Facing Oral Diseases - Risk Factors and Markers with Diagnostic Potential

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Medical diagnosis has been defined as the process (or the conclusion reached through that process) of identifying a disease by its signs, symptoms and results of various biological assessments. Detection of disease, as such, is however not the only purpose of diagnosis. Diagnostic procedures may be used also to:

- Identify people at risk of developing disease (*at risk*),
- Detect early stage disease in clinically asymptomatic individuals (*screening*),
- Classify disease categories (*classification*),
- Predict likely responders to specific treatments (*treatment planning*),
- Monitor treatment efficacy and detect disease recurrence (*monitoring*).

This introductory overview in particular has its focus on choosing and evaluating periodontal risk factors and markers with diagnostic potential. Pocket formation, loss of clinical attachment and loss of bone are pathognomonic for periodontal disease, and presence of disease can easily be diagnosed with a periodontal probe and a radiograph. Rather than diagnosing presence of disease, potential periodontal diagnostic markers should therefore have prognostic value, or should be useful for selecting or changing treatments, and evaluating their success. Prophylactic and therapeutic intervention based on probability of disease, rather than an explicit diagnosis poses specific challenges with regards to determining the diagnostic potential of a biological or clinical parameter.

A biological phenomenon may be chosen as candidate diagnostic marker based on a plausible implication in a pathologic process. The initial evaluation of the diagnostic potential then traditionally focuses on accuracy, i.e. the degree to which the factor correctly identifies the presence or absence of the disease in question. For the evaluation of dichotomous tests, Yerushalmy (1947) proposed the indicators 'sensitivity' and 'specificity'. Tests are often judged primarily with respect to these two indicators (high sensitivity is desired in order not to miss any positive cases, whereas high specificity is sought to avoid false positives), underestimating the importance of the predictive value, which varies depending on the prevalence of the condition within a population. The predictive value of a periodontal test may be different in a periodontist's office and in a general practice because the prevalence of disease is higher in the referred population. The same holds true if a test is used in the context of primary prevention or for the maintenance of subjects previously treated for periodontal disease.

Another possible way of assessing the value of a potential diagnostic marker is by asking whether the information affects the management of the patient. Some test results, both positive and negative, will lead to a change in management, whereas in other circumstances a positive or negative result will lead the clinician to continue with the same management plan. One and the same test can have variable utility depending on the information already available before the test is done. Hence, its clinical value largely depends on questions such as these:

- Does the test provide truly new information?
- Is there a treatment alternative?
- Is it cheaper to treat than to test?
- What are the unwanted effects of an intervention?
- What are the consequences of no treatment?

As an example, a systematic review has focused on the question of whether microbial testing influenced the management of patients with periodontal diseases compared to treatment prescribed without this information. Thirteen studies were identified reporting on microbiological identification as an aid in treatment planning, and 11 studies reporting a differential clinical response depending on the detection or lack of detection of specific organisms (Listgarten et al, 2003). Certain antimicrobial regimes, above all the combination of amoxicillin plus metronidazole, have been shown to be efficacious particularly against some oral microorganism difficult to suppress with mechanical means alone (Pavicic et al, 1991; 1994; van Winkelhoff et al, 1989, 1992). However, other studies show considerable

adjunctive benefits to mechanical treatment of the same regimen even if specific target organisms can not be identified (e.g. Rooney et al, 2002). If microbiological testing is advocated to select subjects for adjunctive systemic antimicrobial therapy because they carry specific periodontal pathogens, one could argue that nobody has ever shown certain patients to be better off, if treated *without* antibiotics. The major arguments to restrict systemic antibiotherapy to a limited range of patients are the avoidance of unwanted systemic effects and the prevention of resistance development in microorganisms in general. Although these concerns demand our attention, to date we lack models that enable us to determine exactly under which specific circumstances the benefit of chemotherapy outweighs its costs and risks for unwanted effects – for the patient, and for society. Due to that, the value of microbiological testing can presently not be determined precisely either.

When discussing the utility of risk factors and markers with diagnostic potential one should furthermore bear in mind that dichotomizing a disease state into yes and no, and a test result into positive and negative, does frequently not represent clinical reality fully. Most diagnostic parameters are continuous initially and are dichotomized at a chosen cut-off level artificially. Because cases with uncertain or equivocal diagnostic status and tests without a definitive result must be excluded, tables assembled for calculating sensitivity and specificity inevitably reflect a distorted picture. Algorithms to assess the effectiveness of non-dichotomous parameters to produce a degree of certainty regarding the presence or absence of disease without imposing an arbitrary threshold, have been proposed (Pretty et al, 2004), but little of this has been applied in the dental field so far.

There are occasions where different tests can be used to make the same diagnosis. Parameters with a diagnostic potential in the context of periodontal health and disease are often highly correlated to each other. Sites with increased probing depths, for example, have an increased tendency to bleed, are associated with anaerobic Gram-negative bacteria (Savitt et al,1984; Mombelli et al, 1991; 1994; 1996) and present high levels of various biochemical markers of inflammation (Tessier et al, 1993; Lamster et al, 1994; Jin et al, 1995). If a diseased site is detected, similar ones will be present elsewhere in the same dentition (Mombelli et al, 2001). The utility of perfunctory assessments of the same parameter at multiple sites, or of multiple related parameters in the same subject should be evaluated properly.

Based on genomic and proteomic techniques a new class of diagnostic tools is currently developed. These new methods will provide exciting new answers to old questions but will also confront us with new problems. Their development opens new opportunities for diagnostics to identify risks, detect early stage pathology, and classify disease on a molecular basis. Future pharmacodiagnostic tests will aim at molecular signatures with response to a particular drug, allowing an efficient identification of patient subpopulations. Genetic polymorphisms of drug metabolizing enzymes, such as the cytochrome P450 (CYP) enzymes 2A6, 2C9, 2C19, and 2D6 and thiopurine S-methyltransferase, drug transporters, such as the MDR-1 gene-product P-glycoprotein, and specific drug targets (e.g. receptors, ion channels, lipoproteins, and genes involved in cell cycle control and development) affect drug response and toxicity (Meisel et al, 2003). The application of this pharmacogenetic knowledge for the selection and dosage of drugs in clinical routine will require extensive research in properly designed prospective studies.

In the perspective of the 'purchaser' - usually the patient or an insurance company - additional criteria for assessing new or traditional diagnostic methods play a role. They include questions regarding the impact of a test on the quality of care offered. Can a new test, for example, replace a more painful, time-consuming or expensive procedure? What are the adverse effects of the test in comparison to the procedures already available, or in comparison to the consequences of not having the information? What is the cost per case diagnosed when those treated due to a false positive result are included? What is the effect of introducing the test on the total cost of care? Not only on an individual level should the benefit of having a particular piece of information outweigh the effort to obtain it; a new diagnostic procedure should also improve the over-all benefit of the total investment in health care.

CONCLUSIONS

Based on standard treatment protocols, the relative costs of diagnostic procedures and treatment planning can be estimated to represent a quarter to one third of the total costs of periodontal care. The current status of evaluating the utility, efficiency and cost-effectiveness of these activities is unsatisfactory. Not everything we can measure will always be helpful. Many traditionally taught methods have never been scrutinized for their exact benefit, and new tests are made available without a properly documented utility. To determine the diagnostic utility (the quality of being of practical use), detailed information is needed on how a test or diagnostic algorithm works in a specific setting and what the consequences of a positive or negative test might be.

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