Detection, Diagnosis and Management of the Early Carious Lesion

A thesis submitted to the University of Manchester for the degree of

Doctor of Philosophy

In the Faculty of Medical and Human Sciences

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School of Dentistry

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LIST OF ABBREVIATIONS

ANCOVA	Analysis of covariance
AUROC	Area under receiving operating curve
CRA	Caries Risk Assessment
CCD	Charge couple device
ECM	Electronic Caries Monitor
EDJ	Enamel dentinal junction
DD	DIAGNOdent
FOTI	Fibre- Optic Trans-illumination
ICDAS	International Caries Detection and Assessment System
In vivo	Clinical study
In vitro	Study conducted in laboratory
Mos	months
NaF	Sodium fluoride
NCCLs	non-cavitated caries lesions
OR	Odds Ratio
ppm	part per million
QLF	Quantitative Light-induced Fluorescence
SE	Standard Error
SD	Standard Deviation
Se	Sensitivity
Sp	Specificity
SPSS	Statistical Package for Social Sciences
UK	United Kingdom
WHO	World Health Organization
Wks	weeks

Original papers

The thesis is based on the following papers:

I. Gomez J, Tellez M, Pretty IA, Ellwood RP, Ismail AI. Non-Cavitated Carious Lesions detection methods: A systematic review. Community Dent Oral Epidemiol, 2013 Jan 25. doi: 10.1111/cdoe.12021

II. Tellez M, Gomez J, Pretty I, Ellwood R, Ismail A. Evidence on existing caries risk assessment systems: are they predictive of future caries? Community Dent Oral Epidemiol. 2012 Sep 15. doi: 5.1111/cdoe.12003.

III. Tellez M, Gomez J, Kaur S, Pretty IA, Ellwood R, Ismail AI. Non-surgical Management Methods of Non-Cavitated Carious Lesions. Community Dent Oral Epidemiol. 2012 Dec 18. doi: 10.1111/cdoe.12028.

IV. Ellwood RP, Gomez J, Pretty IA. Caries clinical trial methods for the assessment of oral care products in the 21st century. Adv Dent Res. 2012 Sep;24(2):32-5.

V. Gomez J, Zakian C, Salsone S, Pinto SC, Taylor A, Pretty IA, Ellwood R. In vitro performance of different methods in detecting occlusal caries lesions. J Dent. 2012 Nov 9. doi:pii: S0300-5712(12)00305-3. 10.1016/j.jdent.2012.11.003.

VI. Gomez J, Pretty IA, Santarpia III RP, Cantore B, Rege A, Petrou I, Ellwood RP. Quantitative Light-induced Fluorescence to measure enamel remineralization in vitro. Accepted for publication Caries Research August 2013.

VII. Gomez J., Pretty I.A., Ellwood R. Use of QLF to Assess Enamel Mineral Changes in a pH cycling study. Submitted for publication.

VIII. Gomez J, Ellwood RP, Martignon S, Pretty IA. Dentist's Perspectives on Caries-Related Treatment Decisions. Submitted for publication.

The University of Manchester

ABSTRACT of the thesis submitted by Juliana Gomez Bulla for the Degree of Doctor of Philosophy entitled Detection, Diagnosis and Management of the early caries lesion- September 2013.

The current evidenced-based caries understanding, based on biological concepts, involves new approaches in caries detection, assessment, and management that should include non-cavitated lesions.

The purpose of the studies presented in this thesis was to investigate the current available evidence on methods to detect non-cavitated lesions (NCCls), the current evidence related to the efficacy of non-surgical caries preventive methods to arrest or reverse the progression of NCCls, the current evidence for the prediction of caries using four caries risk assessment systems/guidelines and a review of the literature related to alternative caries clinical trial methods for oral care products. The purpose of the in vitro studies was to study the performance of different caries detection methods (ICDAS, ICDAS photographs, FOTI, QLF, OCT, Soprolife) in detecting early caries lesions and in particular and to assess the QLF ability to detect changes after remineralisation/demineralisation cycles. The last study was a cross-sectional study aiming to investigate the caries management decisions for early caries lesions among dentists. The results of the systematic reviews (Paper I-IV) suggest a large variation of Sensitivity, Specificity and lack of consistence on the definition of disease among the detection methods assessed. The evidence on Caries Risk Assessment Systems is limited and the current systems seem not to predict future disease. In terms of Caries Management, according to the evidence fluorides continue to be the most effectiveness anti-caries agent. The evidence on abbreviated clinical trials showed excellent discrimination between anti-caries products in short clinical trials with fewer subjects using more sensitive caries detection methods. Paper V, showed that all the caries detection methods assessed in this study, except for OCT (0.65), were strongly correlated with Histology. In papers VI and VII, QLF showed the ability to detect differences between two NaF toothpastes (550 ppm F, 1100 ppm F) and a fluoride placebo treatment in two pH cycling models. Finally, the results of the questionnaire on Caries Related Treatment Decisions (Paper VIII) revealed that 60% of the dentists are practising prevention in occlusal early lesions. However, a large number of dentists are still oriented towards a restorative approach and do not base their treatment decisions on individual caries risk. The main conclusions from this thesis are that: 1) A comprehensive management system should include initial caries lesions; 2) Visual examinations is still the standard method of detection, other methods may be included for monitoring purposes; 3) QLF was able to detect remineralisation of artificial carious lesions and inhibition of demineralisation in sound enamel after two remineralisation/demineralisation pH cycling models; 4) The results of the cross-over study indicate that Colombian dentists have not yet fully adopted conservative treatment for early caries lesions.

DECLARATION

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

COPYRIGHT STATEMENT

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My sister, Jimena, my best friend. I love her dearly and thank her for all her unconditional love, support and her never-ending encouragement. A special thought for my beloved grandmother who will always be in my memory.

This thesis is dedicated to my parents for being the most amazing loving parents possible. Thank you both for giving me the confidence and courage to follow my dreams and stand up for my ideals. I thank you for your encouragement and unfailing belief in me and for teaching me the value of education. For this and much more, I am forever in their debt.

Finally, words are not enough to express my gratitude to Jorge Mario, my husband. This thesis is also dedicated to you. This work is as much yours as it is mine, for your endless patience with an often-absent wife. I would like to thank you for your endless love and encouragement throughout this entire journey. I hope that the dedication of this thesis in some way compensates for the time lost between us. I am truly thankful for having you in my life.

CHAPTER 1

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INTRODUCTION

The Author

I qualified from the School of Dentistry, University el Bosque in Bogota, Colombia in 1998. After three years in practice I decided to undertake a Postgraduate diploma in Paediatric Dentistry in Paris, France. I completed the Paediatric Postgraduate Clinic programme in 2005. Since my return to Colombia in 2006, I worked in Private Practice, Public Practice in a Children' Hospital and as a Research assistant at the Universidad El Bosque, where I participated in multiple clinical studies until 2010. It was a desire to continue the academic career, thus the interest in a PhD. During my PhD, I have been also participating actively in the development of the International Caries Classification and Management System (ICCMS) developed by the ICDAS group. The author is currently appointed to start working at the Dental Health Unit at the University of Manchester, where she will perform investigations into clinical trials.

This thesis was planned to be undertaken in three phases; an initial phase to evaluate the available evidence on Caries detection, Caries Risk and Caries Management and alternatives technologies in clinical trials. The second phase consisted in a series of in vitro studies based on the validation of different caries detection methods against histology and especially to test the ability of QLF to detect mineral changes in two pH cycling models. Finally, a survey to describe caries management decisions in early carious lesions among dentists was developed.

Introduction to the Thesis

This thesis is presented using the University of Manchester alternative thesis format sometimes referred to as the journal format. This format allows incorporation of sections that are in a format suitable for submission for publication in a peer-reviewed journal into the thesis. This structure aligns with the learning aims of a PhD. The peer-reviewed process of the publications should lead to a higher quality research.

This thesis was planned to be undertaken in three phases; an initial phase to evaluate the available evidence on Caries detection, Caries Risk Systems, Caries Management

and Caries Clinical Trial Methods for the Assessment of Oral Care Products. The second phase consisted in a series of in vitro studies based on the validation of different caries detection methods against histology and in particular in two further pH cycling models (remineralisation/demineralisation) to determine the ability of Quantitative light-induced fluorescence to detect mineral changes. Finally, a survey to describe caries management decisions among dentists was developed.

This thesis contains three sections:
- Literature review
- Main chapters including published and submitted papers
- Summary of the findings

1. Introduction

Dental caries is the most prevalent chronic disease worldwide. When initial lesions are taken into account into the clinical assessment, only few individuals are truly unaffected. In most industrialised countries 60-90% of school-aged children are affected and nearly 100% of the adult population is affected (1). However, over the recent years, the patterns of disease presentation have changed. The progression of non-cavitated lesions seems to be slower, allowing preventive strategies to be implemented when the lesions have the greatest opportunity to arrest. Traditional methods combined with more sensitive methods may improve the caries diagnostic and also help the clinician in monitoring non-operative treatments. Also, clinical trials involving thousands of subjects and for long periods of time are today unrealistic and the use of cavitated endpoints unethical (2).

Dental caries is a process involving an imbalance of the interaction between the tooth surface and the microbial biofilm resulting in net demineralisation. If this imbalance progresses, the loss of minerals will progress to a frank cavitation. During the past years, the paradigm of caries as an end-point detected at a cavitated stage has shifted into one which caries is considered as a continuum process that can be detected and treated at early stages. It is at the early stages that preventive strategies can arrest the progression of the lesion and promote remineralisation. Therefore, the assessment of non-cavitated lesions becomes essential. Over the years, new approaches in caries detection, assessment, and management including non-cavitated lesions have been developed based on the biological understanding of the caries process.

Clinical caries measures involving "pre-cavitation" lesions have been in fact reported in caries clinical trials since 1965 (3) and have been described and used in clinical research and practice already for more than 50 years (4). Numerous systems (5, 6, 7) have been developed since the 60`s (3) to score non-cavitated lesions. However, some approaches still used in dental practice and in clinical trials have been focused on detecting lesions at a cavitation stage informing only restorative decisions (7).

Several conferences have also been held during the past years focused on caries detection and management. In the last Consensus on Diagnosis and Management of Dental Caries, the inability to accurately identify early caries lesions and the need for a change in the system with respect to the non-surgical management of non-cavitated lesions was highlighted (8). The Consensus Panel concluded the evidence-base for current methods of detection and activity assessment of non-cavitated lesions was not sufficiently strong to recommend their formal adoption (9). An International Consensus Workshop on Caries Clinical Trials (ICW-CCT) (10) concluded among others:

- Lesion detection implies an objective method of determining whether or nor the disease is present, lesion assessment which aims to characterise once it has been detected and caries diagnosis which implies a human professional summation of all available data.
- Visual diagnosis is the standard of caries diagnosis; the use of additional methods should be explored further.
- Bitewing radiography add information to the diagnosis
- The future of clinical trials, recording only cavitated lesions as an outcome is becoming outmoded.
- Caries measurement methods should accurately capture any signs of the manifestations of the caries process at any given point in time, be able to monitor different levels of de/remineralisation and differentiate product effects in terms of lesion initiation and lesion behaviour (progression, arrest and/or regression).

In spite of all this evidence available, preventive strategies have not been utilized efficiently by the profession. There are a number of reasons for this – perhaps due to failure to observe successful outcome, financial pressures and the inability to detect lesions at an early stage sufficient for effective prevention. The key problem is that operative care has remained the central management strategy for caries control in general practice, which has impacted negatively caries epidemiology, clinical outcomes, and patient's quality of life among others.

Another issue on the caries diagnosis and decisions to treat is the lack of consensus among dentists (11-14). The notion of caries detection preceding the treatment decision is not always how dentists based their decisions. Suggestions have been made about dentists not following a hypothetico-deductive process for taking decisions. Instead, dentists tend to use caries scripts to make the diagnosis process. A caries script is a summary of the clinician's experience with similar clinical presentations. During the exam, if a pattern of the caries script is recognized, a rapid decision in terms of treatment is taken, and a proper diagnose is skipped and replaced by scripts in the form "this-type-of-lesion-needs-this-type-of-treatment" (15).
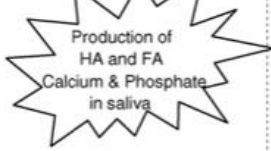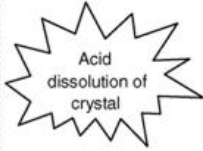
It was the aim of this thesis to investigate the actual evidence on caries detection, caries risk and caries management, to explore the caries detection performance of ICDAS, ICDAS photographs, FOTI, QLF, Soprolife and OCT and to understand the accuracy of QLF to measure mineral changes after remineralisation/ demineralisation cycles. Finally, to describe dentists' treatment decisions related to non-cavitated caries lesions. Are dentists doing what they should be doing according to evidence found in this thesis?

2. The Caries Process

2.1. Dynamics of the caries lesion formation

Dental caries is recognised, as a dynamic process where an imbalance leads to mineral loss. This imbalance begins when the local pH decreases from a pH of 7.0 to a pH of less than 5.0 within the biofilm fluid and along the interface between the biofilm and enamel surface. As pH is lowered in the oral fluids, saliva and plaque fluids, the super saturation with respect to hydroxyapatite is reduced leading to a enamel dissolution (16). However, if fluoride is present in the biofilm fluid, and the pH is not lower than 4.5, at the same time that hydroxyapatite is dissolved, fluorapatite is formed (16). Calculations have shown that a pH drop of one unit within the pH range 4-7 gives rise to a 7-fold increase in the solubility of the hydroxyapatite (17). The more fluoride the apatite contains the less soluble it will be as the pH drops (Figure 1.1).

Figure 1.1. Demineralisation and remineralisation cycle for enamel caries (adapted from Pretty) (18).

			Critical pH of HA		Critical pH of FA			
pH	6.8	6.0	5.5	5.0	4.5	4.0	3.5	3.0

Production of HA and FA Calcium & Phosphate in saliva

Demineralisation Dissolution of HA FA forms if fluoride available Remineralisation FA reforms

Acid dissolution of crystal

8.0	6.8	6.0	5.5	5.0	4.5	4.0	3.5	3.0
Formation of calculus		Remineralisation Demineralisation		Caries			Erosion	

HA is hydroxyapatite   FA is flurorapatite

Sound enamel consists of hydroxyapatite crystals tightly packed showing a glass-like appearance. The intercrystalline spaces are filled with water and organic material. When the tooth erupts into the oral cavity, the enamel is fully mineralized, but its surface is under modifications over time (19). Thus, the enamel integrity of the enamel in the oral environment is dependent on the composition of the surrounding fluids (saliva or biofilm fluid) (20). After tooth eruption, the exposed tooth surface is covered by an acquired enamel pellicle, consisting of an acellular base layer of protective proteins bind to hydroxyapatite, proline rich proteins, and mucinous proteins derived from the saliva. One function of the enamel pellicle is to provide a lubricating layer to allow for efficient mastication. A second function is to provide protection from demineralisation (20). When the caries process begins, at the ultrastructural level the intercrystalline spaces become wider, indicating a partial dissolution of the crystal surfaces. Under *in-situ* conditions the first enamel changes are visible as opaque changes after air-drying; the porosity is increased and a subsurface lesion is formed after 14 days. After three or four weeks of biofilm retention conditions, the surface shows a complete dissolution of thin perikymata and pits of Tomes' processes, with visual signs of opacity, even without air-drying (21).

As the enamel is a micro-porous solid composed of crystals, and because the caries lesion is the result of acids reacting with individual crystals, it is reasonable to consider the intercrystalline spaces as being the most important pathways for the diffusion of ions into and out of the enamel, particularly at initial stages of lesion formation. Histological studies have shown that white spot lesions consist of four

layers: - the first one is intact and well-mineralized; - the second layer is very porous and it is the largest of the four regions; - the third zone consists of tiny pores as well as interprismatic areas and cross striations, and the later is the translucent zone, which is also the deepest (22). Compared with the subsurface, the surface contains more fluoride, less water, carbonate is more highly mineralized and the enamel crystals are differently oriented (22). The increase in the internal enamel porosity due to demineralisation will cause a loss of translucency producing the characteristic chalky surface of the white spot lesion. The white spot lesion is the earliest clinical sign that can be seen by the human eye and by this time the process has been going on for months. At this stage lesions can still be remineralised (21).

Studies conducted by Holmen (1987) showed that caries normally occurs in "protected areas" where dental plaque can accumulate undisturbed by mechanical forces. Sites such as the gingival margin, the approximal surfaces and occlusal surfaces are known as natural plaque-stagnation areas (21). During tooth eruption, more favourable conditions for bacterial accumulation are offered because those teeth do not participate in mastication for a long eruption period (23, 24). In teenagers, the distal surfaces of second premolars and the mesial surfaces of the second molars are prone to lesion development (25). Root caries are more common in elderly patients (26). In these deposits a continuous metabolic activity results in periods of demineralisation and re-deposition of minerals. These changes are not clinically visible, and represent active enamel lesions, that can be turned into inactive lesions as the biofilm is removed at regular intervals. This transition is a result of a treatment aiming at arresting lesion progression (19).

In the case of failure to remove plaque from retentive tooth areas, a diet high in frequently consumed refined carbohydrates, the dynamic equilibrium between demineralisation and remineralisation will be tipped towards demineralisation, and this will result in clinically detectable white spot. The characteristic chalky surface of the white spot lesion is because there is an increase in the internal enamel porosity due to demineralisation, which causes a loss of translucency. The white spot lesion is the earliest clinical sign that can be seen by the human eye, and yet, by this time the process has been going on for months (21).

Dentine caries consist of four zones, however the most relevant clinically are the infected layer and the affected layer (Figure 1.2). The infected layer is highly infected and not capable of repair and the affected zone is able to repair and the caries can be arrested (27).

Figure 1.2. Section of dentine caries showing infected and affected zones.
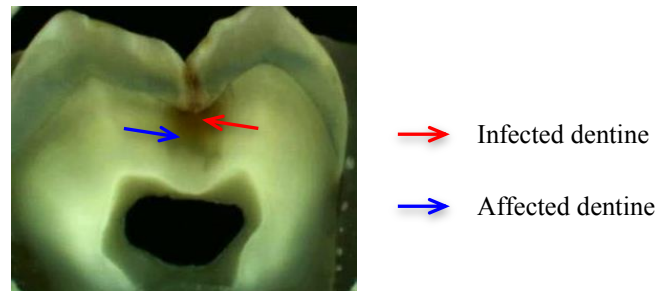
The caries process can also be modelled in pH-cycling models. The advantage of the models is that much can be learned about processes involved in a much shorter period of time. The thousands of experiments that have been conducted and reported in the literature for both *in vitro* and *in vivo* experiments readily confirm the caries lesion is formed by a continuous process starting at the atomic level on the crystal surface in the subsurface of the tooth, and progressing deeper and deeper into the enamel (28).

2.1.2. Arrest of caries lesion

The caries lesion may be arrested at any stage by removing the cariogenic biofilm (19). In 1966, Backer-Dirks examined 184 buccal surfaces in the same children at 8 years and again at 15 years. The surfaces were classified in three categories: "sound", "caries white", and "carious cavity". Of 72 white-spots lesions only 9 progressed to a cavity stage, 37 (51%) were sound at age 15, while 26 remained stable. The disappearance of the white opaque lesions in the buccal surfaces was considered to take place by either, remineralisation, surface abrasion, or both. The conclusion of the study is that if favourable conditions for accumulation along the gingival margin of erupting first maxillary molars lead to early development of "white spot" lesions; further eruption leads to changes in the local environment, which favour mechanical

removal or suppression of cariogenic plaque, causing either arrestment of further progression or complete disappearance of lesions (4).

Remineralisation occurs when calcium and phosphates, originating from saliva or other sources, recrystallize build on existing crystals. In this process, fluorides have a considerable function of speeding up the process. The mineral formed during the remineralisation will be stronger, especially if fluoride ions are incorporated into the surface, these ions can attract calcium ions, which then attract phosphate ions, and finally build a fluorapatite-like remineralised in the crystal surface. This also means the demineralisation by acid can be markedly inhibited by a sufficient concentration of fluoride ions on the crystal surface (29).

The lesion arrest is the result of mechanical removal of cariogenic plaque. Plaque removal results not only in arrest of further progression, but also in regression of enamel lesions. The use of the word "remineralisation" has often been associated with lesion arrest (19). However, cavitated lesions can still arrest with plaque removal. The dentine pulp complex is not passive and can respond to carious attacks by multiplying of neural tissue, migration of immunological cells and production of secondary and tertiary dentine (27).

Remineralisation often takes place in the surface layer, becoming blocked to diffusion of ions in and out of the lesion. Therefore, it has been questioned whether a complete remineralisation can occur under in vivo conditions (30) probably because the surface layer of the lesion forms a diffusion barrier avoiding the uptake of minerals into the subsurface (31). It must be remember that a lesion can persist lifelong as a caries scar; this can be white or colour due to exogenous uptake on stain (20).

3. Caries Detection and Severity Assessment

Caries diagnosis has been defined as "the art or act of identifying a disease from its signs and symptoms" and caries detection is the signs and symptoms identified (26).

There is often confusion in the literature in the terminology used for caries detection and caries diagnosis. In the last decade, three terms have been agreed in terms of direct relevance to preventive caries care: (1) *lesion detection:* implies an objective method of determining whether or not disease is present; (2) *lesion assessment:* aims to characterise or monitor a lesion, once it has been detected, and (3) *caries diagnosis:* should imply a human, professional, summation of all available data (10).

The continuous process of caries has been represented by an iceberg as a metaphor to conceptualize dental caries. The iceberg (Figure 1.3) represents the whole arrange of lesions and shows how traditional methods may leave undetected a large number of early lesions depending at which diagnostic threshold the methods are used (32).

Figure 1.3. 'Iceberg od Dental Caries': Diagnostic Thresholds in Clinical Trials and Practice (10).
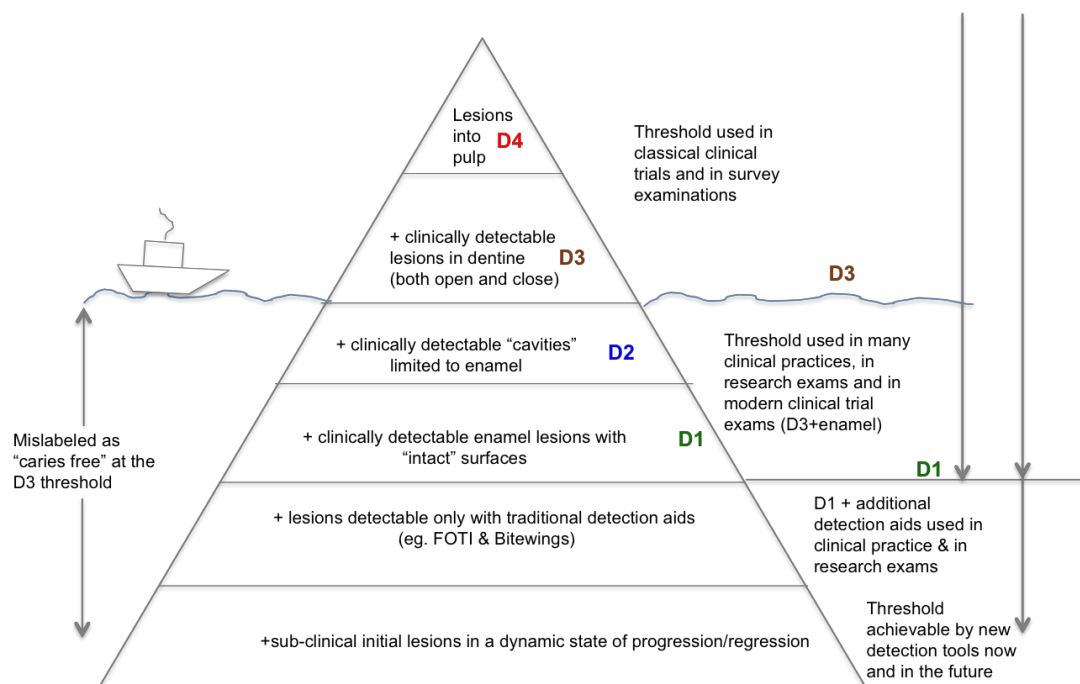
Caries detection methods are frequently introduced into the market without much prior scientific evaluation. It has been stated that a good detection method should be valid and reliable (7). A valid method results in measurements compared with a gold standard. In caries, the detection performance has been assessed using at 2x2 contingency table containing the distributions of the true positives, true negatives,

false positives and false negatives. Sensitivity and specificity are widely used measures to describe and quantify the diagnostic ability of a test (33) and are expressed as values between 0 and 1 (100%). Those values will depend on the distribution of caries on the studied sample. Often the caries prevalence of the sample studied in the in vitro studies is high (50-90%) compared with real clinical situations, overestimating the sensitivity at disease level. The inclusion of too many sound surfaces in a sample of a study will cause an overestimation of specificity (34). The variation of the sensitivities and specificities varies depending on the thresholds level. It has been shown that when the detection of the disease is made at the non-cavitated level, the DMF can be doubled and the sound surfaces were decreased to approximately one-quarter (5). The concept of reliability of a method is also important. A reliable diagnostic is a method that can be used by one or different examiners so they should obtain identical results. A caries detection method should also be responsive (able to detect small changes in caries status), pragmatic, simple and affordable providing maximum cost-benefit (7).

3.1. Visual Criteria

The most common method of caries detection is the visual examination of the tooth surfaces. Different caries indices have been developed in order to standardise and quantify the disease.

3.1.1. Caries indices

The DMFT/dmft index

Originally described as D for decayed teeth, M for missing teeth, due to caries and F for filled teeth. This index gives equal weight to untreated decayed, missing or well-restored teeth, is invalid when teeth have been lost for other reasons than caries, it can overestimate the caries experience in teeth with preventive restorations, and it gives little information about treatment needs. The DMF index is a system that can be applied for the whole tooth (DMFT) or for each surface (DMFS), for primary teeth (dmft) and for permanent teeth (DMFT) (35).

Ekstrand criteria

Ekstrand et al. (1995) suggested a visual score system to assess the depth of lesion penetration. The scale describes the following scores: - no or slight-in-enamel translucency after drying (5secs); -opacity or discoloration hardly visible on wet surfaces but distinctly visible after drying; - opacity or discoloration distinctly visible without drying; -localized enamel breakdown in opaque or discoloured enamel and/or grey discoloration from the underlying dentine; -cavitation exposing dentine (6). This method recognizes the physical phenomenon of the white spot very early lesion, clinically assessed only after air-drying. One of the most significant advantages of the system is its correlation with histology. White spot lesions, which require air-drying, are most likely to be limited to the outer ½ of the enamel. The depth of a white or brown spot lesion obvious without air-drying is located some place between the inner 1/2 of the enamel and the outer 1/3 of the dentine. Localized enamel breakdown due to caries, with no visible dentine, indicates that the lesion extends to the middle 1/3 of the dentine. In addition, a greyish, brownish or bluish shadow of the dentine shining up through apparently intact enamel also indicates a lesion extending to the middle 1/3 of dentine. Frank cavities with visible dentine indicate that a lesion has been extended to inner 1/3 of dentine (6) (36).

ICDAS

The International Caries Detection and Assessment System (ICDAS) was developed in 2001 by an international group of researchers. The system was proposed as a strategy to integrate the modern detection systems into one standard system (37). The ICDAS incorporate concepts from the Dundee Selectable Threshold Method for caries diagnosis (DSTM) (38), the research conducted by Ekstrand et al. (6, 36) and other caries detection systems described in the systematic review conducted by Ismail (2004) (39). The ICDAS is the subdivision of stages of the continuum of dental caries into a variable number of discrete and predictable categories based upon the histological extent of the lesion within the tooth (40, 41)– as shown in Figure 1.4 (42).

ICDAS identifies caries lesions on the basis of their clinical visual appearance. The

criteria consists on 7 scores: 0=Sound, 1=First visual change in enamel (seen only after prolonged air drying or restricted to within the confines of a pit or fissure), 2=Distinct visual change in enamel, 3=Localized enamel breakdown (without clinical visual signs of dentinal involvement), 4=Underlying dark shadow from dentine, 5=Distinct cavity with visible dentine, 6=Extensive distinct cavity with visible dentine (37).

The examination is visual aided by a ball-ended explorer and should be carried out on clean and dry teeth (37). The assessment of lesion activity is also very important when using ICDAS. Lesion activity assessment will help on the treatment decisions, particularly when preventive options should be implemented (43). ICDAS has shown to be an accurate and reproducible method to detect early lesions and also to detect changes in longitudinal follow-up (44, 45). Recently, the International Caries Classification and Management System-ICCMS has been integrated with ICDAS in order to provide practitioners with a tool to integrate and summarised tooth and patient information, including caries risk status. The ICCMS should be able to help planning, reviewing and monitoring caries in clinical and public practice (42).

Figure 1.4. ICDAS codes based on the histological extent of lesions.
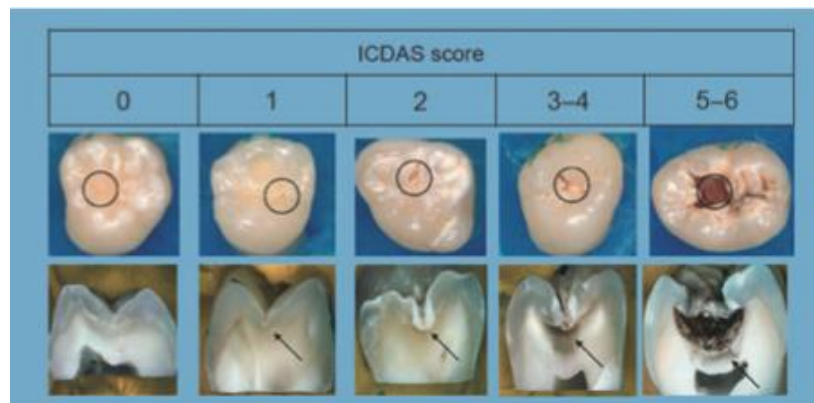
3.2. Non-visual Criteria

In the past years quantitative methods for detecting and monitoring of carious lesions have been introduced. Some reasons for the development of these methods are: 1) quantitative methods can detect earlier carious lesions than conventional methods, 2) quantitative methods can be more reliable than qualitative methods, and

3) quantitative assessments can monitor the course of the disease (46). Many of caries detection methods have shown a good performance in vitro. However, the cut-offs used to classify the data into sound, enamel caries or dentine caries have not been finally determined in vivo.

