A Vision in Periodontal Research: Predicting Disease

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Predicting reliably which of our patients will develop periodontitis remains an elusive goal for periodontists. As clinicians, we would greatly desire to be able to perform a simple diagnostic test that would indicate, with adequate sensitivity and specificity, which of our patients are at greatest risk for developing disease. In order to develop and validate such a system, large scale longitudinal clinical trials would be required. This concept was explored at a break-out session of the recent Philips Oral Healthcare Emerging Trends Symposium in Cologne. The discussion, while not scientifically rigorous, was lively and imaginative and led to the development of an idea for the 'perfect clinical trial' which was interpreted by the participants as the clinical trial that they would best like to undertake. Such a trial would aim to develop a method for identifying patients at risk for periodontitis before they actually demonstrated clinical signs of the disease. The discussion focussed on ideas rather than detail about process, and the participants realised that this study, while very desirable in concept, would need a great deal of thought, planning and preliminary experimentation before it could become reality. All of these issues would impact on the practicality of undertaking such a study, which would require significant funding.

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Surely one of the greatest challenges that faces the periodontal community is that of identifying patients who will go on to develop periodontal disease in later life before they actually do. We are all too aware that a diagnosis of chronic periodontitis is largely a historical diagnosis – that is, by the time a diagnosis is reached, by definition that patient has already experienced destruction of the periodontal tissues, a process that is, generally speaking, irreversible. To be able to examine a patient, perhaps perform a simple diagnostic test, and then be able to determine whether or not that patient is about to undergo the (assumed) transition from gingivitis to periodontitis would be of great clinical benefit. The patient could be informed, would be monitored closely and preventive treatment strategies could be implemented. Such a treatment approach, were it possible, would surely embody all that is implied in that term "periodontal medicine".

But how could such a process be implemented? We know that periodontitis results from a complex interplay between a pathogenic subgingival microflora and a susceptible host, modified by a variety of environmental and acquired risk factors for the disease. Periodontitis is a complex chronic disease, and identifying the incidence of disease (i.e. the number of new cases per year in a given population) is incredibly difficult. We rely on crude diagnostic tools (the periodontal probe and the radiograph) that reveal only a historical perspective on the breakdown events that have occurred. We have no idea when examining a patient whether or not their periodontal disease is currently "active" (implying ongoing attachment loss and bone resorption) or "quiescent" (implying a period of lesser or no periodontal breakdown between periods of active disease).

It is now widely accepted that the nature of the host response to the bacterial challenge is a key

determinant of disease expression. Thus, certain patients (hyper-responders) mount an aggressive, upregulated immune-inflammatory response that is primarily defensive by intent (to combat the bacterial challenge) but also results in significant damage to the host tissues. Such a host response is characterised by the release of pathologically high levels of cytokines (such as interleukins), prostanoids (such as prostaglandins) and destructive enzymes (including the matrix metalloproteinases). To a significant degree, the nature of the host response is likely to be genetically determined – that is to say, in certain patients (for example, those with a given, as yet unspecified, genotype), the chronic challenge presented by the subgingival microflora leads to an upregulated inflammatory response characterised by the increased local production of a variety of inflammatory mediators. Research is presently being conducted by several groups around the world to identify genetic markers that are associated with periodontal disease. Typically, these studies focus on genetic variants known as single nucleotide polymorphisms (SNPs). The hypothesis being tested is that if a patient possesses a given SNP, they might produce more of a certain inflammatory mediator in response to the bacterial challenge, leading to the clinical signs of disease. Studies have focussed on SNPs in the IL-1 gene cluster, for example. However, very few studies have actually linked genotype to clinical expression of inflammatory mediators and then, in turn, to clinical phenotype (i.e. clinical presentation of disease). Given the complex nature of periodontal disease, and the large number of inflammatory and regulatory pathways that are involved in the disease process, it seems unlikely that any one SNP, or even a combination, will fully account for the clinical variations in disease expression that we see in our patients.

Therefore, we are still a long way from our ideal scenario – the ability to identify patients who would otherwise develop disease before they actually do. How could a research project to investigate this issue be designed? Several areas would need to be considered, including the patient population, the outcome measures that would be studied, the presence of any confounding factors and, by necessity, the efficiency of such a study in terms of health care economics.

Clearly, in order to identify the incidence of periodontitis, a research study would need to involve a large number of patients (several hundreds, if not thousands) and would aim to recruit those patients in whom there is a chance of chronic periodontitis developing. So, adults aged between 30 and 55 years would be recruited. Patients younger than this typically do not present with chronic periodontitis, and in patients older than this, it may be difficult to identify adequate numbers of patients with sufficient remaining natural teeth that are periodontally healthy. The adults recruited must not have any evidence of chronic periodontitis at the start of the study (though gingivitis would be permissible). Smokers would be permitted, as smokers are particularly susceptible to periodontal disease. The participants would agree to take part in a longitudinal, observational study that would, by necessity, be of several years' duration. They would need to undergo a complete periodontal examination (measurement of probing depths, recession and attachment loss) on a regular basis, perhaps even as frequently as every six months, and certainly not at intervals greater than one year. Measurement of plaque levels would also be a very useful clinical outcome measure. Radiographs would not be used (unless indicated for the participants' routine clinical care) due to ethical reasons. Co-variables that would need to be accounted for include smoking, any local risk factors for periodontal disease, socio-economic status, dental awareness, oral hygiene and systemic factors such as pregnancy. Given the large number of participants that would be involved, it may be appropriate to undertake much of the research in the primary dental care setting, and clearly, a multicentre approach would be required.

