 controls, wherein it failed to statistically correlate the candidate genes that were significant in association studies, but except for one gene i.e, glocosyltransferase gene (GLTD61) in the human genome.

The advent of high-throughput technologies (e.g., SNP genotyping, NextGen sequencing, Omits techniques, HOMIM [human oral microbe identification arrays]) to determine the genetic, protein, and bacterial profiling of the individual has proven to be extremely useful in stratifying patients and provide individuated therapy. Some pharmaceutical companies provide customized platforms for SNP genotyping; some of these platforms screen for thousands of SNPs. Such methodology permits a broad spectrum of patient genetic records compared to other diagnostic screening tests looking for one or two SNPs. Also, it can be analyzed for SNPs of genes that influence the bone remodeling process such as RANKL and OPG, which can provide insights on the rate of bone remodeling.[12] Another clinical application is the use of proteomics technology to detect protein signatures in periodontitis that can be used for early diagnosis and prevention of disease progression.[13]



As shown in the flow process above, the integration of genetic risk factor analysis and other systemic risk factors for arriving at proper individualised therapy for the patients as also explained in the figure 2 where in

earliest changes can be seen by molecular detection so, incorporating these value added diagnostic methods will change the diagnosis and treatment aspects that involve individualised therapy.

From that above mentioned perspective, medical institutions have started establishing biobanks of DNA to accelerate the realization of the personalised approach to oral health care.[14] When PUBMED and medline search was initiated statewide and national population-based biobanks in the United States do not currently exist. Although many privately owned biobanks exist across the United States, legislatively mandated public biobanks are more appropriate for population-based repositories and are currently in the formative stages of development. The legislation was introduced in the US Senate in 2006.[15] In Europe, biobanks exist but they are lacking strict regulatory guidelines. Recently, a group of experts from the European Commission issued a report entitled, ‘‘Biobanks for Europe, a Challenge for Governance.’’ It deals with ethical, confidentiality, and regulatory challenges of international biobank research and provides recommendations.

Another way to implement an individualised approach in periodontal therapy is the use of systems biology. This comprehensive technique relies on the use of computational methods (e.g., mathematical modeling, simulation technologies) often combined with high-dimensional datasets to span the multiple scales of organization that characterise biologic systems. It can be applied for complex diseases, including inflammation.[16] Also, it allows for a rational modulation at the individual level by analyzing all the biologic components involved in the process.

CONCLUSION

Periodontal diseases are multifactorial: genetics and environmental factors interact with each other to determine the susceptibility of the host to bacterial insults resulting in inflmamtion. Therefore, host–microbial–environmental interactions are major determinants for the development of periodontal diseases thus, for the relationship between genotype and phenotype. Referring to evidence based clinical trials and meta-analyses to guide therapeutic procedures will become less practical in the near future because the new techniques incorporate the influence of genetic and environmental parameters that nowadays are considered confounding factors when comparing different groups in clinical studies.

Finally, the approach to periodontal disease should no longer be limited to treating diseases; we should understand the biologic principles dictating the progression of the disease to efficiently target it and subsequently better manage our patients. Individualised periodontal therapy is the upcoming concept of medical treatment for an enhanced clinical outcome.

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