3.2.1. Radiography

Radiographs are the most used detection aid using the bitewing technique. The aim of the bitewings is to detect approximal caries lesions that cannot be detected in the visual inspection. The most common used criteria to assess approximal caries lesions are: 0=no radiolucency; 1=radiolucency confined to the outer half of the enamel; 2=radiolucency in the inner half of the enamel; 3=radiolucency in the dentine-broken enamel junction but not in dentine junction; 4=outer half of dentine; 5=inner half of dentine (47) (Figure 1.5).

Figure 1.5. Radiographic scores used to classify depth of approximal lesions.
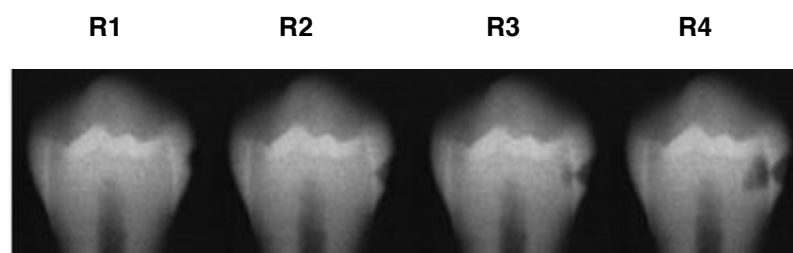
Reproduced with permission. Espelid I, Tveit AB, Mejáre I, Nyvad B. Caries - New knowledge or old truths? The Norwegian Dental Journal 1997;107:66-74.

Digital radiographs seem to be safer to the patient, requiring less irradiation and can be stored electronically. However, they have only a potential of 256 grey levels compared to conventional radiographs containing millions of grey levels; this would suggest that digital radiographs would have lower resolution; sensitivity and specificity have been found to be lower than traditional radiographs. However, algorithms to enhance grey scales can be applied increasing its sensitivity and specificity (18).

It has been shown in the literature that the use of radiographs is more sensitive than clinical inspection for detecting approximal lesions and for occlusal lesions in

dentine, for estimating depth of the lesion, and for monitoring lesion behaviour. However, detection performance for occlusal enamel lesions is lower (9, 48). Furthermore, in occlusal surfaces, the contribution of the radiographs seems to be minimal (49). When an occlusal lesion is detected on a bitewing radiograph, the lesion may have already reached the middle third of dentine and hence beyond the scope of remineralisation interventions (50). Moreover, radiography cannot distinguish between active and arrested lesions and sometimes between non-cavitated and cavitated lesions (51). This last fact should be definitely be determined before undertake any operative intervention. It has been suggested that temporary tooth separation can offer to clinicians the ability of determining if the lesion is active/inactive, cavitated/non-cavitated (52). The most common caries detection method is the combination of visual-tactile examination supplemented by bitewing radiography. However, some studies have shown the decrease of performance when using the combination of both methods. The accuracy of the visual-tactile examination alone will depend on the method used for this purpose, the use of probes for tactile assessment and the ability to perform tooth separation to detect approximal lesions (53)

Radiographic examination should be included as part of the initial patient assessment and also in the process of monitoring lesion behaviour over time. Radiography can add information about the clinical stages of the caries process at approximal surfaces and the more advanced stages on occlusal surfaces (51).

3.2.2. Fibre-Optic Transillumination (FOTI and DiFOTI)

The method of transillumination is based on the phenomenon of light scattering to increase contrast between normal and carious enamel. Sound enamel is comprised of modified hydroxyapatite crystals that are densely packed, 'producing an almost transparent structure. Dentine appears orange, brown, or grey underneath enamel and this can help in the discrimination between enamel or dentine lesions. In a recent review, only three in vitro studies reported findings for NCCLs using FOTI (54-56). The Sensitivity scores for FOTI ranged from 0.21 to 0.96, and the Specificity ranged from 0.74 to 0.88 (48). DIFOTI (Digital Fibre-optic Transillumination) replace the human eye with a CCD sensor. The transillumination method may support a

treatment decision-making but it is not able of monitoring dental caries lesions as the bitewing radiographs (57). Recent developments in ordinal scales for visual assessments, such as the ICDAS scoring system, may enable a more robust framework for visual exams into which FOTI can be added (18).

Figure 1.6. Examples of FOTI images.
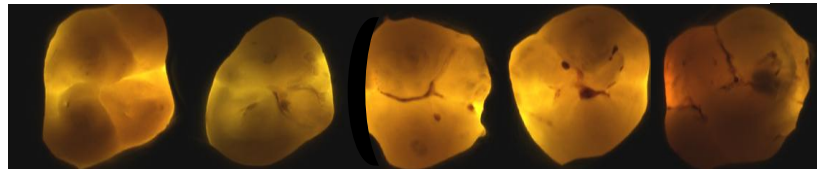
A: No shadow; B: Thin-grey shadow into enamel; C: Wide-grey shadow into enamel; D: Microcavitated lesion shadow <2 mm in dentine; E: Shadow >2 mm in dentine.

3.2.3. Electric Caries Monitor (ECM)

Demineralisation, in theory, creates porosities; the porosities will fill with water and ions from saliva causing electrical conductivity changes (58). The ECM device employs a single, fixed-frequency alternating current, which attempts to measure the 'bulk resistance' of tooth tissue (59). The degree of electrical conductance is dictated by the properties of the substance including porosity, the contact area, the thickness of the tissue, hydration of the enamel, and ionic content of dental fluids (60).

The method has shown promising results showing superior performance to FOTI and radiography in early lesions (48). However, previous studies have shown the presence of stain as a confounder factor (56). Another issue is the wide variations on reproducibility, possibly due to inconsistent probe contact with the tooth surface (61).

3.2.4. Fluorescence

QLF (Quantitative light-induced fluorescence)

QLF is a diagnostic aid for detection, quantification and monitoring of early enamel demineralisation. QLF operates on the principle of enamel autofluorescence, detecting and quantifying the loss of fluorescence associated with demineralisation (18). The technique is based on the principle of the excitation of the dentine with blue light (370 nm) and would make it to fluoresce into yellow-green region. When a lesion is present, an increase of light scattering makes appear the lesion as dark spots on a bright green background. The loss of fluorescence images can be quantified with respect to adjacent healthy tissue (62). The fluorescent image of the tooth is recorded and digitalised and analysed quantitatively. The loss of fluorescence is obtained by reconstruction of the fluorescence of healthy enamel, assuming that is 100%. The decrease in fluorescence is determined by calculating the percentage difference between the actual and the reconstructed surface. Any area with a decrease in fluorescence over 5% is considered as a lesion (63). The reliability of the QLF in vivo appears to be excellent for the quantification of initial caries lesions on smooth surfaces (63). QLF has shown good sensitivity in vivo (45). However, the specificity is sometimes compromised due to the confounding factors. Correlations of up to 0.82 have also been reported for QLF metrics and lesion depth (18). QLF has also shown the ability to detect and quantify changes of mineral content and size of lesions by demonstrating a dose response between F and non-F dentifrices in short-term clinical trials (64, 65).

Figure 1.7. QLF images compared with histological sections.
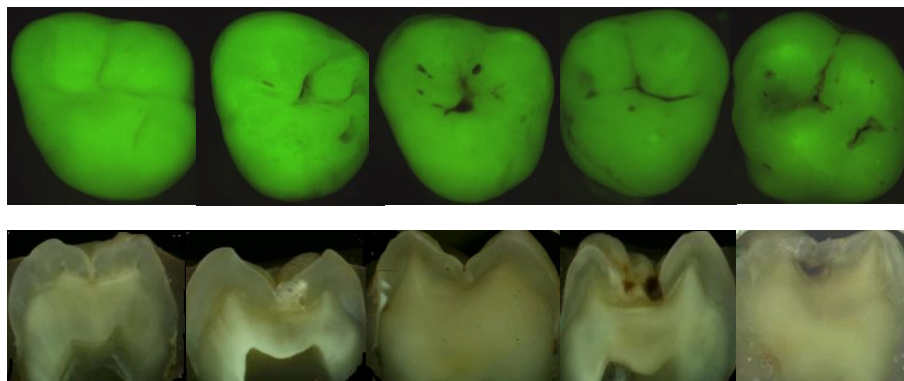
Laser fluorescence—DIAGNODent

The DIAGNODent (DD) provides a quantitative method for caries detection. The LF device consists of 655 nm monochromatic light that is emitted from a tip/sensor and can detect back-scattered fluorescence from the tooth (66). At 655 nm, the fluorophores have been identified as bacterial porphyrins. The DD scores ranges between 0 and 99. This number offers the possibility to monitor lesion behaviour (60).

In previous systematic reviews considering fluorescence methods (LF), a tendency of higher specificity than sensitivity, except for the dentine threshold was observed. The main issue of low specificities at the dentine level is the over prescription of operative treatment (9, 67) The performance of LF seems to be better for more advanced lesions (67).

The systematic review (Chapter 2) in this thesis identified several weaknesses in the evidence for DD. It was found a wide variation in design features including the threshold for DD scores, the validation methods and the outcomes expressed among others. In general, DD evidence seems to be stronger for smooth and occlusal caries detection than for approximal and for permanent dentition than for the primary dentition. Factors that may influence the outcome of the measurements in different ways are the presence of plaque, calculus and/or staining on the tooth surface, and the degree of dehydration of tooth tissue, among others (68). Hence, there is a poor correlation between LF readings and the mineral content, but possibly better correlation with the presence of infected dentine. Initial lesions are less infected than dentinal lesions (69), which hamper the performance of fluorescence-based methods in detecting such lesions as the method detects the presence of bacterial metabolites. Previous studies suggest that white-spot lesions formed in vitro, without the involvement of bacteria, do not produce a significant increase of fluorescence, although more advanced lesions (D_2 and D_3) produce a distinctive fluorescence, indicating that DD measures the fluorescence of bacteria or their metabolites (70).

3.2.5. Optical Coherence Tomography (OCT)

OCT is a high-resolution, non-invasive imaging technique that constructs cross-sectional images of internal biological structures (71). This technology is based on the principle of optical interferometry using a low coherence light source that is split into two beams, which then are reflected back, one from the investigated tissue and the other from a reference mirror, and combined together to create an interference pattern that contains depth-information from the sample (72). The OCT system used a wavelength of 850 - 1310 nm resulting in image depths of 0.6-2.0 mm. Previous studies have shown that OCT has the potential to detect and quantify demineralisation based on an increase light scattering from porous structures within the tooth in in vitro caries-like models (72, 73). However, *in vitro* models did not reflect the complexity of natural lesions; in particular they were not subsurface lesions (73). Previous studies have shown the potential use of OCT to detect and quantify demineralisation based on an increase light scattering from porous structures within the relatively new, there is still much work to be done to assess its full potential.

Figure 1.8. Example of OCT images of carious lesion. The arrow indicates increased scattering of light matching the location of demineralised lesion at the fissures
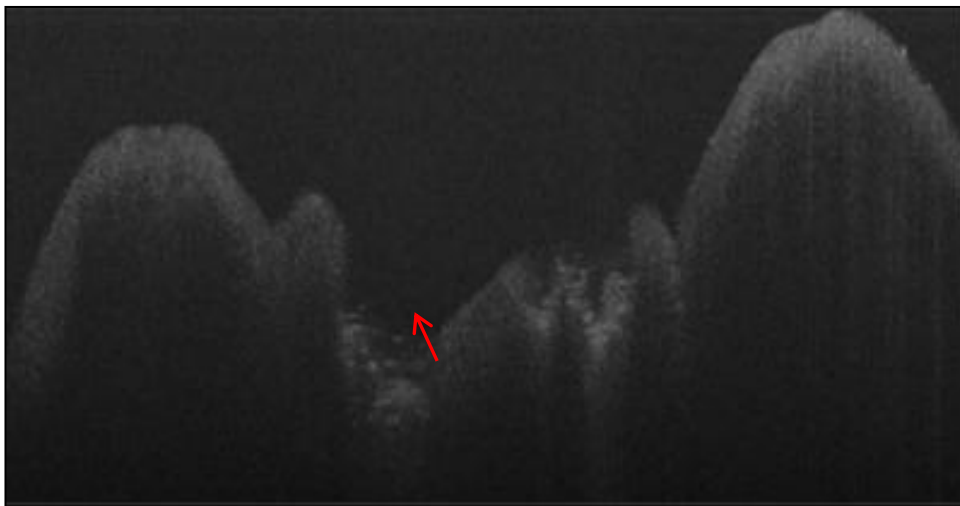
3.2.6. Caries activity assessment

The modern caries diagnosis is a process that involves three different steps: lesion detection, severity assessment and, finally the activity assessment (74). In order to explain the dynamics of the caries process, it has been recommended to record the activity status of lesions. The need of an intervention will depend on the activity assessment, where most of the time, active lesions will require an intervention (operative or non-operative) (31).

Previous research, showed ultrastructural examinations of the caries process involving crystals dissolution in the enamel, rendering the surface softer. The intercrystalline spaces increase and the light is refracted and back-scattered more than the sound enamel, this effect produces the appearance of the white spot lesion (75). Caries lesion progression can be arrested at any stage providing a mechanical removal of the biofilm. The transition into inactive/arrested lesions involves changes in the characteristic of the surface.

Caries activity assessments had a predictive validity. Therefore, 'active' non-cavitated lesions had a considerably greater risk of progressing to a cavity than 'inactive' non-cavitated lesions, being more visible in subjects exposed to fluoride (76).

The ICDAS system can be used for the lesion activity assessment (LAA). The lesion activity assessment is based on the clinical appearance of the lesions (ICDAS), whether or not the lesion is in a plaque stagnation area, the gingival status and the tactile sensation with a ball-ended WHO probe. The typical characteristics of an active lesion include white opaque colour, loss of lustre and roughness, presence of plaque and gingival inflammation. On the other hand inactive lesions are shiny and feel smooth on probing. The colour vary from white to brown or black, but is not determinant for an activity diagnosis (7).

These criteria are scored in a form of points based on the predictive value (77) and are based on the physical properties of surface, with chalky rough surfaces being active, and smooth, shiny surfaces being inactive. Arrested lesions usually have a

brown colour and active lesions a white appearance (77). Because there is no reference method for caries activity, its validation may not be carried out in a classical gold standard approach. More research is still needed in this area before a recommendation can be made. However, caries activity is important for the determination of an intervention and the improvement of treatment decisions.

4. Caries risk assessment

The multifactorial nature of the caries process and the fact it is a dynamic but not continuous disease makes difficult to assess the risk because there are multitude of variables at different moments in the life of an individual. Diet, saliva, and microorganisms have been described as biological determinants that influence the rate of progression of caries. Other factors that may influence the caries process and differ between individuals and populations are known such as socio-economic or behavioural aspects are known as risk modifiers factors (78).

Risk is determined as the probability of an individual to develop new caries lesions during a specified period (79) and the probability of change in size or activity of existing lesions over the time (80). Previous research showed the greatest predictor of dental caries is the past experience of caries (81). While the past experience of caries is the most important criteria for caries risk assessment, the information is obtained too late to be useful for the prevention of caries as irreversible events have already occurred (82). Usually, information on demographic, social, behavioural, clinical examination and other complementary tests are needed to conduct a risk profile for each patient. Unfortunately there is no consensus in the literature on "risk factor" and "risk indicator". A risk factor is often associated with illness but may not be a predictor. For example there is a relationship between caries and *S. Mutans*, but the evidence as a future predictor is low (83).

Although a risk assessment is intended to be individual, its effectiveness should be evaluated and measured also in populations (80) and evaluated through analysis of factors that interact directly in the caries process. Caries risk assessment is one of the cornerstones in patient caries management and should be carried out and documented in patient's chart either for treatment planning or as a didactic aid for

patient motivation (80). However, the existing evidence on Caries Risk Assessment systems is limited and comes from cross-sectional studies where various multivariate regression techniques were deployed to identify methods for classifying individuals based on their caries risk status (84). These studies are inadequate for correctly identifying the individuals at risk for caries, which is the determining characteristic of an ideal CRA system. Longitudinal prospective studies, on the other hand, assess the prediction of new caries development, which, with limitation, is stronger than a single assessment of risk factors. Unfortunately, there are few prospective studies of good quality available.

In summary, dental caries continues to be one of the most prevalent disease and a significant burden for the health systems. In recent years evidence has shown the limitation of relying on a restorative approach to manage dental caries. The current biological understanding of the caries process has led to develop new philosophies based on early detection, preventive management and preservation of tooth structure. However, this approach has not always been reflected in dental education and activity profiles of health providers, which largely focus on restorative procedures.

Different stages to classify dental caries have been proposed based on activity, visual signs and extent of the lesions. Additional methods such as radiographs, QLF, FOTI and ECM can be also used for monitoring disease in particular in clinical trials assessing efficacy of anti-caries dental care products.

The evidence seems to be inconclusive in terms of providing firm guidance to clinicians on detection, management of non-cavitated caries lesions and risk-adjusted caries management systems. Therefore, in the first phase of this thesis, the aim was to assess the available evidence on NCCLs in terms of detection, management and prediction of disease of current available caries risk systems. In the second phase, three in vitro experiments were conducted looking at the performance of different caries detection methods and in particular QLF and finally in the third phase, a cross-sectional study looking at dentist caries related treatment decisions was conducted.

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CHAPTER 2

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Non-Cavitated Carious Lesions Detection Methods: A Systematic Review

Non-Cavitated Carious Lesions detection methods: A systematic review

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Rationale- Paper I

Although the importance of detecting carious lesions at an early stage is well established, the diagnosis and management of dental caries continues to be focused on cavitated lesions and restorative management. The purpose of this review is to identify the evidence on the performance of caries detection methods in relation to early, non-cavitated lesions.

Abstract

The aim of this study was to critically appraise the performance of detection methods for non-cavitated carious lesions (NCCLs). A detailed search of Medline (via OVID), the Cochrane Collaboration, Scielo and EMBASE identified 2054 publications. After title and abstract review by three investigators (JG, MT, AI), 124 publications were selected for further review. The final publications evaluated the following methods: Visual (V), Caries Lesion Activity Assessment (CLAA), Laser Fluorescence (LF), Radiographic (R), Fibre-optic Transillumination (FOTI), Electrical Conductance (EC) and Quantitative Light-induced Fluorescence (QLF). All included studies used histological assessment as a gold standard for in vitro studies or clinical/visual validation for the in vivo designs. They reported outcomes measures such as sensitivity (SE), specificity (SP), area under the receiver operating characteristic curve (AUROC) and reliability. Data were extracted from the selected studies independently by two reviewers and checked for errors. The quality of the studies was evaluated as described by Bader et al. (2002). Of the 124 articles, 42 were included that described 85 clinical assessments. Overall, the quality of evidence on detection methods was rated 'poor', except for EC that was rated 'fair'. The SE rates were as follows: V (0.17–0.96), LF or DIAGNOdent (DD) (0.16–0.96), R (0.12–0.84), FOTI (0.21–0.96), EC (0.61–0.92) and QLF (0.82). The SP rates were as follows: V (0.46–1.0), LF (0.25–1.00), R (0.55–0.99), FOTI (0.74– 0.88), EC (0.73– 1.0) and QLF (0.92). There is a large variation in SE and SP values for methods and a lack of consistency in definition of disease and analytical methods. EC and QLF seem to be promising for detection of early lesions. In the light of lack of evidence, visual methods should remain the standard for clinical assessment in dental practice.

Introduction

Dental caries is the result of a disequilibrium between the tooth surface and the plaque biofilm. The balance between mineral loss and gain can shift to favour either re- or demineralisation (1, 2) so that early or non-cavitated carious lesions (NCCLs) can be arrested or remineralised (3). Recently, there has been an increased interest in this area of caries management, not least because of the changing disease severity observed in Western populations (4). Agreement on classification of lesions and interventions to conservatively manage early lesions is necessary to promote this approach (5). Over the last decade, there were many attempts to develop protocols to achieve these goals (6).

Even though the importance of management of non-cavitated (NC) enamel lesions has been recognized since the early 1900s, dental caries has been traditionally detected at the cavitation stage, and its management has been strongly focused on operative treatment. New methods of detection of early carious lesions have received significant research attention over the last 20 years. These issues were discussed at the National Institutes of Health Consensus Development Conference on Diagnosis and Management of Dental Caries through Life in 2001. The Consensus Panel concluded that the evidence base for current methods of detection and activity assessment of NCCLs was not sufficiently strong to recommend their formal adoption (7).

The shortcomings of conventional caries detection methods and the need for supplementary methods have long been acknowledged. The most widely used method of caries detection is visual–tactile (8). Other non-invasive techniques for detection of early caries have been developed and investigated such as DIAGNOdent (DD), Fibre-optic Transillumination (FOTI) and Electrical Conductance (EC). The majority of published studies on the detection systems mentioned above have shown acceptable (at least not inferior to traditional methods) performance and reproducibility for the detection and quantification of dentinal lesions. However, the results for NCCLs have been somewhat contradictory and limited due to the low number of studies published at this threshold. This review aims to critically appraise the published evidence related to the sensitivity (SE), specificity (SP), area under the

receiver operating characteristic curve (AUROC) and reliability of detection systems in relation to NCCLs, by type of surface (free smooth versus occlusal versus approximal) and type of dentition (primary versus permanent).

Materials and methods

The publications included in this review evaluated the following methods: Visual (V), Caries Lesion Activity Assessment (CLAA), Laser Fluorescence (LF) including DIAGNOdent (DD) and Quantitative Light-induced Fluorescence (QLF), Radiographic (R), Fibre-Optic Trans-Illumination (FOTI), and Electrical Conductance (EC). A systematic search for the articles (not restricted to English) published between 1966 and March 2011 was carried out using Medline, Ovid, Embase, Cochrane Oral Health Group's Specialized Register, Cochrane Central Register of Con- trolled Trials and Scielo. The search filter is described in Table 2.1. Reports in the grey literature, defined as theses, dissertations, product reports and unpublished studies, were not included. Hand searching of Table of Contents of Caries Research published since 1980 was also conducted.

The search of Medline on Ovid plus hand searching identified 1993 citations, with 61 additional citations identified from other databases (Figure 2.1).

Initially, two investigators followed predefined inclusion and exclusion criteria to select the relevant articles. The inclusion criteria were as follows:

• Studies were conducted either in vitro or in vivo using natural carious lesions.
• Early NC (enamel or dentine) caries lesions were assessed.
• Results were validated versus gold standards (histological validation for in vitro studies and clinical visual validation for the in vivo studies).
• Outcomes were expressed as SE, SP, AUROC, or data were provided to compute these statistics. For activity assessment, the relative risk (RR) was also considered.

In addition, studies were excluded because of incomplete descriptions of sample selection, diagnostic criteria and small sample sizes (<20 lesions). Studies reporting multiple surfaces at the same time, methods not commercially available, and those

reporting other levels of histological analyses different than sound versus non-cavitated (S versus NC) and sound versus non-cavitated and cavitated (S versus NC and C) were also excluded. Inclusion and exclusion criteria were applied by examining titles and abstracts, and if the information relevant to the eligibility criteria was not available in the abstract or the abstract was not available, the full article was selected for further review. Two reviewers (JG, MT) agreed on the inclusion or exclusion status of 124 articles. After further review with a third reviewer (AI), 42 articles were finally included. After training and calibration, two reviewers extracted data independently. The tables were checked for consistency, and corrections were made through consensus discussions.

The quality score for each included article was assessed using the rating scale developed by Bader et al. (7). The final score resulted from the assessment of 11 elements of internal validity, including issues involving sample size, selection of teeth and surfaces, setting, validation method, validation criteria, validation reliability, lesion prevalence, number of examiners, examiner reliability and lesion criteria (Table 2.2). The quality scores ranged from 0 to 20, and this information was included in the evidence tables for all final studies (scores were re- scaled to a 0–100 scale). High quality was defined as most study scores at or above 60, and average quality was defined as most study scores at or above 45. The reviewers achieved 90% agreement on classifying the quality of the studies.

The three possible ratings for a diagnostic method were:
Good: The number of studies is larger than three, the quality of the studies is generally high, and the results of the studies represent narrow ranges of observed SE and SP (no more than 0.15 on a scale of 0.0–1.00).

Fair: There are at least three studies, the quality of the studies is at least average, and the results represent moderate ranges of observed SE and SP (no more than 0.35).

Poor: There are fewer than three studies; the quality of the available studies is generally lower than average, and/or the results represent wide ranges of observed SE and SP (more than 0.35).

A separate evidence table was prepared for each detection or assessment method (Appendix 1). The majority of the studies provided statistics for the full range of carious lesions from non-cavitated to cavitated lesions (S versus NC and C). For those studies that reported the original raw data, the reviewers computed SE and SP for non-cavitated lesions (S versus NC).

Results

Of the 124 papers, 82 were excluded. From the 42 studies finally included, 85 separate assessments were identified. Table 2.3 presents the number of studies assessed by each detection method, ranges of sensitivity and specificity, Area Under the Receiver Operating Characteristic (AUROC) Curves, quality scores, and strength of the evidence. Figures 2.2 and 2.3 show graphically the clustering of the Se and Sp values by each detection method for both S vs. NC and C (Table 2.3) and S vs. NC (Table 2.4) studies. The findings for each method are summarized as follows (Appendix 1):

Visual Criteria

Appendix 1 summarizes the findings describing the assessment of the visual method (9-33). The following criteria were used for the clinical examination in these studies:
• International Caries Detection and Assessment System (ICDAS) (34): (ten studies)
• Ekstrand (21, 35): (eight studies)
• Study-specific criteria: (five studies)
• Other criteria: Fyffe (22), Nyvad (36) and Pitts and Fyffe (37): (five studies)

The majority of studies using visual criteria were conducted in vitro (24/28) and had a wide range of sample sizes (37–621 tooth sites). There was an average of three examiners per study. The gold standard used for the validation varied among the studies. Light microscopy validation was reported in 24 studies, three used operative removal, and one study used visual inspection. Most of the studies described the criteria for the validation method but did not report reliability. Reliability of the clinical criteria was reported in 26 studies (weighted or un-weighted Kappa values ranged from 0.34 to 0.96). The prevalence of carious lesions ranged from 19% to 97% for in vitro studies.

The SE scores for the visual/clinical studies ranged from 0.20 to 0.96, and SP ranged from 0.5 to 1.00. Only 12 of 28 studies reported ROC values. Area under the curve data (Az) ranged from 0.72 to 0.92. The quality scores for all the visual/clinical studies ranged from 50 to 75 on a 100 scale, with a mean of 58.2 (average quality). The strength of the evidence for visual/clinical detection methods was rated as "poor" due to the extensive variation in SE and SP values among the studies. However, the quality score of the visual studies was the second higher when compared to the other methods.

Type of surface. For visual/clinical studies when data were recalculated for S versus NC only (Table 2.5), SE values were higher for occlusal than approximal surfaces. However, SP was higher for the latter. No major differences were observed in SE and SP ranges by surface when compared to data evaluating S versus NC and C lesions (Table 2.6).

Type of dentition. Higher SE values were observed for primary dentition when compared to permanent, although there was also more variation in the results from the data looking at S versus NC only (Table 2.7). The SP range was narrower for primary dentition with no differences when compared to the data that evaluated S versus NC and C lesions (Table 2.8).

Lesion activity assessment

Only one in vivo study reported activity findings. RR and confidence intervals of active non-cavitated (ANC) or inactive non-cavitated caries lesion (INC) progressing to cavity/filling or extracted between baseline and 3-year follow-up are reported. The study demonstrated that ANC lesions had higher risk to progress than INC lesions. Only one examiner participated in the study. Reliability was reported at 0.74 (Kappa). The quality score was 70 and the highest amongst all the methods. The strength of the evidence for activity assessment was rated 'poor'.

Radiography

Twenty-three studies reported findings for NCCLs using radiographs, and 19 were conducted in vitro (9, 10, 14, 15, 21, 25, 28–30, 32, 38–43) (For the summary of the studies using radiographs, see appendix 2). The sample sizes ranged from 37 to 29 870 tooth sites, and an average of three examiners participated per study. Several validation methods were used including visual (2), operative removal (2) and histology (19). The majority of the studies provided the criteria for the validation but did not report their reliability. Reliability was reported in 18 studies (Kappa values ranged from 0.17 to 0.89). The histological prevalence of lesions ranged from 2% to 94%.

The SE scores ranged from 0.12 to 0.84, and the SP ranged from 0.55 to 0.99. Only 8 of 29 studies reported ROC values. Area under the curve data (Az) ranged from 0.58 to 0.87. SE was higher for studies looking S versus NC and C lesions than only when data were recalculated for S versus NC (Tables 2.3 and 2.4). The quality scores for all the radiographic studies included were on the lower end, ranging from 40 to 65 on a 100 scale, with a mean of 53.6. The strength of the evidence for radiography was rated as 'poor'.

Types of surfaces. In general, higher SP values and narrower ranges were observed for both occlusal and approximal surfaces. Studies looking at S versus NC and C lesions reported higher SE values for both types of surfaces when compared to those including only NC lesions.

Types of dentition. Narrower ranges of SE and SP were observed for studies in primary dentition considering S versus NC and C lesions.

DIAGNOdent

Twenty-one studies reported findings for NCCLs using DD (9, 14, 16, 19, 25–27, 29, 30, 32, 40, 44–49), and most of them relied on in vitro designs (16/21). Appendix 3 contains the summary of the studies using DD. Study sample sizes varied greatly (37–621 sites), and an average of 2.9 examiners per study was found. For the selected studies, several validation methods were used including visual (1), operative removal (4) and histological examination (16). The majority of the studies described

the criteria for the validation but did not report their reliability. Reliability for DD was reported in 20 studies, and Kappa values ranged from 0.54 to 0.94. The histological prevalence of lesions ranged from 34% to 89%. There was an array of DD cut-off points used in these publications. For example, cut-off points defining demineralisation in enamel ranged from 0–4 to <15.