What, then, would be the diagnostic test that could be used to supplement the clinical procedures outlined above? If we wish to move away from the retrospective, crude diagnostic tools of the periodontal probe and the radiograph, perhaps there is a biochemical marker that could be measured that would reflect the transition from gingivitis to periodontitis. For example, as the inflammatory process extends from the gingival tissues into the underlying periodontium and alveolar bone, perhaps markers of bone resorption would become detectable; supporting that bone resorption was taking place, and thus confirming that the patient was in the process of developing periodontitis. There are several ways by which a sample could be obtained from a patient and assayed

for a variety of mediators. One would be a gingival biopsy, although this would be hard to justify on ethical grounds, and certainly would not be appealing to potential participants. Another method would be to collect gingival crevicular fluid (GCF), given that we know that the composition of GCF reflects the inflammatory status of the underlying periodontal tissues. However, GCF sampling remains a technique sensitive process, and even a cursory glance at the literature reporting GCF sampling and measurement of inflammatory mediators will reveal huge intra- and inter-individual variations in mediator content and concentration. This variability relates no doubt to the difficulty of collecting representative GCF samples, although individual variation also must play a part.

Perhaps a potential source of samples that has been often overlooked is saliva. Since GCF flows from the gingival margins and is mixed with saliva, then it is possible, in theory at least, that markers of gingival inflammation could be identified in pooled saliva samples gathered from patients. Numbers and/or types of inflammatory cells present in saliva may also be investigated as a possible diagnostic marker. Sampling saliva would also yield much greater volumes for assay (several ml) compared with GCF samples, which are typically < 1µl. With modern, sensitive assay systems, including multiplex systems that can analyse a variety of mediators in a single sample, analysis of saliva could be an attractive research option. Furthermore, saliva samples can be very easily and non-invasively obtained. A great deal of preliminary research would be required to justify the use of saliva as a diagnostic fluid, however. A variety of cross-sectional studies would need to be undertaken to identify whether or not it is possible to quantify inflammatory mediators in saliva samples, and whether the concentrations are reproducibly different in health, gingivitis or chronic periodontitis. Indeed, the saliva levels could also be correlated with GCF levels of mediators in the preliminary experiments. It may be that the absolute concentrations of mediators are not the important factor, rather the ratios or proportions of mediators, some of which may be pro-inflammatory and others of which may be protective.

Assuming that it was possible to identify markers in saliva that could distinguish between health, gingivitis and periodontitis in cross-sectional studies, the next step would be to monitor the levels of these markers longitudinally in the research population discussed above. Thus, on each occasion when the participant attended for full periodontal examination, they would also be asked to provide a saliva sample. After conducting the study for a number of years, it would become apparent that a certain proportion of the participants had developed periodontitis during the study period (the criteria for confirming a diagnosis of periodontitis would also need to be defined – for example, ≥ 2mm attachment loss at ≥ 5% of periodontal sites. It would then be possible to go back to the saliva samples to identify whether the clinical diagnosis of periodontitis was preceded by any changes in the biochemical profiles for those individuals. For example, if may be that the levels of markers of bone resorption increased shortly before the clinical diagnosis of periodontitis was made. If so, then such markers, whatever they may be, could be considered as a test for the transition to periodontitis. Ultimately, it would be revolutionary for the practice of periodontics if such markers could be incorporated into a chair-side diagnostic test. Patients would provide a saliva sample that could be analysed during their consultation with the dentist. If such markers were detected, the dentist could be alerted to the incidence of periodontitis, and could institute strict preventive management and behavioural changes to try to prevent the development of disease. The clinical benefits of such a strategy to individual patients are very clear.

In this proposed clinical trial, participants would be asked to commit to long-term follow-up over a number of years, and they might ask what the benefit would be for them. The answer would be that they would receive regular examinations to identify the development of periodontitis, and if the disease did develop, then it would be diagnosed early, allowing for maximal benefit when therapeutic and preventive regimens were implemented. They would also be receiving a free oral health screening on a regular basis. Another important aspect of the research would be to investigate participant outcomes – in other words, obtain "consumer" input on what outcomes are important to the participant. This could involve validated tools assessing quality of oral health, and could include open-ended questions about which matters are important to participants (e.g. to be free of pain, to have non-bleeding gums, to preserve teeth etc.), and what they would like to achieve by participating in the research.

Such qualitative assessments are all too often lacking in periodontal (and dental) research studies.
On a population and health care efficiency level, the benefits of such an approach are apparent too. If periodontal disease is detected early, or even before it has developed, and then is prevented from developing, then costly periodontal treatment strategies may be avoided, such as non-surgical and/or surgical therapy and subsequent long term periodontal maintenance care. Complex restorative treatments, such as fixed or removable prostheses or implants, may also be avoided. There would be a clear cost benefit for any diagnostic test that identified incipient periodontitis, allowing the condition to be treated early and thereby potentially avoiding subsequent costly treatments.
In an ideal world, dentists would have at their disposal a simple diagnostic tool (such as collecting a saliva sample) that would identify those patients who are at risk of undergoing the transition to periodontitis. Before such a test would be available, however, a large scale longitudinal study such as that described above would need to be conducted to confirm whether or not such a test would actually work. In other words, would it identify those patients (with adequate sensitivity and specificity) who would subsequently develop periodontitis? And before such a longitudinal study could be conducted, preliminary experiments would be required to ascertain whether saliva (or any other biological fluid) would be able to reliably distinguish between health, gingivitis and periodontitis. Clearly, there is much research to be done, and in many ways, the research would be considered to be high risk as there would be no guaranteed outcomes. This creates the problem of funding, as any funding agency would need to take a long-term view, and would need to be aware that there may be no definitive outcome. However, such a study, if it were successful, would completely transform the practice of periodontics as we know it today.

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