The SE scores for DD ranged from 0.16 to 0.96, and the SP ranged from 0.25 to 1.00. Area under the curve data (Az) were reported for 9 of 23 studies and ranged from 0.69 to 0.95. The quality scores for all the DD studies included were on the lower end, ranging from 40 to 65 on a 100 scale, with a mean of 53 (average quality). The strength of the evidence for DD was rated as 'poor'.

Type of surface. Better performance was observed for smooth free surfaces followed by occlusal and approximal surfaces (Table 2.7).

Type of dentition. Narrower ranges of all performance measures were observed for permanent dentition when compared to primary dentition for studies that evaluated S versus NC and C lesions (Table 2.8).

Electrical conductance

Six in vitro studies reported the findings for NCCLs lesions using EC in permanent dentition and occlusal surfaces (10, 16, 21, 50–52). Appendix 4 summarizes the findings of the studies using ECM. Sample sizes ranged from 30 to 152 sites with an average of 1.6 examiners per study. The histological prevalence of lesions ranged from 47% to 80%.

The SE scores ranged from 0.61 to 0.92, and the SP ranged from 0.73 to 1.00. Area under the curve data (Az) ranged from 0.85 to 0.88. The quality scores ranged from 40 to 60 on a 100 scale, with a mean of 50.7. The strength of the evidence for Electronic Caries Monitor (ECM) was rated 'fair'.

Fibre-optic transillumination

Only three in vitro studies reported findings for NCCLs using FOTI (10, 15, 16) (Appendix 5). Two studies evaluated the diagnostic performance in permanent teeth and occlusal surfaces, while the third study focused on the approximal surfaces only.

Sample sizes ranged from 59 to 152 sites with an average of two examiners participated per study. The histological prevalence of lesions ranged from 24% to 74%. The SE scores for FOTI ranged from 0.21 to 0.96, and the SP ranged from 0.74 to 0.88. Two of three studies reported ROC values that ranged from 0.85 to 0.88, with no major differences by type of surface. Due to the limited number of studies on FOTI and the average quality score (51), the strength of the evidence for this diagnostic method was rated as 'poor'.

Quantitative light-induced fluorescence

One in vivo study reported the findings for QLF in smooth surfaces and permanent dentition (53) (Appendix 5). The reference standard considered was the visual examination. SE and SP were calculated with the row data provided for both S versus NC and S versus NC and C lesions. Sample size comprised 23 402 sites, and only one examiner participated in the study. Reliability was reported at 0.72 (Kappa). The clinical prevalence of lesions was 16%.

The SE scores ranged from 0.82 to 0.83, and the SP value was 0.92. There were no ROC data presented. The quality score was 65. The strength of the evidence for QLF was rated 'poor'.

Multisystem

Two in vitro studies looking at S versus NC and C lesions reported the findings using a variety of systems (Combinations of FOTI/visual versus visual, FOTI, DD and ECM and visual versus radiographs (bite-wings), QLF, ECM, DD) (16, 31) (Appendix 5). The studies evaluated the diagnostic performance in permanent teeth and occlusal surfaces only. The sample sizes in the selected studies ranged from 96 to 152, with an average of two examiners participating per study. Reliability was reported in one study (Kappa: 0.95). The histological prevalence of lesions ranged from 27% to 32%.

The SE scores ranged from 0.80 to 0.94, and the SP ranged from 0.56 to 0.70. Area under the curve data (Az) reported ranged from 0.77 to 0.92. The quality scores for these studies averaged as 55. As with QLF, the performance of studies using multi-system was better when compared to other single detection methods. However, there

were only two studies for analysis. Hence, the strength of the evidence was rated as 'poor'.

Discussion

Dental caries is a dynamic process with early carious lesions going through many cycles of de- and remineralisation. If net demineralisation outbalances net remineralisation, this may ultimately be manifested clinically as a 'cavity' (1). Identification of initial (NC) lesions is the optimum time to instigate preventive options to interrupt the progression of the mineral loss (54). However, current approaches used in dental practice for detecting, diagnosing and managing dental caries have been focused on informing restorative decisions and may demonstrate a lack of validity for early caries lesions. Visual inspection has been the most frequently validated diagnostic technique for caries detection (55) but has low SE and reliability associated with high SP. The reliability has shown to be lower when the lesions are NC (56, 57). In this review, we found a wide discrepancy between the results for the visual assessment and remarkably wide ranges of SE (0.17–0.96) and SP (0.46–1.0).

For approximal early caries, this review corroborates the findings of a previous systematic review reporting low sensitivities (7, 58). High SE is more important when detecting early caries lesions, as the detection of true positives becomes important when a preventive intervention is needed.

One important source of heterogeneity found within the articles examined is the variation introduced by different diagnostic thresholds. Another important finding was the inconsistent use of the acronyms D1 and D2, which very few studies defined properly in the tables/text. For example, many studies reported the analysis based on the D1 level combining codes referring to enamel and dentine or collapsing sound and enamel lesions versus the remaining codes. When raw data were provided in the selected study, calculations for SE and SP were carried out to provide information on the diagnostic performance NCCLs only. Where data were re-calculated, a general decline diagnostic performance of the visual criteria was seen when compared with the values reported originally.

The disease definition by both the diagnostic method (test) and the gold standard posed a problem in this review. For example, the disease definition by the gold standard varied from sound versus enamel and dentine, and sound and enamel versus enamel and dentine with cavitation to sound, outer half of enamel versus inner half of enamel and den- tine among others. Another source of heterogeneity is that the population used for the in vitro studies was not always reported, and there were no standards for the histological validation. Several factors posed a direct effect on the internal/external validity of the appraised studies. The prevalence of carious lesions in the samples of studies included in the review represents a barrier to generalization of the results and a potential threat to internal validity. Prevalence of lesions in any *in vivo* or *in vitro* sample should be reasonably representative of the population prevalence for the same type of lesion on the same surfaces. The prevalence of both histological and clinical caries varied widely, and it is unknown to what extent this factor may have compromised the assessment of the performance of the diagnostic test. Therefore, it is important to understand the behaviour of diagnostic systems and how they vary in high versus low prevalence areas. In the quality scores, the low prevalence of caries was scored higher, reflecting in a more accurate way the behaviour in a real population.

Most of the studies were performed in vitro with histological validation. The histological validity of methods for diagnosing carious lesions has a variety of limitations, many of which represent potentially serious threats to internal and external validity, decreasing the likelihood of generalizing the results to the dental practice. As for *in vivo* studies, some used operative removal as gold standard, which by itself may be biased as a validation method. Current gold standards such as histology and transverse micro-radiography are far from being ideal, as they do not provide information on the activity status of the carious lesions. The extent to which differences in the validation methods contributed to differences in reported diagnostic performances is unknown. There is a need to develop robust gold standards or outcomes for the validation of new diagnostic systems *in vivo*. The use of dose response models offers both construct validity and important information on the thresholds of new tests (59).

Because there is no reference method for caries activity, its validation may not be carried out in a classical gold standard approach. More research is still needed in this area before a recommendation can be made. However, the findings from the only study included in this review suggest that CLAA is important for the determination of an intervention and the improvement of treatment decisions (60).

The strength of evidence was judged by a quality rating scale that reflects a subjective nature giving an overall rating for each method. However, for the individual assessments, the quality scores tended to cluster in the middle of the 0–100 scale of possible scores. The mean quality scores for the in vivo and in vitro studies were similar (59 and 53, respectively). The performance was likely to be better for the in vivo studies. Lower scoring studies typically had several features that represented threats to either internal or external validity.

Most studies did not report reliability measures just for NCCLs, but for all the potential codes included (S versus NC and C lesions), diminishing the possibility of evaluating the internal validity of the studies for this type of lesions only. In addition, there is a clear need to report other diagnostic performance and reliability measures than SE, SP and kappa values when referring to the probability of detecting carious lesions. Only five studies reported predictive values, and three studies, likelihood ratios. These outcomes may be a more suitable alternative for referring to the probability of detecting caries and its reliability in dealing with varying grades of disease.

Regarding DD, weaknesses in the identified evidence are plentiful and raise some limitations of early caries detection studies using this diagnostic tool. There is a wide variation in design features including the threshold for DD scores, the validation methods and the outcomes expressed among others. In general, DD evidence seems to be stronger for smooth and occlusal caries detection than for approximal and for permanent dentition than for the primary one. Factors that may influence the outcome of the measurements in different ways are the presence of plaque, calculus and/or staining on the tooth surface, and the degree of dehydration of tooth tissue, among others (48). Hence, there is a poor correlation between LF readings and the mineral content, but possibly better correlation with the presence of infected dentine.

Initial lesions are less infected than dentinal lesions (61), which hamper the performance of fluorescence-based methods in detecting such lesions as the method detects the presence of bacterial metabolites. Previous studies suggest that white-spot lesions formed in vitro, without the involvement of bacteria, do not produce a significant increase of fluorescence, although more advanced lesions (D2 and D3) produce a distinctive fluorescence, indicating that DD measures the fluorescence of bacteria or their metabolites (62). The SE of the radiography at the enamel level has shown poor results. Furthermore, in occlusal surfaces, the contribution of the radiographs seems to be minimal (41).

The variations in sensitivities and specificities values were less pronounced for the six clinical studies employing EC, than for the other methods. However, only one of the EC studies used more than one examiner, and they were all were conducted in vitro. Future studies *in vitro* and *in vivo* are therefore recommended.

Only one in vivo study using QLF reported data in which SE and SP values were calculated. Nevertheless, QLF has shown in clinical trials the ability of detecting and monitoring changes in early caries lesions (63, 64). The objective nature of the electrical methods and QLF may provide an advantage in detecting and monitoring carious lesions.

Although we considered conducting a meta-analysis, the results of several characteristics of the included studies discouraged the use of this technique. The studies did not all assess the same 'outcomes,' because criteria for diagnosis were different in different studies creating a high degree of heterogeneity rendering them unsuitable for data pooling. Future studies should include NCCLs as an outcome measure and conduct data analysis at this level in addition to collapsing 'NC and C' carious lesions. There is a need for standardization regarding the histological validation criteria, definition of disease, and minimum number of examiners, reliability and overall reporting methods. In vitro and/or in situ studies are still required, both to develop and to evaluate new diagnostic techniques. However, they should simulate as closely the clinical environment in a laboratory setting (59).

Conclusions

The reproducible detection of NCCLs has been recognized as a diagnostic dilemma for many years – and one that is becoming increasingly important given the shift in caries presentation within Western populations. Even a decade after the call of the NIH Consensus Conference on Dental Caries Throughout Life for more intensive research to understand and measure NC lesions, the field has not moved forward significantly (5). This review showed a large variation in SE and SP values for methods and a lack of consistency in the definition of disease and analytical methods. Based on the limited number of studies conducted with various single and combined advanced detection methods, the inherent flaws associated with detecting early lesions by radiography and the graded strength of the evidence in this review, the diagnosis of NCCLs might be more accurately achieved in combination of the visual method and the use of other methods such as electrical methods and QLF.

Authors' contributions

JG contributed to the protocol, design, acquisition of data, analysis and interpretation of data and wrote the manuscript. MT contributed to the protocol, acquisition of data, analysis and contributed to the manuscript. IAP and RE contributed to the protocol and to the manuscript. AI contributed to the protocol, acquisition of data, analysis and contributed to the manuscript.

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Table 2.1. Systematic Search Strategy

1	Dental Caries/	32452
2	caries.mp.	38616
3	((tooth or teeth) and (decay$ or lesion$ or cavit$ or carious or deminerali$ or reminerali$)).mp.	22335
4	exp "Sensitivity and Specificity"/	325577
5	sensitivity.mp.	622950
6	specificity.mp.	686879
7	((pre-test or pretest) adj probability).mp.	900
8	post-test probability.mp.	251
9	predictive value$.mp.	138211
10	likelihood ratio$.mp.	5874
11	or/4-10	1119911
12	or/1-3	53832
13	limit 12 to yr="1966 - 2011"	51288
14	limit 13 to humans	44975
15	11 and 12 and 13 and 14	1993

Table 2.2. Quality Rating Form (Bader&Shugars, 2002) (9)

Number of sites assessed:

3   150 or more

2   75-149

1   40-74

0   fewer than 40

Area assessed for any site:

1   Entire surface (occlusal, proximal, etc.)

0   Specific site on surface.

Setting:

2   In vivo

0   In vitro

Tooth selection:

3   Both posterior and anterior teeth

2   Only posterior or only anterior teeth

1   Selected posterior or selected anterior teeth

0   Single tooth type (e.g., max. or mand. 3rd molar)

Validation method:

2   Light microscopy (stereo/mono) w/wo dye

1   Other visual or radiographic assessment of sectioned tooth

0   Assessment of unsectioned tooth

Validation criteria:

1   Criteria explicitly stated

0   Criteria not explicitly stated

Validation reliability:

1   Interevaluator or intraevaluator reliability reported

0   No validation reliability reported

Caries prevalence (calculate score for each lesion type evaluated):

2   Less than 20%

1   20-49%

0   50% or more or no data reported

Test reliability reported:

2   Interevaluator and intraevaluator reliability reported

1   Interevaluator reliability reported or intraevaluator reliability reported

0   No reliability reported

Criteria for caries call:

1   Specified prior to evaluation

0   Developed post hoc

Number test evaluators:

2   4 or more

1   2 to 3

0   1

Table 2.3. Summary of performance measures for all detection systems (sound versus non-cavitated and cavitated lesions)

Diagnostic Method	# of Studies	Range Sensitivity	Range Specificity	Range AUROC	Range Quality Score	Average Quality Score	Strength of Evidence
Visual	28	0.20-0.96	0.50-1.0	0.72-0.92	45-75	57.5	Poor
DIAGNOdent	21	0.16-0.96	0.25-1.0	0.69-0.95	40-65	53.4	Poor
Radiography	23	0.12-0.84	0.55-0.99	0.58-0.87	40-65	53.6	Poor
FOTI	3	0.21-0.96	0.74-0.88	0.85-0.88	50-55	51.7	Poor
EC	6	0.61-0.92	0.73-1.00	0.80-0.93	40-60	47	Fair
QLF	1	0.83	0.92	NA	65	65	Poor
Multisystem	2	0.80-0.94	0.56-0.70	0.77-0.92	55	55	Poor

Table 2.4. Summary of performance measures for all detection systems (sound versus non-cavitated lesions)

Diagnostic Method	# of Studies	Range Sensitivity	Range Specificity	Range AUROC	Range Quality Score	Average Quality Score	Strength of Evidence
Visual	11	0.17-0.83	0.46-0.95	NA	50-65	59	Poor
DIAGNOdent	0	-	-	-	-	-	-
Radiography	7	0.14-0.38	0.59-0.98	0.58	40-65	53.3	Poor
FOTI	0	-	-	-	-	-	-
EC	1	0.63	0.87	NA	60	60	Poor
QLF	1	0.82	0.92	NA	65	65	Poor
Multisystem	0	-	-	-	-	-	-

Table 2.5. Summary of performance measures for all detection systems by type of surface (sound versus non-cavitated lesions)

Diagnostic Method	# of Studies	Surface	Range Sensitivity	Range Specificity	Range AUROC
Visual	9	Occlusal	0.44-0.83	0.46-0.90	0.73
	2	Approximal	0.17-0.22	0.88-0.95	NA
DIAGNOdent	0	-	-	-	-
Radiography	5	Occlusal	0.14-0.38	0.59-0.90	NA
	2	Approximal	0.16-0.17	0.94-0.98	0.58
FOTI	0	-	-	-	-
EC	1	Occlusal	0.63	0.87	NA
QLF	1	Smooth	0.82	0.92	NA
Multisystem	0	-	-	-	-

Table 2.6. Summary of performance measures for all detection systems by type of surface (sound versus non-cavitated and cavitated lesions)

Diagnostic Method	# of Studies	Surface	Range Sensitivity	Range Specificity	Range AUROC
Visual	23	Occlusal	0.20-0.96	0.50-1.00	0.72-0.92
	5	Approximal	0.20-0.95	0.50-0.95	0.80-0.83
DIAGNOdent	15	Occlusal	0.43-0.96	0.66-1.00	0.81-0.95
	4	Approximal	0.16-0.82	0.25-0.96	0.69-0.92
	2	Smooth	0.87-0.88	0.92-0.93	NA
Radiography	11	Occlusal	0.12-0.78	0.55-0.97	0.59-0.76
	12	Approximal	0.23-0.84	0.67-0.99	0.58-0.87
FOTI	2	Occlusal	0.21-0.96	0.74-0.88	0.88
	1	Approximal	0.74	0.85	0.85
EC	6	Occlusal	0.61-0.92	0.73-1.00	0.80-0.93
QLF	1	Smooth	0.82	0.92	NA
Multisystem	2	Occlusal	0.80-0.94	0.56-0.70	0.77-0.92

Table 2.7. Summary of performance measures for all detection systems by type of dentition (sound versus non-cavitated lesions)

Diagnostic Method	# of Studies	Dentition	Range Sensitivity	Range Specificity	Range AUROC
Visual	5	Permanent	0.22-0.66	0.66-0.90	0.73
	6	Primary	0.17-0.83	0.46-0.95	NA
DIAGNOdent	0	-	-	-	-
Radiography	5	Permanent	0.14-0.38	0.59-0.94	NA
	2	Primary	0.17	0.98	0.58
FOTI	0	-	-	-	-
EC	1	Permanent	0.63	0.87	NA
QLF	1	Permanent	0.82	0.92	NA
Multisystem	0	-	-	-	-

Table 2.8. Summary of performance measures for all detection systems by type of dentition (sound versus non-cavitated and cavitated lesions)

Diagnostic Method	# of Studies	Dentition	Range Sensitivity	Range Specificity	Range AUROC
Visual	15	Permanent	0.22-0.96	0.50-1.00	0.72-0.92
	13	Primary	0.20-0.92	0.51-0.95	0.73-0.90
DIAGNOdent	11	Permanent	0.46-0.96	0.69-1.00	0.86-0.95
	10	Primary	0.16-0.82	0.25-0.96	0.69-0.92
Radiography	18	Permanent	0.12-0.78	0.55-0.97	0.61-0.76
	5	Primary	0.20-0.54	0.78-0.99	0.58-0.64
FOTI	2	Permanent	0.21-0.96	0.74-0.88	0.88
EC	6	Permanent	0.61-0.92	0.73-1.00	0.80-0.93
QLF	1	Permanent	0.82	0.92	NA
Multisystem	2	Permanent	0.80-0.94	0.56-0.70	0.77-0.92

Figure 2.1. Flow diagram: manuscript identification and inclusion

Steps	Articles
Initial Medline OVID Search	1,993
Initial Embase Search	1,671
Initial Cochrane Search	14
Initial Scielo Search	47
Total articles for review with no duplicates	2,054
Surviving title review	646
Surviving abstract/paper review	124
Included in final review	42

Figure 2.2. Plot sensitivity and specificity by detection methods (non-cavitated and cavitated/*in vivo/°in vitro

Figure 2.3. Plot sensitivity and specificity by detection methods (non-cavitated/*in vivo/°in vitro)
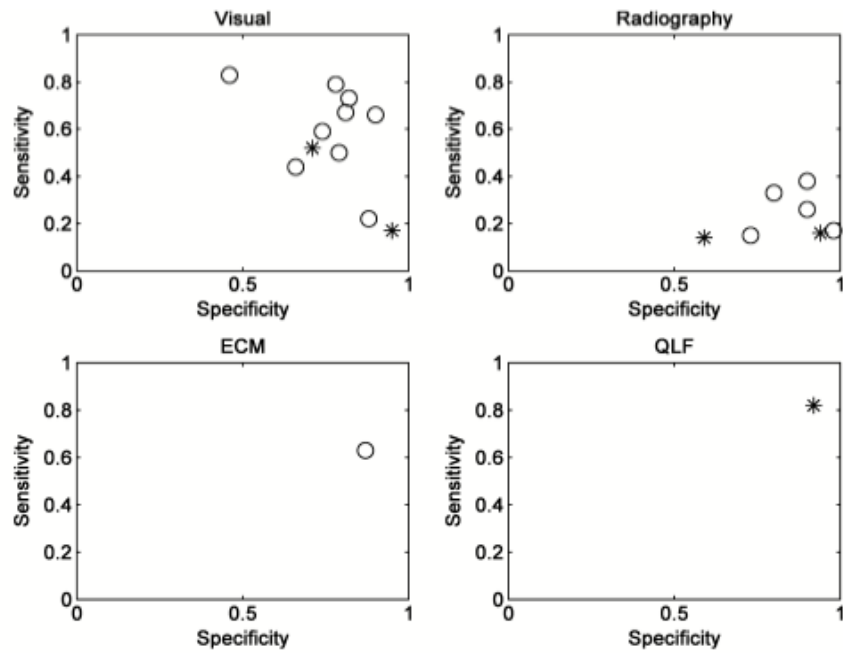
Appendix 2.1. Summary of Studies of Visual Methods

Author	Study Type	Dentition	Sites (N)	Teeth	Sites	Examiner	Criteria for clinical examination
Akarsu et al. 2006	E in vivo	Permanent	165	Molars	Occlusal	2	Ekstrand
Akarsu et al. 2006	E + D in vivo	Permanent	165	Molars	Occlusal	2	Ekstrand
Ashley et al. 1998	E + D in vitro	Permanent	103	Molars/ Premolars	Occlusal	1	Downer
Ashley et al. 2000	E + D in vitro	Primary	58	Molars	Occlusal	1	Ekstrand
Braga et al. 2010	E in vitro	Primary	50	Molars	Occlusal	2	ICDAS
Braga et al. 2010	E + D in vitro	Primary	50	Molars	Occlusal	2	ICDAS
Braga et al. 2010	E in vitro	Primary	50	Molars	Occlusal	2	Nyvad
Braga et al. 2010	E + D in vitro	Primary	50	Molars	Occlusal	2	Nyvad
Braga et al. 2009	E in vitro	Primary	98	Molars	Occlusal	2	ICDAS
Braga et al. 2009	E + D in vitro	Primary	98	Molars	Occlusal	2	ICDAS
Braga et al. 2009	E in vitro	Primary	98	Molars	Occlusal	2	Nyvad
Braga et al. 2009	E + D in vitro	Primary	98	Molars	Occlusal	2	Nyvad
Braga et al. 2009	E + D in vitro	Primary	131	Molars	Approximal	2	SS
Cortes et al. 2000	E + D in vitro	Permanent	59	Molars	Approximal	4	Ekstrand
Cortes et al. 2003	E + D in vitro	Permanent	152	Molars	Occlusal	1	Ekstrand
Deery et al. 1995	E + D in vitro	Permanent	112	Molars	Occlusal	7	PF
Deery et al. 2006	E + D in vitro	Permanent	37	Molars/ Premolars	Occlusal	3	Fyffe
de Paula et al. 2011	E + D in vitro	Permanent	64	3rd molars	Occlusal	2	SS
Diniz et al. 2009	E in vitro	Permanent	163	Molars	Occlusal	2	ICDAS
Diniz et al. 2009	E + D in vitro	Permanent	163	Molars	Occlusal	2	ICDAS
Ekstrand et al. 1997	E in vitro	Permanent	100	Molars/ Premolars	Occlusal	3	Ekstrand
Ekstrand et al. 1997	E + D in vitro	Permanent	100	Molars/ Premolars	Occlusal	3	Ekstrand

S=sound; E=enamel; D=dentine; SS=Study Specific; PF=Pitts and Fyffe

Appendix 2.1. Continued

Author	Gold	Definition of disease (Gold)	Prevalence	Quality Score	Sensitivity	Specificity	ROC	Reproducibility (inter)
Akarsu et al. 2006	OR	S vs E	25	50	0.52*	0.71*	NA	NA
Akarsu et al. 2006	OR	S vs E-D	76	50	0.71	0.89	NA	0.34(K-intra)
Ashley et al. 1998	H	S vs E-D	60	55	0.6	0.73	NA	0.42(K-intra)
Ashley et al. 2000	H	S vs E-D	51	45	0.78	0.95	NA	0.73(K-intra)
Braga et al. 2010	H	S vs E	26	60	0.5*	0.79*	NA	NA
Braga et al. 2010	H	S vs E-D	52	60	0.85	0.79	NA	0.91(K)
Braga et al. 2010	H	S vs E	26	60	0.83*	0.46*	NA	NA
Braga et al. 2010	H	S vs E-D	52	60	0.85	0.83	0.88	0.94(K)
Braga et al. 2009	H	S vs E	43	60	0.79*	0.78*	NA	NA
Braga et al. 2009	H	S vs E-D	63	60	0.92	0.79	0.9	0.82(K)
Braga et al. 2009	H	S vs E	43	60	0.67*	0.81*	NA	NA
Braga et al. 2009	H	S vs E-D	63	60	0.89	0.81	0.85	0.96(K)
Braga et al. 2009	H	S vs E-D	62	60	0.72	0.8	0.8	0.32(K)
Cortes et al. 2000	H	S vs E-D	89	50	0.95	0.53	0.83	0.95(K)
Cortes et al. 2003	H	S vs E-D	77	55	0.96	0.57	0.92	0.87 (K-intra)
Deery et al. 1995	H	S vs E-D	97	60	0.6	0.5	NA	0.60(K)
Deery et al. 2006	H	S vs E-D	86	50	0.77	0.73	NA	0.4(K)
de Paula et al. 2011	H	S vs E-D	88	55	0.63	1	0.82	0.61(K)
Diniz et al. 2009	H	S vs E	95	65	0.44*	0.66*	NA	NA
Diniz et al. 2009	H	S vs E-D	95	65	0.93*	0.57*	0.73	0.51(K)
Ekstrand et al. 1997	H	S vs E	47	60	0.66*	0.90*	NA	NA
Ekstrand et al. 1997	H	S vs E-D	76	60	0.90*	0.90*	NA	0.54(K)

S=sound; E=enamel; D=dentine; H=Histology; OR=Operative removal; V: visual; TS: Tooth separation*Calculated value; K=Kappa; Quality Score is based on a scale of 0 to 100; NA= not available

Appendix 2.1. Continued

Author	Study Type	Dentition	Sites (N)	Teeth	Sites	Examiner	Criteria for clinical examination
Fyffe et al., 2000	E + D in vitro	Permanent	160	Molars/Premolars	Occlusal	20	DSTM
Jablonski-Momeni et al., 2008	E in vitro	Permanent	93	Molars/ Premolars	Occlusal	4	ICDAS
Jablonski-Momeni et al., 2008	E + D in vitro	Permanent	93	Molars/ Premolars	Occlusal	4	ICDAS
Jablonski-Momeni et al., 2009	E + D in vitro	Permanent	146	Molars/ Premolars	Occlusal	4	ICDAS
Kavvadia et al., 2008	E + D in vivo	Primary	405	Molars	Occlusal	2	SS
Lussi et al., 2001	E + D in vivo	Permanent	332	Molars/ Premolars	Occlusal	7	SS
Mendes et al., 2006	E + D in vitro	Primary	110	Molars	Occlusal	2	Ekstrand
Mitropoulos et al., 2010	E in vitro	Permanent	40	Molars/ Premolars	Approximal	2	ICDAS
Mitropoulos et al., 2010	E + D in vitro	Permanent	40	Molars/ Premolars	Approximal	2	ICDAS
Neuhaus et al., 2010	E + D in vitro	Primary	37	Molars	Occlusal	2	ICDAS
Novaes et al., 2009	E in vivo	Primary	621	Molars	Approximal	2	ICDAS
Novaes et al., 2009	E + D in vivo	Primary	621	Molars	Approximal	2	ICDAS
Pereira et al., 2009	E + D in vitro	Permanent	96	Molars	Occlusal	3	Ekstrand
Rocha et al, 2003	E in vitro	Primary	50	Molars	Occlusal	2	Ekstrand
Rocha et al, 2003	E + D in vitro	Primary	50	Molars	Occlusal	2	Ekstrand
Shoaib et al., 2009	E + D in vitro	Primary	107	Molars	Occlusal	3	ICDAS
Shoaib et al., 2009	E + D in vitro	Primary	112	Molars	Approximal	3	ICDAS

S=sound; E=enamel; D=dentine; SS=Study Specific; DSTM=Dundee Selectable Threshold Method; PF=Pitts and Fyffe; NA= not available

Appendix 2.1. Continued

Author	Gold	Definition of disease (Gold)	Prevalence	Quality Score	Sensitivity	Specificity	ROC	Reproducibility (inter)
Fyffe et al., 2000	H	S vs E-D	40	75	0.2	0.93	NA	0.62 (K-intra)
Jablonski-Momeni et al., 2008	H	S vs E	47	60	0.41*	0.76*	NA	NA
Jablonski-Momeni et al., 2008	H	S vs E-D	76	60	0.57	0.73	NA	0.62(K)
Jablonski-Momeni et al., 2009	H	S vs E-D	NA	60	0.57	0.73	0.72	0.66(K)
Kavvadia et al., 2008	OR	S vs E-D	94	55	0.76	0.51	NA	0.94(ICC)
Lussi et al., 2001	OR	S vs E-D	67	65	0.62	NA	NA	NA
Mendes et al., 2006	H	S vs E-D	75	60	0.87	0.52	0.8	0.54(K)
Mitropoulos et al., 2010	H	S vs E	15	50	0.22*	0.88*	NA	NA
Mitropoulos et al., 2010	H	S vs E-D	60	50	0.92	0.5	NA	0.51(K)
Neuhaus et al., 2010	H	S vs E-D	72	55	0.82	0.65	0.73	0.35(K)
Novaes et al., 2009	V-TS	S vs E	64	65	0.17*	0.95*	NA	NA
Novaes et al., 2009	V-TS	S vs E-D	70	65	0.20	0.95	NA	0.62(K)
Pereira et al., 2009	H	S vs E-D	57	55	0.67	0.59	0.75	NA
Rocha et al, 2003	H	S vs E	42	55	0.73*	0.82*	NA	NA
Rocha et al, 2003	H	S vs E+D	58	55	0.82	0.85	NA	0.46(K)
Shoaib et al., 2009	H	S vs E-D	19	60	0.75	0.9	NA	0.68(K)
Shoaib et al., 2009	H	S vs E-D	65	60	0.66	0.85	NA	0.7(K)

S=sound; E=enamel; D=dentine; H=Histology; OR=Operative removal; V: visual; TS: Tooth separation*Calculated value; K=Kappa; Quality Score is based on a scale of 0 to 100; NA= not available

Appendix 2.2. Summary of Studies of Radiographic Methods

Author	Study Type	System	Dentition	Sites (N)	Teeth	Sites	Examiner
Akarsu et al., 2006	E in vivo	CR	Permanent	165	Molars	Occlusal	2
Akarsu et al., 2006	E + D in vivo	CR	Permanent	165	Molars	Occlusal	2
Ashley et al., 1998	E + D in vitro	CR	Permanent	103	Molars/ Premolars	Occlusal	1
Braga et al., 2009	E + D in vitro	CR	Primary	131	Molars	Approximal	2
Castro et al., 2007	E + D in vitro	CR	Permanent	150	Molars/ Premolars	Approximal	7
Castro et al., 2007	E + D in vitro	DR	Permanent	150	Molars/ Premolars	Approximal	7
Cortes et al., 2000	E + D in vitro	CR	Permanent	59	Molars	Approximal	4
Ekstrand et al., 1997	E in vitro	CR	Permanent	100	Molars/ Premolars	Occlusal	3
Ekstrand et al., 1997	E + D in vitro	CR	Permanent	100	Molars/ Premolars	Occlusal	3
Hintze et al.,1996	E + D in vitro	CR	Permanent	130	3rd Mol/ Premolars	Occlusal	4
Hintze et al.,1996	E + D in vitro	CR	Permanent	130	3rd Mol/ Premolars	Approximal	4
Kavvadia et al., 2008	E + D in vivo	CR	Primary	405	Molars	Occlusal	2
Lussi A et al., 2006	E + D in vitro	CR	Permanent	150	Molars	Approximal	5
Machiulskiene et al., 1999	E in vivo	CR	Permanent	29,870	Posterior	Approximal	1
Machiulskiene et al., 1999	E + D in vivo	CR	Permanent	29,870	Posterior	Approximal	1
Mitropoulos et al., 2010	E + D in vitro	CR	Permanent	40	Molars/ Premolars	Approximal	2
Mitropoulos et al., 2010	E + D in vitro	DR	Permanent	40	Molars/ Premolars	Approximal	2
Neuhaus et al 2010	E + D in vitro	CR	Primary	37	Molars	Occlusal	2
Novaes et al., 2009	E in vitro	CR	Primary	621	Molars	Approximal	2
Novaes et al., 2009	E + D in vivo	CR	Primary	621	Molars	Approximal	2
Rocha et al, 2003	E in vitro	CR	Primary	50	Molars	Occlusal	2
Rocha et al, 2003	E + D in vitro	CR	Primary	50	Molars	Occlusal	2
Russell et al., 1993	E + D in vitro	CR	Permanent	120	NA	Occlusal	3
Russell et al., 1993	E + D in vitro	CR	Permanent	120	NA	Approximal	3
Russell et al., 1993	E + D in vitro	DR	Permanent	120	NA	Occlusal	3
Russell et al., 1993	E + D in vitro	DR	Permanent	120	NA	Approximal	3
Wenzel et al.,1990	E in vitro	CR	Permanent	46	Molars/ Premolars	Occlusal	4
Wenzel et al.,1990	E + D in vitro	CR	Permanent	46	Molars/ Premolars	Occlusal	4
Wenzel et al.,1990	E in vitro	DR	Permanent	46	Molars/ Premolars	Occlusal	4
Wenzel et al.,1990	E + D in vitro	DR	Permanent	46	Molars/ Premolars	Occlusal	4

S=sound; E=enamel; D=dentine; CR: Conventional Radiography; DR: Digital Radiography; NA= not available

Appendix 2.2. Continued

Author	Criteria for clinical examination	Gold	Definition of disease (Gold)	Prevalence	Quality Score	Sensitivity	Specificity	ROC	Reproducibility (inter)
Akarsu et al., 2006	S vs E	OR	S vs E	25	50	0.14*	0.59*	NA	NA
Akarsu et al., 2006	S vs E-D	OR	S vs E-D	76	50	0.65	0.55	NA	0.31(K-intra)
Ashley et al., 1998	S vs E-D	H	S vs E-D	60	50	0.19	0.8	NA	0.56(K-intra)
Braga et al., 2009	S vs E-D	H	S vs E-D	62	60	0.54	0.78	0.6	0.41(K)
Castro et al., 2007	S vs E-D	H	S vs E-D	50	60	NA	NA	0.7	0.43(KCC)
Castro et al., 2007	S vs E-D	H	S vs E-D	50	60	NA	NA	0.6	NA
Cortes et al., 2000	S vs E-D	H	S vs E-D	89	55	0.84	0.83	0.9	0.84(K)
Ekstrand et al., 1997	S vs E	H	S vs E	47	60	0.26*	0.9*	NA	NA
Ekstrand et al., 1997	S vs E-D	H	S vs E-D	76	60	0.57*	0.89*	NA	0.52(K)
Hintze et al.,1996	S vs E-D	H	S vs E-D	NA	45	NA	NA	0.8	NA
Hintze et al.,1996	S vs E-D	H	S vs E-D	NA	45	NA	NA	0.6	NA
Kavvadia et al., 2008	S vs E-D	OR	S vs E-D	94	55	0.2	0.78	NA	NA
Lussi A et al., 2006	S vs E-D	H	S vs E-D	59	55	0.68	0.67	NA	NA
Machiulskiene et al., 1999	S vs E-D	H	S vs E	60	50	0.46	0.93	NA	0.67(K)
Machiulskiene et al., 1999	S vs E-D	H	S vs E	60	50	0.46	0.94	NA	0.72(K)
Mitropoulos et al., 2010	S vs E-D	H	S vs E-D	72	55	0.36	0.82	0.6	0.23(K)
Mitropoulos et al., 2010	S vs E	V	S vs E	64	65	0.17*	0.98*	NA	NA
Neuhaus et al 2010	S vs E-D	V	S vs E-D	70	65	0.23	0.99	0.6	0.65(K)
Novaes et al., 2009	S vs E	H	S vs E	42	55	0.15	0.73	NA	NA
Novaes et al., 2009	S vsE-D	H	S vs E+D	58	55	0.62	0.73	NA	0.53(K)
Rocha et al, 2003	S vs E-D	H	S vs E-D	NA	55	0.12	0.95	NA	0.3(K)
Rocha et al, 2003	S vs E-D	H	S vs E-D	NA	55	0.25	0.9	NA	0.3(K)
Russell et al., 1993	S vs E-D	H	S vs E-D	NA	55	0.15	0.97	NA	0.3(K)
Russell et al., 1993	S vs E-D	H	S vs E-D	NA	55	0.25	0.9	NA	0.3(K)
Russell et al., 1993	S vs E	H	S vs E	17	40	0.33*	0.8*.	NA	NA
Russell et al., 1993	S vs E-D	H	S vs E	89	40	0.73*	0.8*	NA	0.29(K)
Wenzel et al.,1990	S vs E	H	S vs E	17	40	0.38*	0.9*	NA	NA
Wenzel et al.,1990	S vs E-D	H	S vs E	89	40	0.78*	0.9*	NA	0.17(K)
Wenzel et al.,1990	S vs E	V	S vs E	2	65	0.16*	0.94*	NA	NA
Wenzel et al.,1990	S vs E-D	V	S vs E-D	5.8	65	0.34*	0.94*	NA	0.89(K-intra)

Appendix 2.3. Summary of Diagnodent Studies

Author	Study Type	System	Dentition	Sites (N)	Teeth	Sites	Examiner
Akarsu et al. 2006	E + D in vivo	DD	Permanent	165	Molars	Occlusal	2
Braga et al. 2009	E + D in vitro	DD	Primary	131	Molars	Approximal	2
Braga et al., 2008	E + D in vitro	DD	Primary	181	Molars	Occlusal	2
Cortes et al. 2003	E + D in vitro	DD	Permanent	152	Molars	Occlusal	1
de Paula et al. 2011	E + D in vitro	DD	Permanent	64	3rd Molars	Occlusal	2
Huth et al., 2008	E + D in vivo	DD	Permanent	120	Molars	Occlusal	NA
Kavvadia and Lagouvardos, 2008	E + D in vivo	DD	Primary	405	Molars	Occlusal	2
Lussi et al.,2001	E + D in vivo	DD	Permanent	332	Molars/ Premolars	Occlusal	7
Lussi et al., 2006a	E + D in vitro	DD (CYL)	Permanent	119	3rd Molars	Occlusal	NA
Lussi et al., 2006a	E + D in vitro	DD (CON)	Permanent	119	3rd Molars	Occlusal	NA
Lussi et al., 2006a	E + D in vitro	DD (TIP)	Permanent	119	3rd Molars	Occlusal	NA
Lussi et al., 2006b	E + D in vitro	DD (TWS)	Permanent	150	Molars	Smooth	5
Lussi al., 2006b	E + D in vitro	DD (WS)	Permanent	150	Molars	Smooth	5
Mendes et al. 2005	E + D in vitro	DD	Primary	77	Molars	Approximal	1
Mendes et al. 2006	E + D in vitro	DD	Primary	110	Molars	Occlusal	2
Neuhaus et al 2010	E + D in vitro	DD	Primary	37	Molars	Occlusal	2
Neuhaus et al 2010	E + D in vitro	DD pen	Primary	37	Molars	Occlusal	2
Novaes et al. 2009	E + D in vivo	DD	Primary	621	Molars	Approximal	2
Rocha et al, 2003	E + D in vitro	DD	Primary	50	Molars	Occlusal	2
Shi et al., 2000	E + D in vitro	DD (CON)	Permanent	76	Molars/Premolars	Occlusal	6
Virajsilp et al., 2005	E + D in vitro	DD	Primary	107	Molars	Approximal	2

S=sound; E=enamel; D=dentine; DD=Diagnodent; TWD=Tapered wedge shaped; WS=wedge shaped; NA= not available

Appendix 2.3. Continued

Author	Cut-off points	Gold	Definition of disease (Gold)	Prevalence	Quality Score	Sensitivity	Specificity	ROC	Reproducibility (inter)
Akarsu et al. 2006	0-6=S vs >6= E+D	OR	S vs E+D	76	50	0.88	0.71	NA	0.54(K-intra)
Braga et al. 2009	0-8=S vs 8.1-30=E+D	H	S vs E+D	62	60	0.82	0.25	0.7	0.002(K)
Braga et al., 2008	0-6=S vs >6= E+D	H	S vs E+D	NA	50	0.64	0.66	NA	0.67(K)
Cortes et al. 2003	0-17=S vs >17= E+D	H	S vs E+D	77	55	0.72	0.91	0.9	0.71(ICC-intra)
de Paula et al. 2011	0-10=S vs >10-99=E+D	H	S vs E+D	88	55	0.72	1	0.9	0.43(K)
Huth et al., 2008	0-6=S vs >6= E+D	OR	S vs E+D	89	60	0.67	0.79	NA	0.88(ICC)
Kavvadia et al, 2008	0-9=S vs >10= E+D	OR	S vs E+D	94	55	0.43	0.88	NA	0.94(ICC)
Lussi et al.,2001	0-4=S vs >4.01=E+D	OR	S vs E+D	67	65	0.96	0.86	NA	0.93(K-intra)
Lussi et al., 2006a	0-6=S vs >6= E+D	H	S vs E+D	78	40	0.88	0.77	NA	0.89(K)
Lussi et al., 2006a	0-7=S vs >7= E+D	H	S vs E+D	78	40	0.91	0.77	NA	0.83(K)
Lussi et al., 2006a	0-7=S vs >7= E+D	H	S vs E+D	78	40	0.96	0.69	NA	0.83(K)
Lussi et al., 2006b	0-6=S vs >6= E+D	H	S vs E+D	59	55	0.87	0.93	NA	0.82(K)
Lussi al., 2006b	0-6=S vs >6= E+D	H	S vs E+D	59	55	0.88	0.92	NA	0.74(K)
Mendes et al. 2005	0-3=S vs >3= E+D	H	S vs E+D	69	45	0.51	0.96	0.8	NA
Mendes et al. 2006	0-7=S vs >7= E+D	H	S vs E+D	75	40	0.61	0.93	0.8	0.63(K)
Neuhaus et al 2010	0-10=S vs >10= E+D	H	S vs E+D	72	55	0.74	0.81	0.8	0.98(ICC)
Neuhaus et al 2010	0-10=S vs >10= E+D	H	S vs E+D	72	55	0.7	0.9	0.8	0.96(ICC)
Novaes et al. 2009	0-5=S vs >5= E+D	V-TS	S vs E+D	38	65	0.16	0.94	0.9	0.44(K)
Rocha et al, 2003	0-5=S vs >5= E+D	H	S vs E+D	58	55	0.6	0.9	NA	0.61(K)
Shi et al., 2000	0-6.8=S vs >6.8= E+D	H	S vs E+D	34	65	0.46	0.95	1	0.96(ICC)
Virajsilp et al., 2005	0-3=S vs >3= E+D	H	S vs E+D	83	55	0.75	0.94	NA	0.97(ICC)

S=sound; E=enamel; D=dentine; H=Histology; OR=Operative removal; V: visual; TS: Tooth separation; K=Kappa; ICC=Intraclass Correlation Coefficient; Quality Score is based on a scale of 0 to 100; NA= not available

Appendix 2.4. Summary of ECM Studies

Author	Study Type	System	Dentition	Sites (N)	Teeth/Sites	Sites	Examiner	Criteria for clinical examination	Gold	Definition of disease (Gold)	Prevalence	Quality Score	SE	SP	ROC	Reproducibility (inter)
Ashley et al., 1998	E + D in vitro	ECM	Permanent	103	Molars/ Premolars	Occlusal	1	S vs E-D	H	S vs E-D	60	50	0.65	0.73	NA	0.68 (K-intra)
Cortes et al.,2003	E + D in vitro	ECM	Permanent	152	Molars	Occlusal	1	S vs E-D	H	S vs E-D	77	55	0.9	0.83	0.93	0.73 (ICC)
Ekstrand et al., 1997	E in vitro	ECM	Permanent	100	Molars/ Premolars	Occlusal	3	S vs E	H	S vs E	47	60	0.63*	0.87*	NA	NA
Ekstrand et al., 1997	E + D in vitro	ECM	Permanent	100	Molars/ Premolars	Occlusal	3	S vs E-D	H	S vs E	76	60	0.65*	0.89*	NA	0.5(K)
Ricketts et al., 1996	E + D in vitro	ECM	Permanent	30	Molars	Occlusal	1	S vs E-D	H	S vs E-D	80	50	0.92	1.0	NA	0.82 (DifM)
Ricketts et al., 1997a	E + D in vitro	ECM	Permanent	76	Molars	Occlusal	1	S vs E-D	H	S vs E-D	64	40	0.61	0.96	0.8	0.92 (ICC-intra)
Ricketts et al., 1997b	E + D in vitro	ECM	Permanent	96	molars	Occlusal	1	S vs E-D	H	S vs E-D	78	40	0.61	0.86	0.81	0.76(K)

S=sound; E=enamel; D=dentine; SE: sensitivity; SP: specificity; *Calculated value; K: Kappa; ICC: Intraclass Correlation Coefficient; DifM: Difference means 1st and 2nd readings ;Quality Score is based on a scale of 0 to 100; NA= not available

Appendix 2.5. Summary of Other Methods

Author	Study Type	System	Dentition	Sites (N)	Teeth	Sites	Examiner	Criteria for clinical examination	Gold	Definition of disease (Gold)	Prevalence	Quality Score	SE	SP	ROC	Reproducibility (inter)
Cortes et al. 2003	E + D in vitro	FOTI/ Visual	Permanent	152	Molars	Occlusal	1	Ekstrand	H	S vs E-D	77	55	0.94	0.7	0.9	0.95 (K-intra)
Pereira et al. 2009	E + D in vitro	Visual +BW, QLF, ECM, DD	Permanent	96	Molars	Occlusal	3	Ekstrand	H	S vs E-D	57	55	0.8	0.56	0.8	NA
Ferreira-Zandona et al. 2010	E in vivo	QLF	Permanent	23402	Molars	Smooth	1	ICDAS	ICDAS	S vs E	16	65	0.82*	0.92*	NA	NA
Ferreira-Zandona et al. 2010	E + D in vivo	QLF	Permanent	23402	Molars	Smooth	1	ICDAS	ICDAS	S vs E-D	17	65	0.83*	0.92*	NA	0.78(K-intra)
Ashley et al. 1998	E + D in vitro	FOTI	Permanent	103	Molars/ Premolars	Occlusal	1	Downer	H	S vs E-D	24	50	0.21	0.88	N/A	0.65(K-intra)
Cortes et al. 2000	E + D in vitro	FOTI	Permanent	59	Molars	Approximal	4	Ekstrand	H	S vs E-D	74	50	0.74	0.85	0.9	0.87(K)
Cortes et al. 2003	E + D in vitro	FOTI	Permanent	152	Molars	Occlusal	1	Ekstrand	H	S vs E-D	27	55	0.96	0.74	0.9	0.78 (K-intra)

S=sound; E=enamel; D=dentine; H=Histology; SE: sensitivity; SP: specificity; *Calculated value; K:Kappa; Quality Score is based on a scale of 0 to 100
NA= not available

CHAPTER 3

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Evidence on Existing Caries Risk Assessment Systems: Are They Predictive of future Caries?

Evidence on existing caries risk assessment systems: are they predictive of future caries?

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Rationale Paper II

Caries risk assessment (CRA) is an essential component of the clinical decision-making process and will influence the management of both lesions and patients more broadly. Many risk factors associated with caries have been identified, but caries experience is still the better predictor of future caries development/progression. Several risk assessment models have been proposed, however, the supporting evidence is inconclusive and frequently based on cross-sectional studies. The objective of this review was to identify whether the current CRA were useful tools in the prediction of future caries experience.

Abstract

Aim: To critically appraise evidence for the prediction of caries using four caries risk assessment (CRA) systems/guidelines (Cariogram, Caries Management by Risk Assessment (CAMBRA), American Dental Association (ADA), and American Academy of Pediatric Dentistry (AAPD)). This review focused on prospective cohort studies or randomized controlled trials. **Methods:** A systematic search strategy was developed to locate papers published in Medline Ovid and Cochrane databases. The search identified 539 scientific reports, and after title and abstract review, 137 were selected for full review and 14 met the following inclusion criteria: (i) used as validating criterion caries incidence/increment, (ii) involved human subjects and natural carious lesions, and (iii) published in peer-reviewed journals. In addition, papers were excluded if they met one or more of the following criteria: (i) incomplete description of sample selection, outcomes, or small sample size and (ii) not meeting the criteria for best evidence under the prognosis category of the Oxford Centre for Evidence-Based Medicine. **Results:** There are wide variations among the systems in terms of definitions of caries risk categories, type and number of risk factors/markers, and disease indicators. The Cariogram combined sensitivity and specificity for predicting caries in permanent dentition ranges from 110 to 139 and is the only system for which prospective studies have been conducted to assess its validity. The Cariogram had limited prediction utility in preschool children, and a moderate to good performance for sorting out elderly individuals into caries risk groups. One retrospective analysis on CAMBRA's CRA reported higher incidence of cavitated lesions among those assessed as extreme-risk patients when compared with those at low risk. **Conclusion:** The evidence on the validity for existing systems for CRA is limited. It is unknown if the identification of high-risk individuals can lead to more effective long-term patient management that prevents caries initiation and arrests or reverses the progression of lesions. There is an urgent need to develop valid and reliable methods for caries risk assessment that are based on best evidence for prediction and disease management rather than opinions of experts.

Key words: CAMBRA; cariogram; dental caries; prediction; risk assessment

Introduction

Caries risk assessment (CRA) is one of the cornerstones in patient-centered caries management. CRA should be included in contemporary treatment plans in order to assist the clinician in the decision-making process concerning treatment, recall appointments, and need for additional diagnostic procedures. An ideal CRA system should have high validity and reliability, and it should also be easy to use in practice at a low cost (1).

Designing a CRA system has so far been based on findings either from cross-sectional studies, where various caries-related factors are identified using statistical models that identify the risk factors or indicators associated with caries status or severity, or from longitudinal studies where factors are related to new caries development over a period of years (2). A correlation between various factors and the development of caries has been shown in a large number of cross-sectional studies. These studies are inadequate for correctly identifying the individuals at risk for caries, which is the determining characteristic of an ideal CRA system. Moreover, caries status or severity, in cross-sectional studies, is determined by past exposure to risk factors over a lifetime that cannot be assessed at any one point in time. Longitudinal prospective studies, on the other hand, assess the prediction of new caries development, which, with limitation, is stronger than a single assessment of risk factors. Unfortunately, there are few prospective studies of good quality available for both children and adult populations.

The preponderance of evidence on CRA comes from cross-sectional studies where various multivariate regression techniques were deployed to identify methods for classifying individuals based on their caries risk status (3–5). The major conceptual limitation of all statistical models using data collected in cross-sectional studies is that they can only ascertain relationships, but never be sure about underlying causal mechanisms. To ascertain causal mechanisms, there is a need to define the biological rationale for the association. Moreover, an important source of concern with a regression model is when there are several independent variables, there is a possibility that multicollinearity, or the correlation among risk factors (6), can lessen or limit the ability of the model to identify risk factors.

The Swedish Council on Technology Assessment in Health Care reported in 2008 (7) that current CRA methods have low accuracy, but they are reliable in identifying those with a low risk of developing caries (8). Several risk assessment systems/ guidelines have been proposed by professional organizations and academic institutions in the past decade. Among the most frequently named systems/guidelines reported in the literature are (i) the CRA Tool proposed by the American Academy of Pediatric Dentistry (AAPD) (9), (ii) the Caries Management by Risk Assessment Philosophy (CAMBRA) advocated by the California Dental Association (10), 3) the American Dental Association (ADA) CRA forms (11), and 4) the Cariogram (12), a computerized program developed to streamline the CRA process with multiple weighted factors and interactions (13). The goal of this systematic review is to answer two research questions regarding these systems: 1) Are current CRA systems/guidelines predictive of future caries? and (ii) What are the outcomes of management based on the use of these systems? This review focuses on identifying and appraising findings from cohort studies or randomized clinical trials.

Methods

A search filter was developed and tested to identify reports where the four CRA systems were evaluated (Table 3.1). The filter was applied to search for all relevant papers in the following databases: Cochrane Oral Health Group's Specialized Register, Cochrane Central Register of Controlled Trials, and MEDLINE OVID (1966 to November 2011). The reports were checked for relevance based on reviews of titles and abstracts. The following inclusion criteria were followed to select relevant studies: (i) used as validating criterion caries incidence/increment, (ii) limited to those with human subjects and natural carious lesions, and (iii) published in peer-reviewed journals. In addition, papers were excluded if they met one or more of the following criteria: (i) incomplete description of sample selection, outcomes, or small sample size and (ii) not meeting the criteria under the prognosis category of the Oxford Centre for Evidence-Based Medicine (systematic reviews (SR) of inception cohort studies, inception cohort studies, SR of retrospective cohort studies or follow-up of untreated control patients in a randomized clinical trial, case-series or poor-quality prognostic cohort study) (14). Bibliographic references of identified systematic reviews, prospective cohort studies and clinical trials, textbooks, and

review articles were also checked. The systematic search strategy included combined MeSH and free-text terms such as 'dental caries', 'risk assessment', 'systems', 'longitudinal studies', 'Cariogram', 'CAMBRA', 'ADA', and 'AAPD'. The primary clinical outcomes considered for this review were caries incidence/increments, and the validity of the system/guide- line was assessed from the data reported on sensitivity (Se), specificity (Sp), negative and positive predictive values (NPV/PPV), and area under the receiver operating curve (AUROC). The data were extracted by one review author (MT) and checked independently by a second author (JG). The quality of the studies was assessed using the criteria reported in the ADA Clinical Recommendations Handbook (15). Internal validity of the studies was evaluated by considering attrition, differential loss to follow up, reliability of measurements, blinding, randomization, and overall comparability between study groups. The studies were categorized as good (meets all the criteria), fair (fails to meet at least one criterion), or poor (have at least one fatal flaw) based on ADA's criteria.

Results

Number of reports

The systematic search strategy yielded 539 scientific publications, and after title review, 137 reports of studies were selected for full review. Thirty-four studies presented general prediction models but did not evaluate any of the four CRA systems, seventeen studies reported data for the Cariogram, but only six of these were prospective studies, and five focused on its validation for caries prediction (1, 2, 8, 16, 17). Seven studies evaluated the CAMBRA guidelines. Six of these studies were narrative descriptions of the philosophy proposed by Featherstone and colleagues (18–22), and one study was a retrospective analysis of electronic data and paper charts to validate the CAMBRA form for children aged 6 and over (23). All the other studies were summary reviews/comments on risk assessment (n = 73). No other published longitudinal studies were identified that would report data on the caries prediction capability of the guidelines proposed by the ADA or the AAPD.

Main characteristics of current guidelines/ systems for CRA

Table 3.2 presents a comparative chart of the characteristics of each CRA system. In general, there are differences in the total number of factors assessed by each system, in the domains considered for the assessment (e.g., sociodemographic, microbiological, salivary) and the target population. CAMBRA guidelines suggest the collection of the largest number of factors (#25) associated with caries for adults, followed by ADA (#19) and Cariogram (#9). For evaluating caries risk for children, CAMBRA suggests the collection of the largest number of factors (#20), followed by AAPD and ADA (#14), and Cariogram (#9). The categorization of high and low risk varies among systems/guide- lines. However, there seems to be an overlap across systems in the main known etiological factors and disease indicators such as caries experience, plaque, fluoride exposure, diet, salivary flow, and overall general health conditions. Following ADA's criteria, 33% of the studies were rated as 'poor', while 77% were rated as 'fair'.

Are caries risk assessment systems/guidelines predictive of future caries activity/caries increment?

Currently, there is only available published evidence on caries prediction for two of the four systems focus of this review. Table 3.3 provides detailed information about longitudinal studies reporting on the caries prediction capability of Cariogram and CAMBRA.

Holgerson et al. (17) designed a study to validate the caries risk profiles assessed with Cariogram against actual caries development in preschool children. In the original Cariogram, nine different parameters are scored and entered into the computer. For this study, only seven parameters were used (caries experience, mutans streptococci counts, relevant diseases or medications, frequency of sugar consumption, oral hygiene, use of fluorides, and clinical judgment), and information on salivary buffer and salivary flow rate was excluded. Almost all new caries lesions appeared in the group assessed with the high risk of developing caries (low likelihood of avoiding caries at baseline ($p < 0.05$). The sensitivity and the negative predictive values were 90%, while the specificity and positive predictive values were around 50%. The percentage of correctly classified children as true positives and true negatives was 63. The quality of this study was rated as fair.

Hänsel Petersson et al. (1) investigated whether a reduced Cariogram model (excluding salivary and microbiological tests) could predict future caries as good as the full risk model in a group of school children (n = 392). Caries incidence after 2 years was correlated significantly with both the complete and reduced Cariogram models. More caries was found among those assessed with high risk compared with those with low risk. For example, the mean DMFT or DMFS increments among those classified at baseline, as 'high Risk' were 1.67 and 2.58, respectively. The DMFT or DMFS for children classified as 'low Risk' were 0.23 and 0.27, respectively. The combined sensitivity and specificity dropped from 1.33 with the full Cariogram to 1.10 when salivary and microbiological tests were excluded. This significant drop in accuracy was mainly the result of the change in specificity values (complete model Sp: 0.60 (95% CI 0.54–0.66), reduced model Sp: 0.20 (95% CI: 0.15–0.25)). Despite these changes in specificity, the area under the receiver operating curve (AUROC) did not differ substantially for the full and reduced models (full 0.751 (95% CI 0.69–0.80) versus reduced 0.723 (95% CI 0.66–0.78)). The study concluded that although the Cariogram can still be used for caries prediction in school children, and specifically to identify those with low risk, the predictive ability was significantly impaired by the exclusion of the salivary tests. The quality of this study was rated as fair (Table 3.4).

Other analyses from two additional studies conducted (2,8) in the same sample of children demonstrated that Cariogram predicted caries increments more accurately than any included single-factor modelled using logistic regression analyses. These studies found that about half of the children remained in the same risk category after 2 years, one-third were assessed in a higher risk category, and 18.4% showed a lower risk, and that those children with increased risk compared with baseline developed significantly more caries than those with an unchanged risk category. No exploration of multicollinearity was discussed in any of these papers, and the statistical significance of 'Cariogram' as the most important independent variable in the prediction of caries increments might be misleading as the inclusion of this variable along with the individual factors of the Cariogram might yield correlated data that convey essentially the same information for prediction. Also, the blinding status of the examiners and the patients regarding their baseline caries risk was not discussed

and that might have impacted the internal validity of these studies. Both studies were rated as fair.

The validity of Cariogram for future caries prediction among adults (55–75 years old) was also explored by Hänsel Petersson in 2003 (16). The mean DMFS increment over 5 years, as related to baseline Cariogram predictions, showed that subjects in the highest risk group demonstrated a mean increment of 9.54 new carious tooth surfaces, whereas the lowest risk group had 1.74 new carious tooth surfaces. Among the risk group who had a low chance of avoiding caries as established by Cariogram, around 18% had no new lesions. For the risk group with a high chance of avoiding caries, 84% had no new lesions after 5 years of follow-up. Overall, the Cariogram in this case was able to predict the caries development in adults into risk groups that reflected the future actual caries outcome. However, no outcomes related to the sensitivity and specificity of the prediction among elderly subjects were explored. The quality of this study was rated as poor.

Domejean et al. (23) published a study that aimed to retrospectively evaluate the validity of the CAMBRA's CRA as related to existing caries and to determine its predictive value for future caries. The study used electronic data and paper charts from UCSF predoctoral dental clinic patients over the age of six who had a baseline CRA between July 2003 and July 2009 (n = 2571). The study concluded that 'visible cavitation', 'caries radiographic penetration of the dentine', and 'interproximal enamel lesions or radiolucencies' at follow-up were significantly related to the overall caries risk at baseline. Of those assessed as extreme- and high-risk patients, 88% and 69.3% developed new cavities at first follow-up. No association was observed between 'white spots' at follow-up and baseline caries risk. No outcomes related to the sensitivity and specificity of the prediction were provided, and the lack of statistical adjustment for important confounders that could have also played a role in the development of new carious lesions is a major limitation of this study. The quality of this study was rated as poor.

What are the outcomes of management based on the use of these systems?

The only study that reports some information to answer this question is the one conducted by Holgerson et al. (17), which was also used to validate caries risk profiles with Cariogram. In this study, children (n = 146) were examined at 2 and 7 years of age. Within the prospective design, a randomized intervention was implemented between the ages of 2 and 4, where the test group was provided sucking tablets with a daily dose of 0.5–1 g xylitol. At baseline, 5% of the children in the control exhibited caries lesions compared with 36% at the age of 7 years. In the intervention group, 6% had decayed teeth at 2 years of age, and the prevalence increased to 38% at 7 years of age. There was no statistically significant difference in caries development between the different risk categories at the follow-up. In addition, sensitivity was lower in the control group [46 95% CI (31–62)] versus the high- risk group [61 95% CI (39–84)], while specificity was higher after 5 years [88 95% CI (71–104)] versus [47 95% CI (29–65)]. Only 37 of 100 children in the intervention group were classified correctly. In general, the validation of the reduced Cariogram resulted in lower values of sensitivity for both study groups.

Less than half of the children maintained the same risk category at baseline and after follow-up, and around 45% exhibited a lowered risk. There was also a low but statistically significant correlation between the individual risk profiles assessed at 2 and 7 years of age among the children in the control group (r = 0.34) (P < 0.05), but not in the intervention group (r = 0.24).

The quality of this study might have been affected mainly by two factors: First, the low prevalence of caries at baseline could have generated a caries outcome after 5 years that was the result of chance rather than a true association between baseline caries risk and caries increments. Second, the preventive program implemented during the 5-year period could have had some impact on the individual caries risk profiles and impaired the predictive ability of Cariogram.

Findings from prediction models in longitudinal studies not using a specific CRA system/guideline

Table 3.5 summarizes the findings from selected predictive models from longitudinal studies conducted after 2001 (13, 24–30). The choice of using the year 2001 as a cut-

off point was because two comprehensive reviews in this area were published in 1998 (31) and 2001 (32). The selected studies ranged in duration from 12 months to 6 years and mainly used multiple logistic regression in the analyses. The ranges associated with the various validation outcomes were as follows: Se (0.59– 0.82), Sp (0.54–0.79), and area under the receiver operating curve (AUROC) (0.67–0.88). Two of the nine studies evaluated used correlation statistics to determine the association between baseline caries risk and caries increments rather than regression techniques. These studies found an average correlation coefficient of 0.70. All the prediction models varied in the number of variables initially modelled and in the number of predictors that came up as 'statistically significant' after the analysis (range of 1–5 significant variables). Caries experience at baseline was found to be significant in almost half of the studies, while other predictors related to dental morphology, presence of salivary microorganisms, and frequency of sugar intake were less consistent across studies. The fact that no combination of risk indicators was consistently considered a good predictor when applied to different populations across different age groups in these statistical models also extends to the CRA systems object of this review. Neither Cariogram nor CAMBRA achieved a level of performance to assure that collecting information on a large number of factors is more accurate than collecting information on just a few.

Discussion

The evidence on the validity for existing guidelines/systems for CRA is weak. The only system with data evaluating its validity in prospective cohort studies is the Cariogram, which was found to be clinically useful in identifying caries risk levels for the elderly and to a more limited extent in assessing children's caries risk. Still, its usefulness for achieving better health outcomes and cost savings across different settings such as private practice and public health scenarios and in populations inside and outside Scandinavia is unknown. The inferences related to CAMBRA's CRA are more limited as no specific prediction outcomes were presented in the study except for the correlation with various caries outcomes generally defined and the baseline caries risk. It is important to note that this study did not show any predictive power of white spot lesions as opposed to Cariogram studies, in which caries risk was found to be predictive of non-cavitated lesions.

There are various methodological challenges when evaluating the validity of a risk prediction system or model. First, using sensitivity and specificity values is somehow problematic because calculating such values demands cut-off points that should also be validated. In addition, baseline prevalence is known to have a profound impact on predictive values, and both baseline caries prevalence and caries increments were rather low in the populations of the selected studies. Second, the accuracy of prediction models must be determined ideally in longitudinal studies, which may also pose ethical challenges as risk-based action through preventive measures in prospective studies may hinder the understanding of the true predictive ability of potential risk factors. Lastly, many authors over the years have strongly advocated that 'past caries' is the best caries predictor, or better than other prognostic variables (31, 32). However, as stated by Hänsel Petersson (2), it is important to recognize that past caries experience is the effect and not the cause of caries disease, so this variable loses its predictive ability, if successful interventions are introduced and risk factors are removed.

The evidence from prediction models of caries increments demonstrates the lack of consistency on the predictors that show statistical significance. This seems to be a constant for both types of dentitions and varying age groups. Despite one prediction study (13) reaching the desired combination of sensitivity and specificity of 160 per cent or more (33), it is still unclear how the specific factors used in this study might be extrapolated for predicting caries risk in other populations, confirming that the predictive validities of the models depend strongly on the caries prevalence and characteristics of the population for which they are designed.

The Cariogram uses the lowest numbers of risk factors and has data to support its use in adults. It is important to consider this as it has been widely recognized that regardless of the accuracy of any CRA system, the data collection process for decision-making by the clinician needs to be quick, inexpensive, and be acceptable to those to whom it is applied (34).

Conclusion

The evidence on the validity for existing systems for CRA is limited. It is unknown if the identification of high-risk individuals with these systems can lead to more cost-effective long-term patient management that prevents caries initiation and arrests or reverses the progression of lesions. There is an urgent need to develop valid and reliable methods for caries risk assessment that are based on best evidence for prediction and disease management rather than opinions of experts.

Authors' contributions

MT contributed to the protocol, design, acquisition of data, analysis and interpretation of data and contribute to the manuscript. JG contributed to the protocol, acquisition of data, analysis and contributed to the manuscript. AI, IAP and RE and RE contributed to the protocol and to the manuscript.

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Table 3.1. Systematic Search Strategy

1	Dental Caries mp. Or dental caries/	36553
2	((tooth or teeth) and (decay$ or lesion$ or cavit$ or carious or deminerali$ or reminerali$)).mp.	24223
3	risk.mp.	1278958
4	Risk assessment.mp.	152295
5	Longitudinal studies.mp.	76342
6	(1or2) and 3 and 4	597
7	limit 6 to humans	839

Table 3.2. Comparative Chart Current Guidelines/Systems for Caries Risk Assessment (Selected Domains)

System	# of factors	Definition of Low risk	Definition of High Risk	Socio-demographic	Caries	Microflora	Saliva flow	Diet	Saliva Buffer	Access to care	Clinical judgement	Bottle use	Xylitol use	Family caries experience	General health conditions	Radiographs	Fluoride explosure	Appliances	Plaque	Enamel Texture	Missing Teeth
AAPD	14 children	Not having moderate risk or high risk indicators	Presence of single indicator in anyarea of 'high risk' category	x	x	x	x	x			x			x	x	x	x	x	x	x	
ADA	14 children/ 19 adults	Score of 0	A single high risk factor or score of 10	x	x		x	x			x			x	x	x	x	x	x		x
Cariogram	9 adults	Large green sector	Small green sector or % of avoiding future caries		x	x	x	x	x		x				x		x		x		
CAMBRA	20 children/ 25 adults	Defined by clinical Judgement	Defined by Clinical Judgement	x	x	x	x	x			x	x	x	x	x		x	x	x		

*Highlighted areas involve those factors common to all CRA systems

Table 3.3. Summary characteristics validation studies (n=6)

Author/year	Location	System	Study design sample size	Duration	Caries prevalence dentition BL (%)	Age BL (years old)	Clinical outcomes	Dropout %	Outcomes
Holgerson et al., 2009	Lycksele, Sweden	Cariogram (7 parameters)	RCT 125	5 years	Primary and Permanent 5	2	High Risk:0–20% chance of avoiding future caries and dmfs/DMFS > 0 including enamel lesions (noncavitated)	18%	Se: 46 (31–62), Sp:88 (71–104), PPV: 90(77–103), NPV: 40 (24–56)
Hänsel P et al., 2010	Halstad, Sweden	Cariogram Full 9 parameters versus 6 reduced	Longitudinal 438	2 years	Permanent 40	10–11	Caries increment DMFS	11%	Full Cariogram: Se: 73 (65–81) Sp:60 (54–66) PPV: 45 (38–52), NPV: 83 (78–88) AUC: 75(69–80) Reduced: Se: 90(85–95) Sp:20 (8, 15–24) PPV: 34(28–39), NPV: 82 (73–91), AUC: 72(66–78). From LRM: Cariogram and past caries experience (baseline DMFS) associated with caries increment $P < 0.001$
Hänsel P et al., 2002	Halmstad, Sweden	Cariogram (7 parameters)	Longitudinal 438	2 years	Permanent 40	10–11	High Risk (HR):0 –20% chance of avoiding future caries and caries increment DMFS–DMFT	11%	DMFS increment: 0.51 ± 1.06; overall caries incidence 30.9%;DMFS incidence HR: 91. 7% LR: 16.8%;
Hänsel P et al., 2010	Halmstad, Sweden	Cariogram (7 parameters)	Longitudinal 438	2 years	Permanent 40	10–11	Caries increment DMFS–DRS and changes in risk profiles	11%	50% remained in same risk category as baseline after 2 years, 1/3 assessed in a HR group while 18.4% showed a lower risk

Table 3.3. Continued

Author/year	Location	System	Study design sample size	Duration	Caries prevalence dentition BL (%)	Age BL (years old)	Clinical outcomes	Dropout %	Outcomes
Hänsel P et al., 2003	Goteborg, Sweden	Cariogram	Longitudinal 208	5 years	DMFT :23.45 year ± Permanent 4.19	55–75	High Risk (HR):0–20% chance of avoiding future caries and Caries increment DMFS	29%	DFS increment HR: 9.54, LR: 1.74;DRS Increment HR: 2.05 LR:0.26
Domejean S et al., 2011	San Francis-co, CA–USA	CAMBRA	Retrospective Cohort 2,571	16 + 12.6 months (overall study 6 years)	Permanent 55%	>6	Visible cavitation/caries radiographic penetration in dentin/interproximal enamel lesions or radiolucencies	80%	88% of extreme–risk patients developed new cavities and 69.3% of high risk

NA, not available; Se, sensitivity; Sp, specificity; PPV, positive predictive values; NPV, negative predictive values; AUROC, area under the receiver operating curve.

Table 3.4. Quality Assessment of Validation Studies (*n=6*)

Author	Blinding	Randomization	Comparability of Groups	Follow-up (at least 80%)	Reliability	All outcomes considered	Control confounding	Quality score ADA
Holgerson et al., 2009	Single Blinded Yes	Yes	Ye s	Yes	No	Yes (NCCls and C)	Yes (Linear Regression)	Fair
Hänsel P et al., 2010	NA	NA	Yes	Yes	Intra: Kappa: 0.961	No (C only)	No	Fair
Hänsel P et al., 2002	NA	NA	Yes	Yes	Intra: Kappa: 0.961	No (C only)	Yes (logistic regression)	Fair
Hänsel P et al., 2010	NA	NA	Yes	Yes	Intra: Kappa: 0.961	No (C only)	No	Fair
Hänsel P et al., 2003	NA	NA	Yes	No	No	No (C only)	No	Poor
Domejean S et al., 2011	NA	NA	NA	No	No	Yes (NCCls and C)	No	Poor

NCCls, noncavitated carious lesions; C, cavitated carious lesions.

Table 3.5. Summary Characteristics of prediction Models in Longitudinal Studies not using a CRA system (*n*=8)

Author/Year	Duration	Dentition	Age BL	Outcome	Caries Prev BL (%)	Significant Risk Factors	Type of Statistical Model	Attrition %	Sensitivity	Specificity	ROC	Additional Analyses
Sanchez-Perez L et al., 2009	4 years	Prim/Perm	6 years	Caries increment (DM fs/d mfs 0 versus DMFS/ dmfs >or = 1)	60	Caries experience (dmfs, DMFS and dmfs + DMFS), snyder test and fissure morphology	LR	14	0.786 (full model)	0.796 (full model)	CE: 0.79, ST (0.67), Fissure Morphology: 0.57	NA
Vanobbergen et al., 2001 3 years	3 years	Prim/Perm	7 years	Net caries increment (last available DMFS6 score-baseline DMFS 6 score) for four-first permanent molars	NA	Baseline dmfs, plaque indices, brushing < than once/day, daily use of sugar-containing drinks,in-between meal snacks	LR	9	0.59–0.66	0.65–0.72	Baseline dmfs only (0.691), Plaque index	NA
Pienihakkinen et al., 2004	3 years	Prim/Perm	2 years	Caries increment cavitated carious lesions and/or fillings (Dd3mfs>0, measures as the increase of d3mfs from the age of 2 years)	3	MS strip incipient caries lesions and use of candies	LR	0	NA	NA	0.81 (95%% CI 0.74–0.88)	NA
Sanchez-Perez et al., 2004	18 months	Prim/Perm	8–10 years	Net increment in caries (sum of new decayed surfaces per child=net increment of decayed surfaces in both dentitions)	3	Baseline dmf + DMFS, active caries, counts of mutans streptococci from plaque, lactobacilli in Saliva and Snyder's test	Liner R	NA	NA	NA	NA	Spearman correlation between final morbidity-clusters and initial risk clusters: *r* = 0.703, (*P* < 0.0001)
Badovinac et al., 2005	4 years	Prim/Perm	First grade children	Carious lesion in the permanent first molars	11.3	Past caries experience at baseline (dmfs + DMFS)	LR	23	dmf+ DMFS>0 child0.694,	0.545	0.64	NA

Table 3.5. *Continued*

Author/Year	Duration	Dentition	Age BL	Outcome	Caries Prev BL (%)	Significant Risk Factors	Type of Statistical Model	Attrition %	Sensitivity	Specificity	ROC	Additional Analyses
				(dmfs+ DMFS > 0)					molar: 0.747			
Zhang Qi et al., 2007	2 years	Prim/ Perm	6-7 years	Caries increment of permanent dentition (D2 surfaces (dentine caries) at follow-up - D2 surfaces	7.6 (prim) and 6.0 (perm)	Past caries experience at baseline, MS Height for age deficit, gingival bleeding, primary dental caries at age 6	Linear R	0	NA	NA	NA	Spearman correlation: MS and caries increment in permanent dentition = 0.12; Adjusted R^2 with past caries experience = 0.17, Adding MS did not change the R^2 value
Peres MA et al., 2009	12 years	Prim/ Perm	At birth (0)	Dental caries (DMFT> or = 1)	NA	Past caries experience at baseline, MS Height for age deficit, gingival bleeding, primary dental caries at age 6	LR	5.6	NA	NA	NA	NA
Gao et al., 2010	12 months	Primary	3–6 years	Caries increment (△dmft > 0)	NA	Malay race, using F other than toothpaste, parents belief of tooth worm, parents not knowing bedtime milk bad, caries estimate by parent	LR	11.6	0.82 (Community Screening Model)	0.81	0.88	NA

NA, Not available; LR, Logistic Regression; Linear R, Linear Regression

CHAPTER 4

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Non-Surgical Management Methods of Non-Cavitated Carious Lesions

Non-surgical management methods of non-cavitated carious lesions

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Rationale Paper III

The biological understanding of the caries process has prompted to look at non-invasive therapies, enhancing the possibility of remineralisation when lesions have the greatest opportunity to arrest/reverse. This represents a paradigm shift from a surgical to a medical model of caries management. While fluoride is still the most effective anti-caries agent, other novel preventive therapies have been developed over the last years. The evidence supporting the efficacy of caries prevention interventions in relation to NCCLs is limited. Therefore, it was the purpose of this review to investigate the efficacy of non-surgical therapies to arrest or reverse the progression of the disease.

Abstract

Objective: To critically appraise all evidence related to the efficacy of nonsurgical caries preventive methods to arrest or reverse the progression of noncavitated carious lesions (NCCls). Methods: A detailed search of Medline (via OVID), Cochrane Collaboration, Scielo, and EMBASE identified 625 publications. After title and abstract review, 103 publications were selected for further review, and 29 were finally included. The final publications evaluated the following therapies: fluorides (F) in varying vehicles (toothpaste, gel, varnish, mouthrinse, and combination), chlorhexidine (CHX) alone or in combination with F, resin infiltration (I), sealants (S), xylitol (X) in varying vehicles (lozenges, gum, or in combination with F and/or xylitol), casein phosphopeptide amorphous calcium phosphate (CPP-ACP) or in combination with calcium fluoride phosphate. All included studies were randomized clinical trials, were conducted with human subjects and natural NCCls, and reported findings that can yield outcomes measures such as caries incidence/ increments, percentage of progression and/or arrest, odds ratio progression test to control, fluorescence loss/mean values, changes in lesion area/volume and lesion depth. Data were extracted from the selected studies and checked for errors. The quality of the studies was evaluated by three different methods (ADA, Cochrane, author's consensus). Results: Sample size for these trials ranged between 15 and 3903 subjects, with a duration between 2 weeks and 4.02 years. More than half of the trials assessed had moderate to high risk of bias or may be categorized as 'poor'. The great majority (65.5%) did not use intention to treat analysis, 21% did not use any blinding techniques. Slightly more than half of the trials (55%) factored in background exposure to other fluoride sources. Conclusions: Fluoride interventions (varnishes, gels, and toothpaste) seem to have the most consistent benefit in decreasing the progression and incidence of NCCls. Studies using xylitol, CHX, and CPP-ACP vehicles alone or in combination with fluoride therapy are very limited in number and in the majority of the cases did not show a statistically significant reduction. Sealants and resin infiltration studies point to a potential consistent benefit in slowing the progression or reversing NCCls.

Introduction

The diagnosis of early carious lesions is essential for nonsurgical management of dental caries (1). The measurement of incipient or noncavitated carious lesions (NCCls) increases the sensitivity and efficiency of clinical trials (2). However, caries trials have often excluded initial lesions because of difficulties they pose for reliable detection (3). More recent studies have demonstrated that early carious lesions can be measured reliably (4) and detecting subtle changes in progressing incipient lesions in enamel would enhance both the possibility of remineralization before changes become irreversible (5, 6) and the modification of the biofilm to reduce the cariogenic challenge (7). Dental research has led to the development of multiple secondary prevention strategies that centre on the prompt treatment for disease at an early stage and include measures, which arrest and/or reverse the caries process after initiation of clinical signs (8). In spite of this, these measures have not been utilized efficiently by the profession as remuneration systems do not encourage their use (7). Unfortunately, operative care has remained the central management strategy for caries control in general practice, which has impacted negatively on caries epidemiology, clinical outcomes, and patient's quality of life among others. A number of novel preventive treatment options are being developed to help dentists better control the caries process. However, scientific information supporting their efficacy in managing NCCls is scarce. There is a need to assess what is known about the efficacy of professional remineralization strategies and caries prevention interventions in varying populations, as a step prior to surgical intervention for NCCls. A previous systematic review of selected caries prevention and management methods (3) reported that the most problematic aspect among the studies included was the lack of standardized criteria for initially identifying NCCls and for assessing their progression. This review included eight studies that had assessed NCCls. However, half of those studies identified the lesions using radiographic criteria, so it was unknown whether they were in fact noncavitated. With the development of modern caries detection and assessment systems that emphasize the importance of early detection (9), it is expected that a more robust literature will be available for critical appraisal and for outlining evidence-based clinical recommendations.

The aim of this systematic review is to critically appraise all evidence related to the efficacy of non-surgical caries preventive methods to arrest or reverse the

progression of NCCls.

Materials and methods

The publications included in this review evaluated the following therapies: fluorides (F) in varying vehicles (toothpaste, gel, varnish, mouthrinse, and combination), chlorhexidine (CHX) alone or in combination with F, resin infiltration (I), sealants (S), xylitol (X) in varying vehicles (lozenges, gum, or in combination with F and/or xylitol), casein phosphopeptide amorphous calcium phosphate (CPP-ACP) or in combination with calcium fluoride phosphate. Fissure sealants were not included in this review as they have been found to be effective in a previous systematic review (3). A systematic search for papers (not restricted to English) published between 1966 and December 2011 was carried out using Medline Ovid, Embase, Cochrane Oral Health Group's Specialized Register, Cochrane Central Register of Controlled Trials, and Scielo. Reports in the grey literature, defined as theses, dissertations, product reports, and unpublished studies, were not included. Bibliographic references of identified systematic reviews, and review articles, were also checked. Hand searching of Table of Contents of Caries Research published since 1980 was also conducted.

• The search of Medline in Ovid plus hand searching identified 450 citations, with 175 additional citations identified from other databases (Fig. 1). Inclusion and exclusion criteria were applied by examining titles and abstracts, and if information relevant to the eligibility criteria was not available in the abstract or the abstract was not available, the full paper was selected for further review. The following inclusion criteria were followed to select relevant studies: a randomized clinical trial was conducted.

• Study was conducted with human subjects and natural carious lesions.

• Analysis of data was conducted at the noncavitated level only.

• Study was published in peer-reviewed journals. In addition, papers were excluded if they met one or more of the following criteria: (i) incomplete description of sample selection, outcomes, or small sample size (defined by number of lesions considered as unit of analysis) and (ii) not meeting the highest evidence criteria under the

therapy category of the Oxford Centre for Evidence-Based Medicine (10) (systematic reviews of randomized clinical trials, and individual randomized clinical trials). The systematic search strategy included combined MeSH and free text terms such as 'enamel caries', 'non-cavitated caries', 'incipient lesions', 'efficacy', 'randomized clinical trial', 'fluorides', 'sealants', 'xylitol', 'cpp-acp', and 'CHX'. The primary clinical outcomes considered for this review were caries incidence/increments, percentage of progression and/or arrest, odds ratio progression test to control, fluorescence loss/mean fluorescence values, changes in lesion area/volume and lesion depth. After training and calibration, data were extracted independently by two reviewers (MT, SK) and reviewed by a third (JG). The tables were checked for consistency, and corrections were made through consensus. The quality of the studies was assessed initially using the criteria reported in the ADA Clinical Recommendations Handbook (11) for randomized clinical trials, which included initial assembly of comparable groups, adequate randomization, maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination), differential loss to follow-up, reliability of measurements, clarity of interventions, blinding, control of confounders, and intention to treat analysis (ITT). The studies were categorized as good, fair, or poor based on ADA's criteria. In addition, two more quality assessments were conducted following Cochrane's recommendations for clinical trials, which rate allocation concealment and blinding as key criteria (12) (low risk of bias: possible bias unlikely to seriously alter the results, medium risk: possible bias that raises some doubts about the results, high risk: possible bias that seriously weakens confidence on the results). Finally, the overall strength of the evidence ratings (poor, fair, good) was assigned by consensus of three authors (MT, JG, SK). No formal weighting scheme was employed in making these judgments, but authors considered all the parameters accounted for in the ADA's quality assessment in addition to sample size and duration of the trial.

Results

Of the 103 papers, 74 were excluded. The reasons for the exclusion were as follows: caries outcome reported at the dentine level only (24.33%), studies that were not randomized controlled trials (RCT) (9.46%), data analysis that collapsed cavitated and noncavitated lesions (8.11%), unknown if incipient lesions were noncavitated

(5.41%), and the remaining 52.69% because of small sample size, not commercially available, used artificial lesions or provided insufficient data.

Twenty-nine studies evaluating different non-surgical methods for noncavitated carious lesions were assessed. The quality assessment varied depending on the criteria used. Following ADA's criteria, 6.9% of the studies were rated as 'fair', while 93.1% were rated as 'poor'. The consensus process conducted by the investigators yielded the following: 6.9% of studies were rated as 'good', 27.6% were rated as 'fair' and 65.5% as 'poor'. Following Cochrane's guidelines, 41.3% of the studies had low risk of bias, 37.9% were ranked as medium, and 20.8% had high risk of bias. The great majority of studies (65.5%) did not use ITT, 13.8% did not have a need to use ITT as there were no dropouts, and only 3.4% did conduct this analysis. In addition, 21% did not use any blinding techniques, 41% reported concealment allocation procedures while this same parameter was not reported in 59% of the publications. Twenty-eight per cent of the studies did not meet the criteria for comparability of baseline characteristics between test and control groups. Slightly more than half of the trials (55%) factored in background exposure to other fluoride sources. Sample size for these trials ranged between 15 and 3903 subjects, with a duration between 2 weeks and 4.02 years. Most of the studies tested the different interventions in permanent dentition (26/29), followed by primary (2/29) and mixed dentition (1/29).

Fluorides (n = 13 studies)
Thirteen trials evaluated the efficacy of varying fluoride (F) vehicles: (i) toothpaste as 1500 ppm NaF, 1250 ppm Amine F, 0.243% NaF/Silica, 1450 ppm sodium-monoflurophosphate (MFP) 1450 ppm, 5000 ppmF, 0.4% stannous F/calcium pyrophosphate (13–17); (ii) varnish as 5% NaF, 6% NaF + 6% CaF, and 0.1% F (18–20); (4) gel as 1.23% acidulated-phosphate-fluoride (APF), 1% NaF neutral (4500 ppm), and 4000 ppm Amine F (15, 21–24); and (iv) mouthrinse as 50 ppm NaF (Willmot). Sample sizes for the trials ranged from 15 to 3093 subjects and were conducted between 2 weeks and 4.02 years (loss to follow-up ranged from 0% to 54.3%). Twelve studies evaluated permanent dentition, and one evaluated primary teeth, and were conducted in Europe, South America, North America, and Asia. Five studies used some type of placebo, four studies used positive and/or negative

controls, and other four studies did not report having any sort of control group. The diagnostic methods to detect noncavitated lesions varied among studies: (i) visual-tactile (VT) (n = 3), (ii) VT + radiography (n = 3), (4) Laser fluorescence alone or in combination with visual (n = 6), and (iv) computerized image analysis (n = 1).

Six of thirteen studies were rated as 'poor', other six studies were rated as 'fair', and only 1 study was rated as 'good' (author's consensus process). Eight of thirteen studies reported overall significant differences between test and control groups. Du et al. (18) reported a decrease in the mean DIAGNOdent (DD) reading in white spot lesions (WSLs) after testing 5% NaF varnish at 3 and 6 months and concluded that topical fluoride varnish application was effective in reversing WSLs after debonding. Even with lower concentrations of F (0.1%), repeated applications of varnish had a favourable effect on the remineralization of WSLs measured by quantitative light-induced fluorescence (QLF) (19). Three trials that evaluated the efficacy of different F gels also reported significant differences between test and control. Agrawal and Ferreira (21, 22) reported that supervised toothbrushing with and topical applications of 1.23% APF gel achieved a change in the percentage of WSLs. In addition, studies using varying methods of laser fluorescence reported that QLF methodology could detect within a 3–6 month periods of supervised toothbrushing, a difference in remineralization between fluoride containing and nonfluoride containing dentifrices (16) and that a dentifrice containing 5000 ppm F was significantly better than the dentifrice containing 1450 ppm F regarding reversal of noncavitated fissure carious lesions detected with DD (17) (Table 1).

Chlorhexidine (n = 1 study)
Lundström and Krasse (25) conducted a study during 1.8 years in 40 subjects 11–15 years old from Sweden, who were randomly allocated to a test group that received CHX digluconate 1% gel in addition to F Varnish (Duraphat, Colgate Oral Pharmaceuticals Subsidiary of Colgate-Palmolive Company, New York, NY, USA) and F toothpaste and a control group [F Varnish (Duraphat) and F toothpaste]. There were no significant differences at baseline or during the course of the orthodontic treatment. This study was rated as poor and with moderate risk of bias (Table 2).

Xylitol (n = 1 study)

Stecksén-Blicks et al. (26) conducted a study during 2 years in 160 subjects 10–20 years old from Sweden, who were allocated to two test groups. Group 1 received lozenges with 422 mg of Xylitol, Group 2 received lozenges with 422 mg of Xylitol and 0.25 mg of NaF. A comparison group did not receive any tablet. There were no significant differences at baseline or after the 2-year period between the study groups. This study was rated as poor and with moderate risk of bias (Table 2).

Casein phosphopeptide amorphous calcium phosphate [CPP-ACP (n = 6 studies)]

Five trials (27–31) evaluated CPP-ACP, while 1 study (32) evaluated casein phosphopeptide amorphous calcium fluoride phosphate (CPP-ACFP). Sample sizes for the trials ranged from 26 subjects to 2720 and were conducted between 3 weeks and 24 months (loss to follow-up ranged from 0 to 19.4%). All studies evaluated permanent dentition, and four of them were conducted in Europe, while two studies were conducted in Australia. Different types of CPP-ACP and CPP-ACFP vehicles were tested (crème, mousse, gum) in addition to F dentifrice, generally NaF 900–1450 ppm. Only one study used a placebo cream, while the others provided F toothpaste/sugar-free gum to the control groups. Four studies used some type of laser fluorescence (QLF-DD) in addition to visual criteria for the detection of noncavitated lesions, one study used visual and standardized bitewing radiography, and another study used visual only (ICDAS) only. There were significant differences between the study groups in two studies. In particular, Morgan et al. (28) concluded that those subjects who had CPP-ACP gum three times per day (10 minutes each time) were 18% less likely to have a surface experiencing caries progression when compared with the subjects chewing the control gum (OR = 0.82, P = 0.03), while Bailey et al. (29) concluded that 31% more of WSLs had regressed with the remineralizing cream than with the placebo at 12 weeks (OR = 2.3, P = 0.04). Two studies were rated as 'fair' (28, 29), while the remaining four studies were rated as 'poor'. No concealment of allocation, limited control for confounding, and lack of ITT were the major issues in these studies (Table 3).

Sealants/Resin Infiltration (n = 6 studies)

Four trials (33–36) evaluated sealants, while two studies (37, 38) evaluated resin infiltration. Sample sizes for the trials ranged from 22 subjects to 91 and were

conducted between 12 months and 3 years (loss to follow-up ranged from 0% to 38%). All studies evaluated permanent dentition except one and were mainly conducted in South America (Brazil, Chile, and Colombia) and Europe (Denmark and Germany). Five studies used a split mouth design and tested sealants only, in combination with F varnish or home-based flossing instructions. Two studies used placebo, while the other studies used as controls F varnish, home-based flossing instructions, and flasks of 0.2% NaF. The diagnostic methods used to assess noncavitated carious lesions comprised visual criteria (Downer and ICDAS), endoscopic examination CDR-CAM, bitewing and digital radiography. All the studies except two (33, 34) reported overall significant differences between test and control groups at follow-up. In particular, Martignon et al. (36) reported that the per cent of caries progression among approximal surfaces that were sealed was lower than those assigned to a home-based flossing control after 12 months (test: 27%, control: 51%) and 2.5 years (test: 46%, control: 71%). A second study conducted by the same author in 2012 (37) that evaluated infiltration and sealants versus placebo found significant differences between infiltration versus placebo (lesion progression 32% versus 70%, respectively, P- value: 0.001) and sealants versus placebo (41% versus 70%, P-value: 0.029) but no statistical difference between sealants and infiltration after a 3-year period. In another study, Paris et al. (38) reported a significant difference between infiltration versus placebo in the percentage of progression in lesion depth (test: 7%, placebo: 37%, P- value: 0.021). No concealment of allocation and lack of ITT were the major issues in the studies rated as 'fair'. All these studies were found to have moderate to high risk of bias except one (38) (Table 4).

Combination (n = 2 studies)

Two trials evaluated the combination of two preventive interventions to reduce early carious lesions. These studies explore the use of an antimicrobial varnish (CHX) in combination with a F varnish (39, 40). Sample sizes for the trials ranged from 80 subjects to 220 and were conducted between 12 and 72 weeks (loss to follow-up ranged from 0% to 5%). One study evaluated permanent dentition, while the other one assessed primary teeth, and they were conducted in Sweden and Brazil. Both studies used visual criteria to detect noncavitated lesions. Guedes de Amorin et al. (40) reported significant differences in WSLs mean variations between test and

control between the first and third months of the study and between the third month and the baseline. The authors concluded that the combined application of CHX and F varnishes was more effective on remineralization of incipient caries than the same agents applied separately. Both studies were found to have high risk of bias (Table 2).

Discussion

Several scales have been used to assess the validity and 'quality' of RCTs (41, 42). Because there is no 'gold standard' for the 'true' validity of a trial, the possibility of validating any proposed scoring system is limited. In this review, we applied three different methods for quality assessment and found large variations in the way a study is decided to be free from bias. ADA's clinical recommendations heavily emphasize the ITT as a key criterion to rank a study 'Good' or 'Fair'. 'Intention to treat' is a strategy for the analysis of RCTs that compares patients in the groups to which they were originally randomly assigned. This is generally interpreted as including all participants, regardless of the treatment actually received, and subsequent withdrawal or deviation from the protocol (43). Clinical effectiveness may be overestimated if an ITT is not undertaken (44). This analysis is therefore most suitable for pragmatic trials of effectiveness, where the objective is to identify the utility of a treatment for clinical practice rather than for explanatory investigations of efficacy, which aim to isolate and identify the biologic effects of treatment (45). In this sense, the information from most of the trials assessed in this review is limited for making decisions about how to treat future patients. In contrast, Cochrane's quality assessment centres on the fact that ranking a study in different risk categories of bias (low, medium, high) will most likely be appropriate if only a few assessment criteria are used and if all the criteria address only substantive, important threats to the internal validity of the study and the extrapolation of the results to different populations (12). Inadequate concealment of allocation and lack of blinding are known to result in over-estimates of the effects of treatment. Hence, ranking the studies based on these two characteristics seemed to be more consistent with the consensus process undertaken by the authors and demonstrated that more than half of the trials had moderate to high risk of bias or may be categorized as 'poor'. A previous systematic review in the topic (3) concluded that the most

problematic aspect among the studies assessed at that time was the lack of standardized criteria for initially identifying these lesions and for assessing their progression. In this regard, there has been a progress as all the studies included in this review objectively assessed NCCls, and the proportion of excluded studies where the definition of the caries outcome was unknown was relatively small. Slightly more than one-third of the studies included used some type of laser fluorescence method alone or in combination with visual criteria to diagnose these lesions. These findings support that some of those methods have the ability to measure demineralization and also remineralization of NCCls, and the measures of mineral density change are primary indicators of the cumulative status of the dental caries lesion (46). The variation in clinical outcomes (caries incidence, increment in WSLs, percentage caries progression, lesion depth, lesion area, and integrated fluorescence loss among others) remains, but it is to some extent a consequence of the new detection methods that are being used in these studies. Also, the reporting of the progression and regression of initial caries lesions rather than the differences in overall caries experience is an important methodological improvement in the conduct of these trials, as previous research had demonstrated that not doing so resulted in poor results and outcomes for remineralization technologies (47).

Based on the number of studies, the quality and the findings, fluoride interventions using vehicles such as varnishes, gels, and toothpaste seem to have the most consistent benefit in decreasing the progression and incidence of noncavitated carious lesions. The interventions that relied on the use of xylitol or CHX vehicles alone or in combination with fluoride therapy are very limited in number and in the majority of the cases did not show a statistically significant reduction in noncavitated lesions. This finding is aligned with the recommendations made by a panel of experts convened by the ADA regarding the efficacy of nonfluoride agents in reducing the incidence of caries and arresting or reversing the progression of the disease (48).

On the other hand, the current evidence *in vivo* supporting the efficacy of casein derivatives has increased in number (from 2 to 6 randomized clinical trials) and in quality during the last 4 years, when the last systematic review on this area was published (49). However, only two studies in the current review reported a slowed progression of carious lesions with the use of a CPP-ACP gum and a cream (28, 29).

It is worth noting that one of these studies employed one of the largest sample sizes among all the trials assessed (n = 2720) (28) and was conducted for a period of 2 years taking into consideration most of the key design and statistical aspects in clinical trials. Future studies using casein derivatives will confirm if this positive findings using gum as a vehicle may be replicated in other populations with higher risk of dental caries.

Finally, sealants and resin infiltration are non-surgical methods that have been tested in different populations with varying levels of caries risk with a relatively higher frequency than other interventions and are pointing also to a potential consistent benefit in slowing the progression or reversing NCCls, which supports clinical recommendations based by the ADA in 2008 (50). However, all the studies that yielded statistical significant differences between test and control groups used 'split mouth designs'. The main purpose of the split-mouth design is to remove all components related to differences between subjects from the treatment comparisons. By making within-patient comparisons, rather than between-patient comparisons, the error variance of the experiment can be reduced, obtaining more powerful statistical tests (51). NCCls may regress, progress, or fluctuate in severity during the period of investigation independent of treatment. Early lesions that are subject to periodic variation could result in the effects of treatment being confounded by fluctuations in the disease process itself.

Conclusion

More than half of the trials assessed had moderate to high risk of bias or may be categorized as 'poor'. Based on the number of studies, the quality and the findings, fluoride interventions using vehicles such as varnishes, gels, and toothpaste seem to have the most consistent benefit in decreasing the progression and incidence of NCCls. The studies, whose interventions relied on the use of xylitol, CHX, and CPP-ACP vehicles alone or in combination with fluoride therapy, are very limited in number and in the majority of the cases did not show a statistically significant reduction in these early lesions. Sealants and resin infiltration studies point to a potential consistent benefit in slowing the progression or reversing NCCls.

Acknowledgements

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Figure 4.1. Flow diagram of identification and inclusion

Initial Medline OVID Search	450
⇩	
Initial Cochrane Search	10
⇩	
Initial Scielo Search	165
⇩	
Total Articles for review	625
⇩	
Surviving Title Review	103
⇩	
Surviving abstract/paper review	29
⇩	
Included in Final Review	29

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*Excluded studies n=74

Table 4.1. Summary information and quality scores for studies on fluoride (*n*=13)

Author/Year	N	Duration	Age at start	Intervention		Dx Method	Loss to Follow up	Definition Outcome	Outcome			Overall Significance	Authors Quality Score	ADA Quality Score	Cochrane (Risk of bias)
				Test	Control				Comparison	Test	Control				
Zantner C et al, 2006	44 (39¶)	6 months	12-38 years	Group 1: NaF TP(1500ppm) Group 2: Amine fluoride TP (1250ppm)	None	QLF	8.5%	WSL (Change in Fluorescence 3 QLF metrics)	BL	Group1: ΔF:-14.41 ± 5.03, Group2: Δ F:-14.41± 2.95	–	NS	Poor	Poor	Moderate
				Group1: NaF TP(1500ppm) Group2: Amine fluoride TP (1250ppm)					Follow ups	Group1: ΔF:-14.19 ± 4.9 to -15.93 ± 4.97 , Group2: Δ F:-14.17± 3.08 to 15.01± 4.52	–				
Du M et al, 2011	110(96¶)	6 months	12-22 years	Varnish 22600 ppmF	Saline solution	Diagnodent	12.7%	WSL (mean DD readings decrease)	BL	17.66±5.36	16.19±5.70	NS	Fair	Poor	Low
									3 months	11.88±4.27	13.75±4.76	S			
									6 months	10.10±4.86	13.10±5.19	S			
Biesbrock RA et al, 1998	3093(1411¶)	3 years	6-13 years	Group 1: 0.243%NaF/silica dentifrice Group2: 0.4%stannous Fluoride/Calcium pyrophosphate	Non-fluoridated placebo/calcium pyrophosphate	Visual-tactile and Radiographic	54.3%	Caries lesion reversals	Year 1	Group1: .65±.99, Group2: .63±.98	.55±.90	NS	Poor	Poor	Moderate
									Year2	Group1: .61±.93 Group2: .58±.96	.46±.82	NS			
									Year 3	Group1: .48±.84 Group2: .43±.84	.33±.64	S (for NAF vs. Placebo)			
Ferreira MAF et al,2005	307(258¶)	3 months	7-12 years	Group 1: 1.23%APF gel for one minute once a week. No F dentifrice	Group 2: Topical application of placebo, Group3: No intervention	Visual-tactile	14%	% WSL	3 months	Group1: 57.9%	Group2: 56.8%, Group3: NR	S	Fair	Poor	Low
Truin G.J. et al, 2007	596(517¶)	4 years	9.5-11.5 years	Neutral 1%NaF gel(4500 ppm)	Placebo gel	Visual-tactile and Radiographic	13.2%	Mean D2S (enamel caries) increment	BL	3.9±2.9	3.6±3.0	NS	Good	Fair	Low
									4 years	2.27±0.22	2.98±0.28	NS			
Truin G.J et al, 2005	773(676¶)	4.02 years	4.5-6.5 years	Oral hygiene + F TP + neutral 1%NaF gel(4500ppm fluoride)	Oral hygiene + F TP + Placebo gel	Visual-tactile and Radiographic	12.6%	D2S (enamel caries) increment	4 years	Permanent 0.55±0.07 Primary 0.39±0.10	Permanent 0.69±0.08 Primary 0.56±0.10	NS	Fair	Poor	Low

Table 4.1. *Continued*

Author/Year	N	Duration	Age at start	Intervention Test	Intervention Control	Dx Method	Loss to Follow up	Definition Outcome	Outcome Comparison	Outcome Test	Outcome Control	Overall Significance	Authors Quality Score	ADA Quality Score	Cochrane (Risk of bias)
Karlsson L et al, 2007	181(135¶)	12 months	13-17 years	Amine Fluoride dentifrice (1250ppm) + Amine Fluoride gel (4000 ppmF)	Amine Fluoride dentifrice (1250ppm) + Placebo gel	QLF and visual-tactile	25.4%	WSL (Change in Fluorescence)	BL	1.62mm2 (lesion area); Δ F: 8.62%	1.75mm2 (lesion area); Δ F: 8.40%	NS	Poor	Poor	Moderate
									12 months	1.73mm2 (lesion area)	NR	NS			
Ferreira JMS et al, 2009	15	1 month	7-12 years	G1: 5% NaF varnish, G2: 6%NaF+ 6% CaF2 varnish	None	Visual-tactile	0%	Mean dimension values of WSL	BL	4.05±1.27	3.62±2.13	NS	Poor	Poor	High
									4 weeks	2.86±1.33	2.33 ±1.53	NS			
Agrawal N et al, 2011	257(239¶)	12 months	9-16 years	1.23% APF gel (baseline and 6 months) + Oral health education at BL	No intervention	Visual-tactile	7%	Change Incipient lesions (Nyvad)	BL	5.04±1.95	4.93±1.90	NS	Poor	Poor	Moderate
									6 months	3.23±1.22	4.36±1.76	S			
									12 months	1.18±1.18	3.03±1.32	S			
Tranaeus S et al, 2001	34(31¶)	6 months	13-15 years	Fluorprotector Varnish (0.1% F)	Professional-tooth cleaning (every 6 W for 6 M)	QLF	8.8%	(mean (SE) Change in average fluorescence)	BL-6 months	A(mm2): − 0.152 ± 0.056* ΔQ − 0.107 ± 0.032*	A(mm2) − 0.006 ± 0.047 ΔQ − 0.008 ± 0.027	S	Fair	Poor	Low
Willmot DR, 2004	26(21¶)	26 weeks	NR	NaF mouth rinse (50ppm), fluoride -free TP	Control mouthrinse (No NaF), fluoride-free TP	Computerized image analysis of calibrated photographic	19.2%	Lesion size and proportion(DWL%); percentage reduction (ADPR) at debond	12 weeks	ADPR:40.0%± 14.5	ADPR:51.5 %±13.3	NS	Poor	Poor	Low
									26 weeks	ADPR: 54.3% ±12.3	ADPR:66.1 %±15.5	NS			
Feng et al., 2006	305(296¶)	6 months	11.82 years	Toothpaste (NaF 1450 ppm F MFP 1450 ppm)	No Fluoride Toothpaste (herbal)	QLF	3%	WSL (mean (SE) Differences between 3 QLF metrics)	3 months Test vs Placebo Δ Values	**Δf**=NaF 0.30 ± 0.20 MFP 0.32 ± 0.22 **A(mm2)** NaF -0.19 ± 0.11 MFP 0.23 ± 0.11 **ΔQ** NaF 2.39 ± 1.56 MFP 3.88 ± 1.69		NaF= NS MFP= S (*A*-ΔQ)	Fair	Poor	Low
									6 months Test vs Placebo Δ Values	**Δf**=NaF 0.71 ± 0.23 MFP 0.69 ± 0.23 **A(mm2)**=NaF -0.42 ± 0.12 MFP -0.39 ± 0.12 **ΔQ**=NaF 5.43 ± 1.77 MFP 6.32 ± 1.90		NaF= S MFP= S (Δf-A-ΔQ)			
Schirrmeister et al., 2007	30	2 weeks	23-39	Toothpaste 5000 ppmF	Toothpaste1450 ppmF	DD	0	Non cavitated (mean (SD) DD readings decrease)	2 weeks	11.9 ± 1.6*	15.6 ± 3.0	S	Fair	Poor	Low

NS, non significant; NR, not reported; APF, acidulated-phosphate-fluoride; MFP, monoflurophosphate; QLF, quantitative light induced fluorescence; WSL, white spot lesions.¶Effective sample size for analysis

Table 4.2. Summary information and quality scores for studies on clorhexidine, xylitol, and combination of interventions (*n*=4)

Author/Year	N	Duration	Age at start	Intervention		Reliability	Dx Method	Loss to Follow up	Definition Outcome	Outcome			Overall Significance	Authors Quality Score	ADA Quality Score	Cochrane (Risk of bias)
				Test	Control					Comparison	Test	Control				
Clorhexidine (CHX)																
Lundstrom F et al, 1987	40 (36¶)	1.8 years	11-15 years old	Gel CHX digluconate 1% + F Varnish Duraphat + F TP	F Varnish Duraphat + F TP	NR	Visual + BW Radiographs	10%	Caries incidence	BL	1.6±1.2	1.6±1.2	NS	Poor	Poor	Moderate
										During ortho treatment	0.4±0.9	1.4±2.1	NS			
Xylitol																
Stecksen-Blicks C et al, 2008	160 (115¶)	2 years	10-20 years old	Group1: Xylitol 422 mg, Group2: Xylitol 422 mg + 0.25 mg NaF lozenges	Not random-no treatment	Inter: Kappa: 0.85	BW Radiographs	28%	Caries incidence (ΔDSe)	BL	Group1: 1.6±1.3 Group2: 2.0±2.5	Group3: 2.0±1.8	NS	Poor	Poor	Moderate
										Year 2	Group1: 3.6±4.4 Group2: 3.7±4.2	Group3: 3.0±3.8	NS			
										ΔDSe	Group1: 2.0±4.0 Group2: 1.7±3.8	Group3: 1.0±3.0	NS			
Combination																
Ogaard B et al, 2011	220	72 weeks	12-15 years old	Cervitec (1% CHX 1%Thymol) once every wk for 3 wks + F varnish every 12 wks until debonding	Positive Control: Cervitec varnish and Control: No treatment	NR	Visual	0%	Increments WS lesions	During treatment	0.04±0.20	0.08±0.30	NS	Poor	Poor	High
Guedes de Amorim R et al, 2008	80 (76¶)	3 months	3-5 years old	Group 1: Cervitec weekly for 4 wks, Group 2: F varnish weekly for 4 wks, Group 3: Cervitec +F varnish weekly for 4 weeks	Group 4: No treatment except restorative	Intra: Kappa: 0.96	Visual	5%	WS lesions (mean difference)	BL	Group1:3.15±2.23 Group2:3.45±2.31 Group3:3.10±2.59	Group 4: 3.25±2.00	NS	Poor	Poor	High
										t1-t2	Group1:-.35±.74 Group2:-.47±.77 Group3: -0.55±.99	Group 4: -.21±0.63	NS			
										t2-t3	Group1:-.61±1.14 Group2:-.58±1.17 Group3: -.85±1.46	Group 4: .58±.77	S			
										t1-t3	Group1:-.89±1.45 Group2: -1.05±1. Group3:-	Group 4: .37±1.01	S			

NR: Not reported, NS: Non significant; WSL, white spot lesions.;¶Effective sample size for analysis

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Table 4.3. Summary information and quality scores for studies on CPP-ACP/CPP-ACFP (*n*=6)

Author/Year	N	Duration	Age at start	Intervention		Dx Method	Loss to Follow up	Definition Outcome	Outcome			Overall Significance	Authors Quality Score	ADA Quality Score	Cochrane (Risk of bias)
				Test	**Control**				**Comparison**	**Test**	**Control**				
Beerens MW et al, 2010	65 (55¶)	3 months	12-19 years	CPP-ACP + NaF 0.2%;900p.p.m (MI paste Plus 35 ml Recaldent)	F-free paste + calcium (Ultradent 100ml)	QLF + Visual	15.30%	Lesion depth ΔF, lesion area %mm2, integrated fluorescence loss IFL	BL	ΔF:8.45±1.17, %mm2:5.07±5.69, IFL: 56.37±73.05	ΔF:9.10±1.75, %mm2:7.29±7.91, IFL: 90.81±111.28	NS	Poor	Poor	Moderate
									6 weeks	ΔF:7.93±1.34, %mm2:5.09±6.53, IFL: 57.14±86.74	ΔF:8.22±2.38, %mm2:5.96±6.38, IFL: 70.17±81.76	NS			
									12 weeks	ΔF:7.52±1.78*, %mm2:5.05±6.98, IFL: 57.76±91.73	ΔF:7.96±2.76*, %mm2:7.17±7.76, IFL: 85.89±97.82	NS			
Andersson A et al, 2007	26	12 months	12-16 years	Brushing w/ CPP-ACP cream no F (Topacal) 3 months + F dentifrice (1000-1100 ppm) for next 3 months	0.05% NaF mouthwash once daily + F dentifrice for 6 month period	Diagnodent + visual	0%	Mean Fluorescence values	BL	7.4±10.2	9.4±9.5		Poor	Poor	Moderate
									1 month	5.5±6.7	7.6±9.2	NS			
									3 months	4.9±5.5	6.8±8.1	NS			
									6 months	4.6±5.1	6.4±7.3	NS			
									12 months	4.4±5.2	6.4±7.5	NS			
Morgan MV et al, 2008	2720(1749¶)	24 months	11.5-13.5 years	CPP-ACP sugar free gum (sorbitol) (54 mg) 3 times per day (10 minutes each session)	Sorbitol based sugar free gum	Standardized Bitewing Radiographs + Visual	35.70%	Caries progression (OR , 95% CI)	BL-24 months	OR:0.82 95% CI (0.68,0.98)		S	Fair	Poor	Low
Bailey DL et al, 2009	45	12 weeks	12-18 years	CPP-ACP tooth mousse 1 g 2 timess per day +F dentifrice NaF 1000 + NaF mouthrinse 900 ppm	Placebo cream	Visual ICDAS	0%	WSL regression/stable/ progression (OR, 95% CI)	BL to 4 weeks	OR:1.40 95% CI (0.84, 2.34)		NS	Fair	Poor	Low
									BL to 8 weeks	OR:1.14 95% CI (0.70,1.87)		NS			
									BL to 12 weeks	OR:1.67 95% CI (0.81,3.45)		S (only for WS with severity 2-3 OR 2.33, 95% CI:1.06,5.14)			
Brochner A et al, 2011	60(50¶)	4 weeks	13-18 years	CPP-ACP- TP + FTP 1100 ppm	FTP 1100 ppmF	QLF + Visual	17%	Lesion depth ΔF, lesion area %mm²	BL	ΔF:6.68±0.58, %mm2:.12±0.16	ΔF:7.04±1.65, %mm2:.19±.43	NS	Poor	Poor	Moderate
Altenburger et al., 2010	32	3 weeks	22-31	CPP-ACP-Toothpaste	Toothpaste1450 ppmF	Diagnodent	0%	Incipient lesion (mean (SD) DD readings decrease)	BL	16.66 ± 1.27	16.87 ± 1.69	NS	Poor	Poor	Low
									1 wk	15.1	15.18				
									2 wk	12.5	14.71				
									3 wk	10.96*	14.78				

NS, non significant; NR, not reported; A; QLF, quantitative light induced fluorescence; WSL, white spot lesions. ¶Effective sample size for analysis

Table 4.4. Summary information and quality scores for studies on sealants/resin infiltration (*n*=6)

Author/Year	N	Duration	Age at start	Intervention		Dx Method	Loss to Follow up	Definition Outcome	Outcome			Overall Significance	Authors Quality Score	ADA Quality Score	Cochrane (Risk of bias)
				Test	Control				Comparison	Test	Control				
Gomez S et al, 2005	50	2 years	10-20 years	Group1: Sealants (Concise) Group2: Sealants or F varnish	F varnish	Visual + BW Radiographs	0%	Number and % enamel caries with no progression	BL	Group 1: 115 Group2: s-38 fv-33	Group 3: 76	NR	Poor	Poor	High
									Year 2	Group 1: 107 (93%) Group 2: S 35 (92.1%) FV-29 (87.9%)	Group 3: 67 (88.2%)	NS			
Florio FM et al, 2001	34(31¶)	12 months	6 years	Group1: Resin GI Vitremer Group 2: 2.26% F varnish Duraphat every 6 months	Flasks 0.2% NaF + 1500 ppm F TP	Visual (Downer) +Digital Radiography	9%	% caries progression	BL	Group1: 0%, Group2: 5.5%	6.10%	NS	Poor	Poor	High
									12 months	Group1: -0.35±0.74, Group2: -0.47±.77, Group3: -0.55±.99	0.21±0.63	NS			
Martignon S et al, 2006	82(72¶)	18 months	15-39 years	Sealant (Concise) + Home -based flossing instructions	Home -based flossing instructions	BW Radiography	12.20%	% caries progression	BL-18 months	43.50%	84.10%	S	Poor	Poor	High
Martignon S et al, 2010	91(56¶)	2.5 years	4-6 years	Sealant (Single one bond)	Home -based flossing instructions	BW Radiography + Visual (ICDAS)	38%	% caries progression	12 months	27%	51%	S	Poor	Poor	Moderate
									2.5 years	46%	71%	S			
Paris S et al, 2010	22	18 months	18-35 years	Resin Infiltration Icon	Placebo: Water as infiltrant instead of HCL gel	BW Radiography + Visual	0%	Progression lesion depth	BL-18 months	7%	37%	S	Good	Fair	Low
Martignon S et al, 2012	39(36¶)	3 years	16-35 years	Group1: Infiltration Icon Group2: Sealant (Prime bond NT)	Placebo	Digital subtraction Radiography + Visual (ICDAS)	5%	% lesion progression	3 years	Group1: 32% Group2: 41%	Placebo: 70%	S (for differences between G1 and Placebo, and G2 and placebo. No differences between G1 and G2)	Poor	Poor	Moderate

NS: Non significant;¶Effective sample size for analysis

CHAPTER 5

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Caries Clinical Trial Methods for the Assessment of Oral Care Products in The 21st Century

Caries clinical trial methods for the assessment of oral care products in the 21st century

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Rationale Paper IV:

Evidence provided from the caries management systematic review demonstrated how abbreviated caries clinical trials can show significant differences between products using detection and monitoring of early enamel lesions and root caries as the primary outcome. It was therefore the purpose of this review to collect the evidence available on alternative methods to conduct clinical trials testing efficacy of oral care products. This is in response to the requirements of reduced trial length, smaller numbers of subjects and with ethical but meaningful endpoints.

Abstract

Traditionally caries clinical trials of oral care products have focussed on the prevention of caries in children and adolescents at the "cavitation" level. Because of a general reduction in caries incidence and use of positive control comparators, studies have grown both in size and duration to improve statistical power. Currently they tend to be of 2-3 years duration, with up to 2,000 high-risk subjects per group. During the last decade there has been a shift in emphasis from a restorative approach to the treatment of dental caries to a therapeutic approach focused on the remineralisation of early caries lesions. However, caries clinical trials of oral care products have not often reflected this paradigm change. This manuscript reviews alternative caries clinical trial methods for oral care products. It is concluded that methods focused on the detection and monitoring of enamel caries and root caries, using visual approaches such as ICDAS and instrumental methods such as QLF, Diagnodent and Electrical Caries Monitors provide viable alternatives to traditional methods. In particular, such approaches more accurately reflect the mode of action of many therapeutic agents and formulations and may reduce the cost and duration of product innovation.

Keywords: dental caries, clinical trials design, caries detection, remineralisation.

Introduction

During the past 20 years, the paradigm of caries being a dis- ease detected at the threshold of restorative intervention has evolved into one in which caries is seen as a continuum of disease from subclinical demineralisation to gross cavitated lesions (1). It is now widely accepted that, throughout the day, the tooth surface is in a continuous state of demineralisation and remineralisation as part of a natural physiological process. Under acidic challenge, when demineralisation predominates over remineralisation, caries will progress, but perhaps more importantly, when remineralisation predominates over demineralisation, the lesion can be reversed or arrested. Depending on the stage in the caries process and the rate of progression of the disease, a range of therapeutic procedures might be applied to favour remineralisation (2).

In tandem with our improved understanding of the disease process, there has also been a significant shift in the epidemiology of dental caries throughout the world. In many populations, the distribution of dental caries has become heavily skewed to a small percentage of the population (3). This has also manifested as fewer lesions *per* person and often a slower rate of progression from the early enamel to cavitation level (4). With slower rates of caries progression, therapeutic interventions are more likely to achieve a favourable outcome.

The second major change in the pattern of dental caries is an increase in the prevalence of exposed root surfaces and hence roots caries in adults. This is a reflection of both a greater number of teeth being retained and an increase in the number of dentate elderly (5).

The impact of the changes in the incidence and rate of progression of dental caries in children and adolescents has had a profound effect on our ability to conduct efficient and cost-effective clinical trials (6). Typically, studies now require large numbers of high-caries-risk participants (4,000+) over long periods of time (2-3 years) and are rarely conducted.

Identification of high-caries-risk individuals typically involves selecting populations in deprived areas, with high sugar intake and/or with limited oral hygiene practices. Study populations are also selected to maximize caries increment by linking study baselines to the eruption of particular teeth such as first molars, premolars, or second molars.

Perhaps the most significant impediment to conducting caries clinical trials is the requirement for the use of fluoride toothpaste or another fluoride therapeutic as a positive control. Because of its widespread acceptance, it is considered unethical to withhold fluoride toothpaste from populations who habitually use it. This means that the efficacy differences to be determined between a test and a positive control product are much smaller than those between a test product and a placebo, and larger sample sizes are required.

An issue also to be addressed within the study design is compliance with the use of products. It is clear that if participants do not use test products, it will not be possible to discriminate between their efficacies. Likewise, if a group of participants changes the oral hygiene behaviours that are responsible for their caries status—for example, a population that has rarely brushed with fluoride toothpaste starts to brush—the expected caries increment and, hence, the ability to discriminate between products would be reduced. A compromise between these two extremes would seem to be sensible, and supervised brushing, in schools, for example, to ensure a degree of compliance is now often included in clinical studies (7).

The ability of oral care products to affect the balance between remineralisation and demineralisation is key to their efficacy, but in traditional caries clinical studies, "cavitated" lesions are used as primary clinical endpoints. From an ethical standpoint, this is at best dubious and might even be considered supervised neglect. Ideally, we would aim to monitor the caries process and use primary endpoints that reflect remineralisation or arrest.

Clearly, as clinical studies become more and more tuned to maximize discrimination between products, their external validity becomes more questionable. For example, the results of a clinical study conducted in a population with high levels of caries due

to high sugar intake might not reflect those with high levels of caries due to poor oral hygiene and lack of use of fluoride toothpaste. The other side of this argument is that if you want to test a product that prevents or treats caries, you need to test it in a population that exhibits caries. Pragmatically, it would seem reasonable that external validity should reflect a population or individual with a propensity to form caries.

The question is often raised that if clinical trials have to be so large and complicated, are the differences detected clinically meaningful? The answer to this question has to be framed within the context of how the product is used and the potential cost-benefit. The difference between a 1,000- and 1,450-ppm-F formulation has been estimated to be a 7.9% (preventive fraction) reduction in DMFS in a three-year clinical trial (8). The clinical significance of such a reduction clearly depends on the underlying caries levels. However, it must also be remembered that although toothpastes are generally tested over 2 or 3 years, the benefits accrue over a lifetime of exposure and would be expected to be significantly higher. It is also clear that, provided that the use of the alternate product requires no behavioural modification, has no safety implications, and has all the aesthetic attributes of the product it will replace, such additional benefits can often be achieved at little additional cost, and the risk/benefit and cost/benefit are highly favourable. When benefits are seen in a national or global context, even small incremental changes in product efficacy might save billions of dollars for consumers and dental service providers.

For many years, *in vivo* human clinical trials have represented the pinnacle of product efficacy testing, and the basic design and acceptance criteria for caries clinical trials have historically been based on guidelines such as those of the American Dental Association (9). The ADA guidelines have recognized a conventional study of at least 2 years' product use as necessary proof of anti-caries efficacy. FDI guidelines have also recognized a conventional two-year study as the basis for approval, but also discuss provisions for shorter studies (10). More recently, the NIH Consensus Development Conference, "Diagnosis and Management of Dental Caries throughout Life", concluded, "The science of clinical research design has advanced rapidly in the past several decades". However, the panel deemed that the design and execution of caries trials and epidemiological studies have not kept pace with the current standard (11).

In 2002, an International Consensus Workshop on Caries Clinical Trials (ICW-CCT) was held at Loch Lomond in Scotland (12). The consensus statement is expansive, but in the context of this review can be summarized:

• Caries in enamel, caries in dentine, and caries on root surfaces are all variations on the same theme.
• Studies should measure changes in the continuum of the caries process and have the ability to measure demineralisation and also remineralisation of lesions.
• Methods capable of recording the continuum of the caries process (including non-cavitated lesions) should be evaluated and their results compared with those of the conventional caries assessment methods over a two- to three-year study.
• Given that the fluoride dose response has been characterized in the literature, this should form the basis of any validation package for new methodologies (13).

Since the Loch Lomond meeting, there has been further development of caries detection and assessment methods, and it is perhaps timely to review alternative methods of conducting caries clinical trials of oral care products, to assess if the above criteria have been fulfilled and alternatives to the traditional caries clinical trial are viable.

Methods

Studies were identified that could be broadly divided into four methods of caries detection and assessment (Appendix):

1. Clinical visual and tactile assessment (Table 5.1)
2. Electric Caries Monitor
3. Diagnodent (Table 5.2)
4. Quantitative Light-induced Fluorescence (Table 5.3)

More detailed reviews of studies reporting alternate clinical trial designs are included in Appendix 1 but are summarized below.

Review & Discussion

A wide range of alternative clinical visual and tactile assessment methods has been used to test the efficacy of fluoride oral care products (Table 5.1). Assessment of the remineralisation of coronal white-spot caries would seem to have greater sensitivity than traditional caries clinical trial methods, particularly when transition matrices are used to assess changes in lesion status (14). The Nyvad criteria (15) may have utility for the identification of high-risk individuals with active lesions and as a clinical outcome (16).

Assessment of the hardness of root-caries lesions to test the efficacy of products also appears to potentially reduce both the size and duration of clinical studies (17-19). In two clinical studies (17, 18), the Electrical Caries Monitor was also used as a secondary outcome. In both studies, significant effects on remineralisation of primary root-caries lesions were seen, with differences in fluoride products seen in as little as 3 months with 50 individuals *per* group. The objective nature of the ECM assessment may provide an advantage over more subjective clinical measures.

Effective supervised brushing in schools, combined with the recruitment of high-risk individuals, shows promise at improving the discrimination of clinical studies. Study results suggest that clinical trials of 1-year duration involving 200 to 300 high-risk participants may have sufficient power to discriminate between fluoride products (20, 21).

Four studies (Table 5.2) report results from clinical trials with the Diagnodent device. For some studies, there was a lack of certainty on the expected magnitude of differences between treatment regimes, making interpretation of results difficult. The work of Du *et al*. (2011) (22) and Schirrmeister *et al*. (2007) (23) presents the most compelling evidence for the use of Diagnodent in clinical studies.

Some care is required in the use of Diagnodent in clinical studies, due to problems with stain- and plaque-confounding assessments, and perhaps further work is required before it can be used routinely in clinical studies. The systematic review of Diagnodent (24) confirms the need for caution in both clinical practice and research

use.

We identified 6 QLF studies (Table 5.3) demonstrating, overall, that QLF is capable of monitoring and quantifying changes in the mineral content and size of lesions. The studies by Feng *et al*. (2007) (25) and Tranaeus *et al*. (2001) (26) detected differences between groups using therapies of known efficacy. Feng *et al*. (2007) (25) provided high-quality evidence for the use of QLF in an abbreviated caries clinical trial by demonstrating a dose response between F and non-F dentifrices. Other studies have reported differences between baselines and follow-up examinations but have failed to separate therapeutic groups. These failures could be explained by lack of statistical power and modest product differences, adding little to the evidence to support or reject the use of QLF.

The QLF studies reported focus on smooth-surface caries associated with natural buccal lesions resulting from poor oral hygiene or associated with orthodontic banding. No studies are available in the literature that report outcomes on occlusal surfaces. As well as the ability to provide numeric information on the degree of mineral loss from lesions, the QLF device imparts other benefits of interest to those conducting caries clinical trials. For example, analysis of the continuous data provided by QLF might enable more powerful statistical methods to be deployed, assisting in the reduction of participant numbers or trial duration. Images can also be analysed remotely, reanalysed by numerous examiners, and archived to provide a research governance benefit. The use of QLF shows great promise for future use in clinical trials.

A concern sometimes expressed with a shift to alternative clinical trial designs is that short-term clinical studies may over-estimate the long-term effects of products. For example, a product that remineralises the lesion surface in "minutes" may result in further mineral being unable to penetrate the lesion. In the case of a number of studies reviewed here, this concern has been mitigated by conducting assessments at baseline and 3- and 6-month intervals and demonstrating sustained lesion improvement (17, 18, 25, 26).

Another concern that has been expressed is in relation to remineralisation models where the etiological factor has been removed. An example of this is the assessment of white-spot lesion remineralisation following orthodontic de-banding. The value of such models to the real-life situation has been questioned. When toothpastes are tested, the benefit derived can be achieved both through the cleaning provided and the delivery of therapeutic agents. It would seem reasonable that, provided the etiological factors in the mouth remain broadly the same, and the toothpastes provide similar cleaning efficacy, any difference between products would be attributable to the therapeutic agent. Such approaches have been used in studies of naturally occurring buccal white-spot lesions (25, 27) and root caries (17, 18) with great success and would seem to have good external validity.

The costs and duration associated with traditional studies has been a significant barrier to the development of new therapies and documentation of their efficacy. There is a need to work with the international regulatory authorities to ensure that the results from abbreviated studies are more widely accepted. To achieve this, the recommendations of the Loch Lomond conference must be heeded. It is heartening to note that a number of dose response studies with products of known efficacy have been conducted, and significant progress has been made on the validation of alternate clinical trial designs. Such approaches may more accurately reflect the modes of action of new agents and formulations and potentially reduce the cost and duration of the product innovation cycle.

Conclusion

Since the Loch Lomond meeting, there has been significant progress in the development of methods for conducting caries clinical trials. Overall, these studies suggest that supervised brushing and high-caries-risk populations help to improve the discrimination of clinical studies. Assessment of study populations by activity criteria may also help to select individuals who are likely to develop caries. Studies assessing the remineralisation of root-caries lesions by visual tactile methods have been shown to have excellent discrimination between products of known efficacy. The ECM also shows great promise as an objective assessment method when used in root-caries studies. QLF assessment of the remineralisation of smooth-surface

enamel lesions demonstrated excellent discrimination between products, and the method shows great promise for future use in clinical trials.

Acknowledgments

Authors' contributions

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Appendix

Caries clinical trial methods for the assessment of oral care products in the 21st century

Methods

We conducted a detailed literature search (not restricted to English) of manuscripts published between 1980 and March 2011, using MEDLINE, Ovid, Embase, the Cochrane Oral Health Group's Specialized Register, and the Cochrane Central Register of Controlled Trials. The initial search identified 614 citations. The inclusion criteria applied were: (1) clinical trials comparing preventive intervention with a fluoride test or control product reporting outcomes of up to 1 year's duration; (2) limited to humans and natural caries lesions; (3) primary coronal and root caries, including the primary and permanent dentition; (4) reported in peer-reviewed journals; and (5) outcomes expressed as mean ± standard deviation of the increment of caries or other measures, such as the percentage change in the prevalence of lesions.

Inclusion and exclusion criteria were applied by examining titles, abstracts, and, where necessary, full papers by dual independent reviews. In total, 32 papers were identified in the search. Three reviewers agreed on the inclusion status of 19 publications. Data were abstracted (single abstraction, subsequent independent review) from the studies.

Studies were identified that could be broadly divided into four methods of caries detection and assessment:

(1) Clinical visual and tactile assessment (Table 5.1)

(2) Electric Caries Monitor

(3) Diagnodent (Table 5.2)

(4) Quantitative Light-induced Fluorescence (Table 5.3)

Clinical Visual and Tactile Assessment

Coronal Caries

Bailey et al. (2009). [NB: All references appear in the main paper.] This study assessed the remineralisation of white-spot lesions following the removal of fixed orthodontic appliances over 12 weeks according to the ICDAS criteria, supplemented with the Nyvad *et al.* (1999) criteria to take into account lesion activity. Forty-five individuals were randomly assigned to two groups. Both groups used fluoride toothpaste (1,100 ppm F), with one of the groups also applying CCP-ACP paste with their finger to lesions twice daily. For the group using the CCP-ACP paste, when all white-spot lesions at baseline were considered (ICDAS codes 1-3), 72% of lesions regressed compared with 59% in the control group (p=0.16). When the ICDAS code 1 lesions were excluded from analysis, 77% reversed in the CCP-ACP group compared with 59% in the control group (p=0.04). Quantitative Light-induced Fluorescence (QLF) and digital photography were also initially included as outcomes for the study, but, due to difficulties in the analysis of lesions at the gingival margin, these data were not reported in the manuscript.

Chesters et al. (2002). This study was one of the first modern abbreviated caries clinical trials assessing the progression and reversal of "white spot" caries. The 2-year study involved over 2,000 participants and compared toothpastes containing 2,500 and 1,450 ppm F. Participants were instructed to brush twice daily at home and also brushed in school under supervision. Significant differences between the groups were seen at both 12 and 24 months for white-spot lesions (D1) when lesion progression and regression were assessed by transition matrices. A traditional assessment of caries increment at the D3 threshold did not detect a significant difference at 12 months, but confirmed the outcome of the D1 threshold assessment at 24 months.

Lima et al. (2008). In a one-year study conducted in Brazil, the mean numbers of lesions progressing for caries-active and -inactive (Nyvad criteria) children, using either a 500-ppm-F or 1,100-ppm-F toothpaste, were compared. All children (aged 2-4 years) brushed twice *per* day at home and had supervised brushing in the nursery

setting. For the caries-inactive children, as might be expected, the rate of caries progression was low, and differences between the two toothpaste groups were not statistically significant. For the caries-active individuals (n = 43), the number of lesions progressing in the group using the 500-ppm-F paste was 3.0 compared with 1.5 in the 1,100-ppm-F group (p < 0.01).

Root Caries

Baysan et al. (2001). This study compared toothpastes containing 5,000 ppm F and 1,100 ppm F. Lesions were assessed as hard, leathery, or soft. After 3 months' use of the products, 38% of those using the 5,000-ppm-F paste had 1 or more lesions becoming hard compared with 11% of those in the control group (p < 0.01). After 6 months, 57% of participants had 1 or more lesions becoming hard in the 5,000-ppm-F group compared with 29% in the control group (p < 0.01).

Ekstrand et al. (2008). This study assessed the ability to arrest and reverse root-caries lesions of both a high-fluoride varnish (22,600 ppm F) and a 5,000-ppm-F toothpaste. These products were compared with standard fluoride toothpaste during an 8-month study in an elderly population. Root-caries lesions were assessed as sound active or inactive based on a scoring system assessing texture, contour, distance from the gingival margin, and colour, as described in the main paper. In total, 189 individuals completed the study. For the control group (standard fluoride toothpaste), 5.6% of participants improved compared with 17.3% in the varnish group and 12.5% in the group using the 5,000-ppm-F paste. Differences between the control group and both test groups were statistically significance (p < 0.05), but the difference between the two test groups did not attain statistical significance (p > 0.05).

Petersson et al. (2007). In this study, the addition of either 250 ppm amine fluoride or placebo mouthrinse to a regular toothbrushing regime was assessed. The participants were aged 55-81 years at baseline. After 3 months, significant differences (p < 0.001) were seen between the two groups, with 11% in the test group compared with 1% in the placebo group having lesions becoming hard. After 12 months, the percentages were 67% and 7%, respectively (p < 0.001).

Supplemental studies

In addition to the above studies, three other abbreviated clinical studies (Biesbrock *et al*., 2003a,b; Stookey *et al*., 2004) have reported statistically significant product differences achieved in 1 year or less. These studies have used traditional caries increments to assess efficacy but have used small sample sizes, in high-risk populations, with product use ensured by supervised brushing. In one study (Stookey *et al*., 2004), the importance of ensuring frequent uptake of brushing (> 60% sessions) was highlighted.

Summary Clinical Visual and Tactile Assessment

A wide range of clinical assessment methods has been used to test the efficacy of fluoride oral care products. Assessment of the remineralisation of coronal white-spot caries would seem to have greater sensitivity than traditional caries clinical trial methods. The use of the Nyvad criteria to assess lesion activity for inclusion of participants in clinical trials may also have utility. In addition, assessment of root-caries lesions to test the efficacy of products would appear to offer the opportunity to reduce both the size and duration of clinical studies. The use of effective supervised brushing in schools also shows promise, improving the discrimination of clinical studies, potentially reducing both their size and duration.

Electric Caries Monitor studies

The Electric Caries Monitor can be used to assess the porosity of root-caries lesions. Broadly, porous lesions filled with water have lower resistance (impedance) than sound or less porous surfaces. An increase in lesion resistance is therefore indicative of a decrease in lesion porosity. The Electric Caries Monitor was used as an objective adjunctive device in the root-caries studies conducted by Baysan *et al*. (2001) and Petersson *et al*. (2007). In both studies, the primary outcome was based on the hardness of primary root-caries lesions, and the ECM was employed to derive a secondary confirmatory study outcome.

Baysan et al. (2001). The clinical visual results and design of this study have been described previously. At the three-month time point, the $\log_{10}$ mean resistance values of lesions in the 1,100-ppm-F group decreased by 0.06, whereas those in the 5,000-ppm-F– group increased by 0.40 (p < 0.001). Between baseline and 6 months, the $\log_{10}$ mean resistance values in the 1,100-ppm-F group decreased by 0.004, whereas in the 5,000- ppm-F– group, they increased by 0.56 (p < 0.001).

Petersson et al. (2007). As previously described, this study assessed the efficacy of an amine fluoride rinse. The $\log_{10}$ mean resistance values for lesions in the test mouthrinse group increased from 1.95 at baseline to 2.21, 2.49, 2.58, and 2.67 at the 3-, 6-, 9-, and 12-month timepoints, respectively. For the placebo mouthrinse group, the $\log_{10}$ mean resistance values remained relatively constant at 1.93, 1.91, 2.01, 2.05, and 2.12, respectively. Significant differences (p < 0.01) between the 2 groups were seen from the 3-month timepoint onward.

Summary Electric Caries Monitor studies

In the two clinical studies using the ECM, the instrument was used as a secondary outcome to clinical assessment the results of which were previously described. In both studies, significant effects on remineralisation of primary root-caries lesions were seen, reflecting the clinical outcomes. The objective nature of the ECM assessment provides an advantage over more subjective clinical measures.

Diagnodent

The Diagnodent device (Kavo, Biberach, Badeb-Wurttemberg, Germany) exists in two forms: a standard instrument and a second-generation "pen" designed to increase access to interproximal sites. The Diagnodent measures fluorescence from bacterial porphyrins, and it is possible that enamel lesions may result in some surface scattering of light that may be detected by the instrument. A LED display indicates the current Diagnodent score and the maximum Diagnodent score. The system is simple to use, although it is a point measurement, and hence its use in longitudinal studies requires precise relocation of the measurement tip between visits.

Altenburger et al. (2010). This study examined the use of CPP- ACP cream as an adjunct to 1,450-ppm-fluoride toothpaste use when compared with the use of fluoride toothpaste (1,450 ppm) alone. Incipient lesions on occlusal surfaces were used, and examination points occurred at 1, 2, and 3 wks. Thirty-two patients completed the study. No significant differences were found between the two groups.

Andersson et al. (2007). This study assessed the difference between a group of individuals using CPP-ACP and toothpaste (1,100-ppm-NaF) and those using a mouthrinse (0.05 NaF) with toothpaste (1,100-ppm-NaF). In total, 26 participants were examined at 1, 3, 6, and 12 months, and buccal surfaces of incisors and canines were examined. No differences between the two groups were detected, although there were some differences between baseline and 6 and 12 months for both groups. The authors did report that there was a significant difference between the number of lesions that resolved completely – 63% in the CPP- ACP regime and 25% in the mouthrinse group – although this was not a primary outcome. The difference expected between these two regimens is unclear, and thus it is difficult to assess the utility of the device in this study.

Du *et al.* (2011). This study compared the use of a fluoride varnish with a control (saline solution) on white-spot lesions found on buccal surfaces. Examination points were at baseline, 3, and 6 months, and 110 subjects started the study, with 96 completing it. Significant differences were found between each examination point and baseline as well as between the test and control groups. This study provides construct validity (the use of high-fluoride *vs*. saline solution) for the use of the Diagnodent device (in this case the "pen" version). The use of an orthodontic model should be noted, since such patients are at risk of developing white-spot lesions and may provide useful study populations in the future.

Schirrmeister et al. (2007). This is a somewhat complex study. At first glance, the authors were comparing 5,000-ppm-F with 1,450-ppm-F dentifrices. However, the design is complicated by the introduction of two application systems: cleaning with a traditional brush and cleaning by an "airflow system". When one ignores the airflow results, there was a significant difference between the fluorescence readings from the

occlusal surfaces of the 30 participants over a two-week test period, with those in the 5,000-ppm-F group having significantly lower fluorescence readings than those in the 1,450-ppm-F group. Again, as with the study by Du, this work suggests construct validity for the use of Diagnodent, in this case assessing occlusal rather than smooth surfaces.

Summary Diagnodent studies

Four studies reported results from clinical trials with the Diagnodent device. For some studies, there was a lack of clarity on the expected magnitude of differences between treatment regimes, making interpretation of results difficult. The work of Du and Schirrmeister present the most compelling evidence for the use of Diagnodent in clinical studies, but readers should be mindful of the systematic review by Bader and Shugars (2004), who urge caution in the use of the device in clinical decision-making.

QLF studies

Quantitative Light-induced Fluorescence is based upon the loss of auto fluorescence of teeth in the presence of demineralisation. Following computer analysis of images captured by either intra- or extra-oral cameras, the degree (DF) and extent (area mm^2) of the fluorescence loss can be reported. In many studies, the "volume" of a lesion is calculated by integrating DF under the lesion as a primary outcome, and this is known as DQ. The system includes the ability to reproduce the orientation of images between visits to ensure consistency of lesion assessment.

Beerens et al. (2010). This was another study examining the action of CPP-ACP toothpaste but using a formulation with added fluoride – so called CPP-ACFP – and a control group that used a fluoride-free control dentifrice with calcium. The study ran for 12 weeks, with examination points at baseline, 6, and 12 wks. In total, 65 participants were recruited, with 54 completing the study (eight were lost from the test and three from the control groups). The authors reported DF, area, and DQ for all participants, and again found no significant differences between the product groups

at either 6 or 12 wks. Differences were detected for DF at 12 weeks for both groups when compared with baseline. Lack of clarity about the difference in efficacy between the two test products, a small sample size, and a differential dropout may account for the lack of statistical significance identified.

Bröchner et al. (2011). This four-week study compared two groups, CPP-ACP toothpaste (with adjunct 1,100-ppm-F brushing) and a control group that brushed with 1,100-ppm-F dentifrice alone. Sixty participants with at least one white-spot lesion were recruited, but only 50 completed the study; two were lost from the control and eight from the test group. Examinations were at baseline and 4 weeks, and the paper reports both DF and area. No significant differences were found between the two groups at 4 weeks, although some metrics demonstrated a difference from baseline – DF and area for test and DF only for the control group. The failure to detect differences between groups within this model likely reflects the small sample size, the short duration of the study, and the differential dropout rates in the two test groups. The study is inappropriate for method validation, since there is a lack of clarity on the difference in efficacy between the two test regimes. The QLF methodology was sufficiently sensitive to detect differences from baseline, providing some element of construct validity.

Feng et al. (2007). This study was directly influenced by the ICW-CCT statement that new caries diagnostic technologies should be supported by a dose response study. With a total of 305 (296 completed) participants, the groups were comprised of 1,450-ppm-MFP, 1,450-ppm-NaF, and a control paste that was fluoride-free. Assessment of white-spot lesions on the buccal surfaces of anterior tooth examinations took place at baseline, 3 months, and 6 months. The study reported a clear dose response, with significant differences detected at 3 and 6 months for both active pastes when compared with the control group. The methodology used school-based supervised brushing, which did result in a decrease in lesion size and severity (DF) in the control group, but there was a clear benefit to the adjunctive use of fluoride. The use of a 3- or 6-month clinical study duration with 100 participants (approx.) *per* group assessed for existing, plaque- related natural, anterior buccal white-spot lesions provides a strong basis for a clinical study methodology using QLF imaging.

Karlsson et al. (2007). This study compared the use of adjunctive fluoride gel (4,000-ppm-F weekly use) with regular toothbrushing with amine F toothpaste (1,250 ppm) with brushing only (with a placebo gel) over a 12-month period. The data reported are DF and area, although the use of graphs and selective narrative text descriptions of the data makes reporting individual outcomes problematic. In total, 181 individuals were recruited, and 135 completed the study; examinations were conducted at 3, 9, and 12 months. Non-cavitated buccal lesions on molars and premolars were assessed. No significant differences were detected between the two groups, although some significant differences were identified between baseline and examination points (DF and area) for the test group but not for the control group. The findings of this study are broadly similar to the others in that inter-group differences were not detected but between-visit differences were.

Tranaeus et al. (2001). This study compared two groups, the first receiving fluoride varnish (BL, 1 week, every 6 weeks for 6 months) and the second receiving professional prophylaxis (BL, every 6 weeks and 6 months). Thirty-one individuals (of 34 recruited) completed the study, and white-spot lesions (on buccal and premolar teeth) were assessed with QLF reporting area and DQ metrics. The study found a significant difference between the two therapeutic groups at 6 months, although it is reported that differences were also seen at the 6-week examination. These claims are supported by QLF images from the study. This study supports QLF assessment of the remineralisation of smooth-surface lesions as an alternative clinical trial methodology.

Zantner et al. (2006). In this complex study, involving examinations at 2, 4, 6, 8, 10, and 12 weeks, as well as longer term follow-up at 4, 5, and 6 months, the authors report a comparison of 1,500-ppm-NaF and 1,250-ppm-amine-F toothpastes. White-spot lesions were identified on incisors, premolars, and molars, and 39 subjects completed the study (of 44 recruited). DF, area, and DQ were reported sporadically in the study report, but the authors found no significant differences between groups at any of the timepoints. It is not clear if differences existed between baseline and any of the examination points. The failure to detect differences in this study probably reflects a small anticipated difference between products.

Summary of QLF studies

Overall, we identified 6 studies demonstrating that QLF is capable of monitoring and quantifying changes in the mineral content and size of lesions. The studies by Feng and Tranaeus detected differences between groups using different therapies. Feng provides evidence for the use of QLF in an abbreviated caries clinical trial by demonstrating a dose response between F and non-F dentifrices. Other studies have reported differences between baseline and follow-up examinations but have failed to separate therapeutic groups. This failure can most likely be explained by the use of underpowered studies aiming to detect modest product differences, and as such adds little to either support or reject the use of QLF in properly designed studies. As well as the ability to provide metric information on the degree of mineral loss from lesions, the QLF device imparts other benefits of interest to those conducting caries clinical trials. For example, images are produced that can be analysed remotely, re-analysed by numerous examiners, and archived. This provides a research governance advantage, since there is an enduring record of the clinical trial that can be accessed and re-analysed at will. The use of QLF shows great promise for future use in clinical trials.

Table 5.1. Randomized Controlled Clinical Trials using Visual and Clinical Criteria

Author	System	Country	Examination Schedule	Total n (completing)	Age (yrs)	Teeth/ Surface	Intervention Test	Intervention Control	Type of Lesion (outcome)	Outcomes Comparison	Outcomes Test	Outcomes Control	Sig.
Chesters et al., 2002	Dundee Selectable Threshold Method (DSTM)	Lithuania	BL-12-24 M	2,387 (2011)	11-14	Permanent All teeth	Toothpaste 2,500 ppm F	Toothpaste 1,000 ppm F	D1 [mean (SE) n lesions progressing (+) or regressing (-)]	12 M 24 M	10.4 ± 0.2 17.4 ± 0.3	11.3 ± 0.3 18.5 ± 0.3	S S
Bailey et al., 2009	ICDAS + Nyvad criteria	Australia	BL-4-8-12 W	45 (45)	12-18	Permanent Buccal	CPP-ACP applied with finger + Toothpaste 1,100 ppm F	Toothpaste 1,100 ppm F	ICDAS Codes 1-3 post-orthodontic (Percentage of lesions reversing)	Codes 123 Codes 2+3	72% 77%	59% 59%	NS S
Lima et al., 2008	Nyvad	Brazil	BL-1 Y	120 (90)	2-4	Primary All teeth	Toothpaste 500 ppm F	Toothpaste 1,100 ppm F	Active non-cavitated (mean n lesions progressing)	Caries-inactive Caries-active	0.33 ± 0.92 3.0 ± 2.9	0.52 ± 0.99 1.5 ± 2.4	NS S
Ekstrand et al., 2008	Root caries	Denmark	BL-8 M	215 (189)	75+	Permanent Buccal	F Varnish-22,600 ppm F / Toothpaste 5,000 ppm F	Toothpaste 1,450 ppm F	Root caries scored as sound arrested or active (% subjects improved)	Varnish 22,600 ppm F Toothpaste 5,000 ppm F	17.3% 12.5%	5.6% 5.6%	S S
Baysan et al., 2001	Root caries	UK	BL-3-6 M	201 (186)	27-90	Permanent Buccal	Toothpaste 5,000 ppm F	Toothpaste 1,100 ppm F	Root-caries lesions (% subject one or more lesions hard)	3M 6M	38.2% 56.9%	10.7 28.6	S S
Petersson et al., 2007	Root caries	Sweden	BL-3-6-9-12 M	100 (70)	55-81	Permanent Buccal	Toothpaste 1,400 ppm F + mouthrinse 250 ppm F	Toothpaste 1,400 ppm F + placebo mouthrinse	Root-caries lesions % lesions becoming hard	3M 6M 9M 12M	11% 34% 51% 67%	1% 1% 1% 7%	S S S S

All references are listed in the main article.

Table 5.2. Randomized Controlled Clinical Trials with the Diagnodent Device

Author	Country	Examination Schedule	Total n	Age (yrs)	Teeth/Surface	Intervention Test	Intervention Control	Type of Lesion (outcome)	Comparison	Mean SD Test	Mean SD Control	Sig. Diff. from Baseline	Sig.
Du et al., 2011	China	BL-3-6 M	110	12-22	Permanent Buccal	Varnish 22,600 ppm F	Saline Solution	WSL [mean (SD) DD readings decrease]	BL	17.66 ± 5.36	16.19 ± 5.70	NS	S
									3 M	11.88 ± 4.27	13.75 ± 4.76	S	
									6 M	10.10 ± 4.86	13.10 ± 5.19	S	
Altenburger et al., 2010	Germany	1-2-3 W	32	22-31	Permanent Occlusal	CPP-ACP-Toothpaste	Toothpaste 1,450 ppm F	Incipient lesion [mean (SD) DD readings decrease]	BL	16.66 ± 1.27	16.87 ± 1.69	–	NS
									1 W	15.1	15.18	NS	
									2 W	12.5*	14.71	S	
									3 W	10.96*	14.78	S	
Andersson et al., 2007	Sweden	1-3-6-12 M	26	12-16	Permanent Anterior Buccal	Toothpaste CPP-ACP / 1,100 ppm F	Daily 0.05 NaF MW / 1,100 ppm F	WSL [mean (SD) DD readings decrease]	BL	7.4 ± 10.2	9.4 ± 9.5	–	NS
									1 M	5.5 ± 6.7	7.6 ± 9.2	NR	
									3 M	4.9 ± 5.5	6.8 ± 8.1	NR	
									6 M	4.6 ± 5.1*	6.4 ± 7.3*	S	
									12 M	4.4 ± 5.2*	6.4 ± 7.5*	S	
Schirrmeister et al., 2007	Germany	BL-2 W	30	23-39	Permanent Occlusal	Toothpaste 5,000 ppm F	Toothpaste 1450 ppm F	Non cavitated [mean (SD) DD readings decrease]	2 W	11.9 ± 1.6*	15.6 ± 3.0	S	S

All references are listed in the main article.

Table 5.3. Randomized Controlled Clinical Trials with QLF to Assess White-spot Lesions

Author	Country	Examination Schedule	Total n (completing)	Age (yrs)	Teeth/ Surface	Test	Control	Comparison	Mean Std Deviation Test			Mean Std Deviation Control			Sig. Diff. from Baseline	Sig.
									Δf (%)	A (mm²)	ΔQ	Δf (%)	A (mm²)	ΔQ		
Brochner et al., 2011	Denmark	BL-4 W	60 (50)	13-18	Permanent Anterior Buccal	CPP-ACP- + Toothpaste 1,100 ppm F	Toothpaste 1,100 ppm F	BL	6.68 ± 0.58	0.12 ± 0.16	NR	7.04 ± 1.65	0.19 ± 0.43	NR		
								4 W	4.45 ± 1.82 *	0.05 ± 0.09*	NR	4.51 ± 2.46*	0.14 ± 0.31	NR	S	NS
Beerens et al., 2010	Netherlands	BL-6 W-12 W	65 (54)	12-19	Permanent Anterior Buccal	Toothpaste CPP-ACFP	Toothpaste F free/calcium	BL	8.45 ± 1.17	5.07 ± 5.69	56.37 ±73.05	9.10 ± 1.75	7.29 ± 7.91	90.81 ± 111.28	S	NS
								12 W	7.52 ± 1.78*	5.05 ± 6.98	57.76 ±91.73	7.96 ± 2.76*	7.17 ± 7.76	85.89 ± 97.82		
Karlsson et al., 2007	Sweden	BL-3-9-12 M	181 (135)	13-17	Permanent Posterior Buccal	Toothpaste amine 1,250 ppm F + Gel 4,000 ppm F once a wk	Amine Toothpaste 1,250 ppm F + Placebo gel	12 M	Graphical representation of data in manuscript						S	NS
Feng et al., 2006	China	BL-3-6 M	305 (296)	11.82	Maxillary Anterior/ Buccal	Toothpaste (NaF 1,450 ppm F MFP 1,450 ppm)	No Fluoride Toothpaste (herbal)	BL-3 M Test vs. Placebo	NaF 0.305 ± 0.204 MFP 0.326 ± 0.220	NaF -0.191 ± 0.112 MFP 0.234 ± 0.116	NaF 2.398 ± 1.560 MFP 3.884 ± 1.693	Variance components model used reporting differences in test groups from placebo - NaF = S MFP = S (ΔF-A-ΔQ)			–	NaF = NS MFP = S (A-ΔQ)
								BL- 6 M Test vs. Placebo	NaF 0.712 ± 0.234 MFP 0.695 ± 0.239	NaF -0.424 ± 0.122 MFP -0.399 ± 0.121	NaF 5.439 ± 1.776 MFP 6.329 ± 1.902					
Tranaeus et al., 2001	Sweden	BL- Every six W- 6 M	34 (31)	13-15	Posterior Buccal	Varnish (0.1%F)	Professional toothcleaning (every 6 W for 6 M)	BL- 6M Δ Values	NR	– 0.152 ± 0.056* (SE)	– 0.107 ± 0.032* (SE)	NR	– 0.006 ± 0.047 (SE)	– 0.008 ± 0.027 (SE)	S	S
Zantner et al., 2006	Germany	2-4-6-8-10-12 W/4-5-6 M	44 (39)	12-38	Anterior/ Posterior Buccal	Toothpaste 1,500 ppm F- NaF	Toothpaste 1,250 ppm F-Amine F	6 M	Graphical representation of data in manuscript						–	NS

All references are listed in the main article.

CHAPTER 6

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In Vitro Performance of Different Methods in Detecting Occlusal Caries Lesions

In vitro performance of different methods in detecting occlusal caries lesions

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Rationale Paper V

The main objective of a caries detection method is the identification of demineralisation on the tooth structure. Several methods have been developed and tested mainly in *in vitro* settings, reporting analyses based on the D1 level combining enamel and dentine codes or collapsing sound and enamel lesions versus the remaining codes. It was the aim of this study to compare the performance of ICDAS, ICDAS photographs, FOTI, QLF, Soprolife and OCT on non-cavitated caries lesions and validating against the current absolute reference for caries detection (Histology).

Abstract

Early caries detection is essential for the implementation of preventive, therapeutic and intervention strategies within general dental practice. **Objective:** The aim of this study was to compare the in vitro performance of the International Caries Detection and Assessment System (ICDAS), Digital Photographs scored with ICDAS (ICDAS photographs), Fibre-Optic Trans-Illumination (FOTI), Optical Coherence Tomography (OCT), SoproLife® camera and two implementations of Quantitative Light-Induced Fluorescence a commercial (QLF-Inspektor Research systems) and a custom (QLF-Custom) system, to detect early and intermediate occlusal lesions. **Methods:** One hundred and twelve permanent extracted teeth were selected and assessed with each detection method. Histological validation was used as a gold standard. The detection methods were compared by means of sensitivity, specificity, Areas Under Receiver Operating Characteristic (AUROC) curves for enamel and dentine levels and with the Spearman's rank correlation coefficient against histology. **Results:** For any enamel or dentine caries detection, the AUROC curves ranged from 0.86 (OCT) to 0.98 (ICDAS and ICDAS photographs, SoproLife® camera) and at the dentine level from 0.83 (OCT) to 0.96 for FOTI. The correlations with histology ranged between 0.65 (OCT) and 0.88 (ICDAS and FOTI). Under in vitro conditions, the assessed detection methods showed excellent intra-examiner reproducibility. All the methods were strongly correlated with histology ($p<0.01$) except OCT which showed a moderate correlation (0.65). **Conclusion:** Even though all methods present similar performance in detecting occlusal caries lesions, visual inspection seems to be sufficient for detection and assessment of lesion depth. Other methods may be useful in monitoring caries lesion behaviour.

Keywords: Caries detection, Visual inspection, Fibre-optic transillumination Quantitative laser fluorescence, Optical coherence tomography.

Introduction

Early detection of carious lesions is highly desirable for the implementation of preventative strategies, such as fluoride remineralisation therapies, when lesions have the greatest opportunity for reversal or arrest (1, 2). Detection of occlusal caries and the evaluation of the lesion depth have frequently been highlighted as a diagnostic problem. Visual and radiographic examinations are the most commonly used methods for caries detection but radiographs are unable to diagnose early enamel caries lesions reliably (2). When an occlusal lesion is detected on a bitewing radiograph, the lesion may have already reached the middle third of dentine and hence beyond the scope of remineralisation interventions (3).

In response to this diagnostic dilemma, enhanced visual scoring systems reflecting the disease process have been developed. However, the conclusion of two systematic reviews in 2001 determined that the current evidence of reliability and reproducibility for visual and visual/tactile detection systems was weak (4, 5). These findings led, in part, to the development of the International Caries Detection and Assessment System (ICDAS). The system is evidence based and intends to develop better diagnosis, prognosis and clinical management at the individual and population levels (6). ICDAS has shown to be an accurate and reproducible method to detect early lesions and also to detect changes in longitudinal follow-up (7-10).

FOTI is a widely accepted method for caries detection and has been extensively used to detect approximal caries for which it is particularly suited (11). The literature reporting the performance of FOTI detecting caries lesions on occlusal surfaces is not extensive (12-13). Recent developments in visual scoring system such as ICDAS may be enhanced when FOTI is added (14).

Non-invasive methods have been developed as potential diagnostic aids for clinicians – principally by facilitating the detection and quantification of early lesions. QLF (Quantitative Light-induced Fluorescence) is one such system based on the measurement of fluorescence loss following enamel demineralisation (14). This method has shown high sensitivities and specificities in detecting enamel lesions (15-17). Another method based upon the imaging and auto-fluorescence of dental tissues

to detect caries is the SoproLife® camera (18). The literature on SoproLife® is limited to preliminary results only.

OCT is a high-resolution, non-invasive imaging technique that constructs cross-sectional images of internal biological structures (19). This technology is based on the principle of optical interferometry using a low coherence light source that is split into two beams, which then are reflected back, one from the investigated tissue and the other from a reference mirror, and combined together to create an interference pattern that contains depth-information from the sample (20). Previous studies have shown that OCT has the potential to detect and quantify demineralisation based on an increase light scattering from porous structures within the tooth in in vitro caries-like models (21, 22). However, these simple models did not reflect the complexity of natural lesions; in particular they were not subsurface lesions (22). Previous studies have shown the potential use of OCT to detect and quantify demineralisation based on an increase light scattering from porous structures within the tooth using in vitro caries-like models (20-21, 23).

The aim of this in vitro study was to compare the performance of ICDAS, FOTI, QLF (Custom and Inspektor Pro systems), SoproLife® camera and OCT in detecting early to intermediate occlusal caries.

Methods

Sample

A total of 112 permanent molar and premolar teeth stored in distilled water with thymol 0.1%, were selected from a pool of extracted teeth from the Indiana Oral Health Research Institute, School of Dentistry, Indiana University with appropriate ethical approval from the local Ethics Committee. The occlusal surfaces were selected_to provide a range of lesions ICDAS 0-4. The teeth were pooled before collection and no patient data were associated with the samples. The teeth were cleaned with water and a toothbrush and air-dried for 5 seconds before each detection procedure. For each tooth one examiner (JG) defined a region of interest (ROI) on the occlusal surface for assessment using each of the methods. The occlusal surfaces on the selected teeth were photographed and the ROI indicated with a rectangle

shape on a power point file. Teeth were allocated an identification number that was maintained throughout the study. Seven caries detection methods were applied; ICDAS, ICDAS photographs, FOTI, OCT, QLF (Custom and Inspektor) and SoproLife. The examinations were repeated in a subsample of teeth after 7 days (30% repeat).

Examiners

One examiner performed all the examinations, except for the FOTI assessment where the scores were compared and a consensus decision was taken in case of disagreement.

Examination Methods

ICDAS/FOTI. The ROI on the teeth was assessed using the ICDAS criteria [10] (Table 1) by an examiner (JG) trained by an ICDAS trainer, with the aid of a WHO probe and air syringe. The examination sites were also scored visually using FOTI by two examiners (JG, RPE). The FOTI tip (0.5-mm) was placed perpendicular to the buccal and the lingual surface. The intensity of the halogen lamp (150W) of the FOTI equipment (Schott Fibre Optics, Doncaster, UK) was set to the maximum. Scores were compared and a consensus decision was reached using the criteria developed as part of the ICDAS program (Table 6.1). The examinations were repeated in a subsample of teeth after 7 days (30% repeat).

QLF/White Light customised imaging system

Images of the teeth were captured under darkroom conditions using QLF Inspektor Pro systems and ΔF analysed at 5% fluorescence loss threshold using the Inspektor Pro analysis software. In addition white light and QLF images were captured using a custom high-resolution QLF/white light dual imaging system. The resultant white light images were scored using ICDAS (JG). The examinations were repeated in a subsample of teeth after 7 days (30% repeat). The QLF (Custom-QLF) images were analysed in Matlab (MathWorks, Massachusetts, USA) using an algorithm previously reported (15) to calculate ΔF at a 5% threshold.

SoproLife®Camera

The system uses light-induced fluorescence to detect dental caries (20). The images

were captured in Mode I (green fluorescence) and in mode II (red fluorescence). Green fluorescence images from the occlusal surfaces were captured and ΔF analysed at a 5%-threshold in Matlab (MathWorks, Massachusetts, USA) using an algorithm previously reported (15). Red fluorescence images of occlusal surface were captured and the region of interest scored visually using the absence (score 0) and presence (score 1) of red fluorescence.

OCT

Images from the region of interest on the occlusal surface were captured (Thorlabs, SS-OCT 1300) and scored visually to assess the depth of caries as sound, enamel caries or caries into dentine. OCT images were captured using a swept-light source centred at 1,315nm scanned over the region of interest. The imaging depth was 3.0 mm and the width was 5.0 mm. Each tooth was placed in front of the OCT scanning probe. The axial resolution was estimated to be approximately 6 μm and the lateral resolution as 5 μm. The lesion-depth measurement was performed using the following criteria (23):

0. No caries. Obtained OCT signal was the same level and shape as that of normal enamel and loss of enamel surface (cavitation) did not occur.
1. Superficial demineralisation of enamel. OCT signal intensity was enhanced within the enamel thickness but loss of enamel surface (cavitation) did not occur.
2. Enamel breakdown due to caries. Continuity of enamel surface is disconnected at the occlusal fissure, where OCT signal was intensified but limited to the enamel thickness.
3. Dentine caries. An intensified OCT signal was obtained beyond the EDJ, with or without loss of enamel surface (cavitation).

The examinations were repeated in a subsample of teeth after 7 days (30% repeat).

Histology

After completion of all the assessments, the teeth were embedded in acrylic blocks with the occlusal surface exposed. The sites were hemi-sectioned in a buccal to lingual direction through a previously identified ROI using a 0.4 mm-thick diamond

saw mounted in a microtome (MODEL 650 Low Speed Diamond Wheel Saw, South Bay Technology, Inc). The cut was vertical, perpendicular to the crown and the exposed surface was polished with lapping paper (30 μm) and photographed using a Jai CV-M91 camera (Jai A/S, Copenhagen, Denmark). The camera was fitted with a ring illuminator, and cross-polarisers were used to minimise specular reflection. A light shield was fitted, which also ensured the exposed surfaces were always in focus and at equal magnification of 4x (24). The images from each tooth were presented together, but the order of the teeth was randomised. The images were then viewed by each examiner on a computer screen at a constant observation distance (1.0 m). Two examiners (JG, IAP) provided a consensus score for each site. The definitive histological score was assigned following the same region of interest selected for all methods. The histological criteria to assess caries lesion depth was judged by a 7-point scale: S= Sound, E1=caries lesion limited to the outer half of enamel; E2= caries lesion into the inner half of enamel; EDJ= caries lesion at the amelodentinal junction; D1=caries limited to the outer third of dentine; D2=caries limited to the middle third of dentine; D3=caries involving the inner half of dentine. The definitive histological score was assigned following the same region of interest selected for all methods. The examinations were repeated in a subsample of teeth after 7 days (30% repeat).

Statistical assessment

Data were entered into SPSS statistical software 16.0 (SPSS Inc.). Intra-examiner reproducibility of ICDAS, ICDAS photographs, FOTI and histology scores was assessed using weighted kappa statistics. To calculate sensitivity and specificity for each method disease positive states according the histological data were defined. At D1 detection threshold all enamel and dentine lesions were classified as caries. At the enamel threshold, sound surfaces and dentine lesions were classified as disease negative and at the dentine level demineralisation extending from the outer third of dentine to the inner third of dentine was defined as disease positive. AUROC curves were calculated at the D1 detection threshold and at the dentine threshold. The strength of the association between each of the detection methods and the histology scores was evaluated with a Spearman's Correlation Coefficient.

Results

A total of 112 teeth were examined. According to the histological gold standard, 23 teeth were sound, 43 had caries from the outer half of enamel until the enamel dental junction and 46 teeth had caries in dentine. Cross-tabulations of ICDAS, ICDAS photographs, FOTI, OCT, QLF-Inspektor Pro, QLF-Custom and SoproLife® camera (Mode I) versus histology are presented in Table 6.2-6.3. The intra-examiner reproducibility (weighted kappa ± SE) were: ICDAS (0.85±0.15), ICDAS photographs (0.84±0.08), for FOTI (0.91±0.13), OCT (0.80±0.10), Soprolife (Mode I) (0.88±0.11) and Histological validation (0.81±0.11).

AUROC curve analysis was performed to find the optimum ΔF QLF and SoproLife® camera green fluorescence threshold values for enamel and dentine. The optimum value was defined by the Youden's index (sum of sensitivity and specificity minus one for each point in the ROC curve). The optimal cut-off points corresponding to the maximum combination sensitivity and specificity observed were split into 3 cut-offs: D1, enamel and dentine thresholds.

Table 6.4 shows the correlation with histology, sensitivity, specificity and AUROC at D1, enamel and dentine level cut-offs. The AUROC curves ranged from 0.86 (OCT) to 0.98 (ICDAS, ICDAS photographs, SoproLife® camera Mode I) at sound level, and at the dentine level from 0.83 (OCT) to 0.96 (FOTI). Sensitivities at the enamel level varied between 0.62 (QLF-Custom) and 0.95 (OCT); specificities varied from 0.39 (OCT) and 0.94 (QLF-Custom,). At the dentine level, sensitivity ranged between 0.32 (OCT) and 0.93 (QLF-Custom) and specificity between 0.80 (OCT) and 0.93 (ICDAS). SoproLife® Mode II (red fluorescence) was dichotomised into 2 cut-offs: 0= absence and 1= presence of red fluorescence. The sensitivity for detecting disease with this method was 0.63 and the specificity 0.95.

The correlation between the gold standard and each method was assessed by Spearman's rank correlation coefficient and the highest correlation was found between visual detection with the ICDAS system and FOTI with the histological assessment (Table 6.4). All the methods were strongly associated ($p<0.01$) with the histology except for visually scored OCT that showed a moderate correlation (0.65).

Discussion

If dentistry is to move from a restorative to a preventive and therapeutic based approach, early caries detection and quantification of lesions to monitor their arrest or progression over the time is essential. All the methods investigated in this study correlate well with histological scores. The sensitivities at the enamel level were high for ICDAS, FOTI and OCT and the specificities at the same level were high for all methods except for OCT (0.39). At the dentine level the sensitivities were high for all methods except for OCT (0.32) and the specificities at this level were high for all the methods.

A possible explanation for the poor specificity at the enamel level and sensitivity at the dentine level for OCT may be explained by the subjective visual assessment of the images rather than the use of an automated algorithm. When the analysis of the OCT scores was performed at the non-cavitated and cavitated level the sensitivity and specificity increased significantly. OCT has been traditionally used in vitro for smooth surfaces and acquiring optimal images of the occlusal surface is problematic due to the varying optical penetration and surface reflectivity (18) and the complex morphology of the fissures. These results therefore need to be interpreted with caution. Some studies have used algorithms to automatically calculate the depth and integrated reflectivity from the lesion area and have shown good correlation with the mineral loss (22, 25). The visual assessment performed in this study was conducted to determine if demineralisation changes were visually observable. The results of the OCT analysis suggest that advanced imaging analysis methods are required to understand and interpret signs of demineralisation seen using this modality. At present, OCT is not ready to be used in clinical practice and requires further research leading to the clinical implementation of this device for the assessment and monitoring of severity of early carious lesions.

This study has shown moderate sensitivity (0.65) for SoproLife® camera Mode II (red fluorescence). Red fluorescence is produced from collagen breakdown products via the Maillard reaction, only seen when caries reaches dentine (26). The present study is the first to compare the SoproLife® method with an established technique to

determine specificity and sensitivity. Limitations of the SoproLife method within the current study may be related to presence of organic deposits, porosities, and crystalline disruption, which are all able to disrupt the auto fluorescence signal, discolouring, and modifying the brightness of the hard tooth structures (18, 26). Despite this, the SoproLife® camera demonstrates very high sensitivity and specificity when green fluorescence Mode I was utilised. However, the actual SoproLife camera does not include any analysis software. In this study, the green fluorescence images were captured and ΔF analysed at a 5%-threshold using an algorithm previously reported (15).

QLF (Custom and Inspektor) has shown excellent sensitivity at detecting disease. The moderate sensitivity at the enamel may be explained by the presence of fluorosis in sample used for this study (10). QLF will detect any demineralisation and cannot make a differential diagnosis; again it is a detection device. In such cases the importance of clinician assessment is clear as device can only detect mineral loss but cannot necessarily differentiate caries from fluorosis. Both types of QLF (Custom and Inspektor Pro systems) used in this study showed similar results. The Custom capturing system is a high-resolution version of the QLF system (Inspektor BV, Amsterdam), using the same excitation wavelengths and has been used in previous studies for the detection and quantification of fluorosis (14) and caries (27). QLF seems to have been rapidly adopted as a standard reference measure in clinical tests of the efficacy of preventive measures (1, 28, 29).

FOTI has been accepted as a diagnostic aid for approximal caries for many years (30-31). This study confirms previous findings for the FOTI technique (11, 13, 30). The findings of the photographs assessed with the ICDAS criteria showed high correlation with the histology (p<0.01). Photographic monitoring of the lesions (using intra oral cameras) could be an economical, practical and reliable method to use in the clinical practice (32).

The ICDAS system has shown superior results when teeth are clean, dry and when the examiners are trained (7-10, 33). The ICDAS results corroborate previous works (33, 34) where half of the lesions diagnosed as ICDAS score 1 were in the inner half of enamel. Half of the lesions scored as 2 by the ICDAS system were already in the

EDJ and in the outer-third of dentine, demonstrating the difficulty for ICDAS to classify lesions in enamel and in the outer third of dentine. In this study, the EDJ has been included at the enamel level to be able to report the performance of the detection methods at that threshold. However, this classification may not be critical when clinical decisions need to be made. Lesions into the outer third of dentine are frequently non-cavitated and may also be managed in a non-operative way (3).

This study relies in only one examiner for all the methods excepting for FOTI. This factor may present difficulties in generalization due to the positive influence of particular skills of some investigators (4). In vitro studies are useful methods of comparing methods as they can be compared to a true gold standard (histological validation). However, it is unclear how results generated in vitro can be translated into the clinical situation. Further research will be required to assess the novel technologies described in this study in vivo and their use as an adjunct to visual - techniques as ICDAS may lend considerable detection yield.

Conclusions

Even though all methods present similar performance in detecting occlusal caries lesions, visual inspection seems to be sufficient to be used in clinical practice for detection and assessment of lesion depth. Complementing traditional diagnostic methods with advanced, more sensitive methods will improve caries diagnostic routines and hence the dental care and treatment of patients. Quantitative methods may also reduce the duration and the subjects of the clinical trials measuring small changes (14). Monitoring will ensure personalized caries management and determining the status of the lesions and will allow clinicians to revaluate the effectiveness of therapies and treatment decisions. The systems described within this study may provide useful tools in the future if true preventive practice is to be facilitated within general dental services. A paradigm shift is required from a surgical to a medical model, allied with care pathways for caries management. Without effective, simple and reliable detection and quantification of early caries the profession will remain focussed on surgical interventions of cavitated lesions.

Acknowledgements

Authors' contributions

JG contributed to the protocol, experimental design, undertook the study, acquisition of data, analysis and interpretation of data and wrote the manuscript. CZ contributed to the experimental design, analysis and contributed to the manuscript. SS and SCP contributed to the experiment. AT contributed to the analysis of the data. IAP and RE contributed to the protocol and to the manuscript

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Table 6.1. Diagnostic criteria for Histology, ICDAS and FOTI

	ICDAS	FOTI
0	Sound	No shadow
1	First visual change in enamel	Thin-grey shadow into enamel
2	Distinct visual change in enamel	Wide-grey shadow into enamel
3	Localized enamel breakdown	Shadow <2 mm in dentine
4	Underlying dentinal shadow	Shadow >2 mm in dentine

Table 6.2. Cross-tabulation of ICDAS, ICDAS Photos, FOTI and OCT scores compared to histological scores

		Histology			
	Cut-off points	Sound (S/E1-D3)	Enamel (E1-EDJ/ S;D1-D3)	Dentine (S-EDJ/ D1-D3)	Total
ICDAS	0	20	0	0	20
	1-2	3	39	6	48
	3-4	0	4	40	44
	Total	23	43	46	112
ICDAS photos	0	21	0	0	21
	1-2	2	36	7	45
	3-4	0	7	39	46
	Total	23	43	46	112
FOTI	0	22	4	0	26
	1-2	1	36	10	60
	3-4	0	3	36	26
	Total	23	43	46	112
OCT	0	12	1	0	13
	1-2	11	41	31	83
	3	0	1	15	16
	Total	23	43	46	112

Table 6.3. Cross-tabulation of QLF (Custom), QLF (Inspektor) and Soprolife compared to histological scores

		Histology			
	Cut-off points	Sound (S/E1-D3)	Enamel (E1-EDJ/ S;D1-D3)	Dentine (S-EDJ/ D1-D3)	Total
QLF-Inspektor	$\Delta F < 0.08$	22	1	0	23
	$0.08 \leq \Delta F < 0.15$	0	31	6	37
	$\Delta F \geq 0.15$	1	11	40	52
	Total	23	43	46	112
QLF-Custom	$\Delta F < 0.125$	21	4	0	25
	$0.125 \leq \Delta F < 0.193$	1	27	3	31
	$\Delta F \geq 0.193$	1	12	43	56
	Total	23	43	46	112
Soprolife Mode I	$\Delta F < 0.101$	22	2	0	24
	$0.101 \leq \Delta F < 0.167$	1	32	8	41
	$\Delta F \geq 0.167$	0	9	38	47
	Total	23	43	46	112

Table 6.4. Areas Under Receiver Operating Characteristic (AUROC) curves; sensitivity and Spearman's Rank Correlation Coefficient with Histology scores

Detection Method	Spearman's Rank Correlation Coefficient	Cut-off points						AUROC (S/E1-D3) (SE)	AUROC (S-EDJ/D1-D3) (SE)
		Sound (S/E1-D3)		Enamel (E1-EDJ/ S;D1-D3)		Dentine (S-EDJ/ D1-D3)			
		SE	SP	SE	SP	SE	SP		
ICDAS	0.88 p<0.01	>0.99	0.87	0.9	0.87	0.87	0.93	0.98 (0.01)	0.95 (0.01)
ICDAS Photos	0.87 p<0.01	>0.99	0.91	0.83	0.86	0.84	0.89	0.98 (0.01)	0.94 (0.01)
FOTI	0.88 p<0.01	0.95	0.95	0.8	0.84	0.78	0.92	0.97 (0.01)	0.96 (0.01)
OCT	0.65 p<0.01	0.98	0.52	0.95	0.39	0.32	0.98	0.86 (0.04)	0.83 (0.03)
QLF (Custom)	0.76 p<0.01	0.95	0.91	0.62	0.94	0.93	0.8	0.94 (0.03)	0.89 (0.03)
QLF (Inspektor)	0.81 p<0.01	0.98	0.95	0.72	0.91	0.86	0.81	0.97 (0.02)	0.92 (0.02)
SoproLife	0.80 p<0.01	0.97	0.95	0.74	0.86	0.82	0.86	0.98 (0.01)	0.9 (0.02)

SE: Standard error

Figure 6.1. Examples of White light, QLF and OCT images
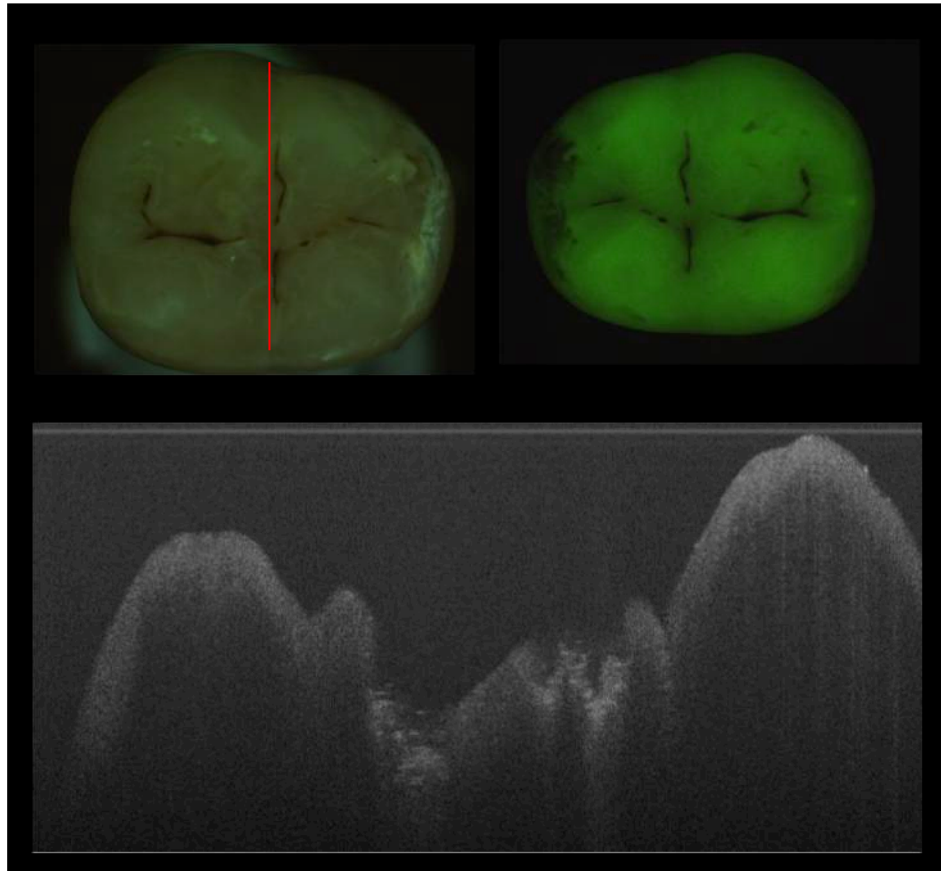
CHAPTER 7

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Quantitative Light-Induced Fluorescence to Measure

Enamel Remineralisation in vitro

Quantitative Light-induced Fluorescence to measure enamel remineralisation in vitro

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Rationale Paper VI

The optical properties of the enamel surface are altered during the caries process. These changes in scattering properties can be detected and quantified by optical systems. Two in vitro pH-cycling models were designed (Paper VI and VII). pH-cycling models can be classified into reversal (remineralising) or progression (demineralising). The first experiment (Paper VI) was a remineralising model using artificial carious lesions and the response variable was the gain of minerals. The purpose of this study was to test the ability of QLF to measure mineral changes after a remineralisation model. Such models more closely represent the more complex dynamic phases seen within biological systems.

Abstract

The aim of this study was to compare the ability of Quantitative Light-induced Fluorescence (QLF) and Surface Microhardness (SMH) to measure the remineralisation of enamel subsurface lesions, using a pH-cycling model including treatment with 0-ppm, 550-ppm, or 1100-ppm NaF dentifrices. **Methods:** Subsurface lesions were created in human enamel specimens (n=36) and exposed to a remineralisation pH-cycling model for 14 days. The pH-cycling model was performed in an automated system where specimens were subjected to a demineralising solution for 20 minutes, treatment for 1 minute and remineralised for 7 hours and 39 minutes, three times daily. The treatments consisted of two sodium fluoride (NaF), silica-containing dentifrices (550 ppm F, 1100 ppm F) and a fluoride placebo (0 ppm). The outcome variables were: change from baseline in surface hardness (ΔZ) and percentage change from baseline in fluorescence from baseline ($\Delta F\%$). An analysis of covariance (ANCOVA) explored differences between different treatment groups (at the $p < 0.05$ level). Associations between QLF and SMH were evaluated using Spearman's correlation coefficient. **Results:** The percentage SMH changes were $14.9 \pm 2.1\%$, $56.6 \pm 9.6\%$ and $103.9 \pm 14.6\%$ for the 0, 550 and 1100-ppm F dentifrices, respectively. The percentage fluorescence changes were $15.6 \pm 7.1\%$, $59.8 \pm 11.9\%$ and $85 \pm 13.2\%$ respectively. The differences between all pair-wise comparisons were statistically significant for both methods (p=0.001). QLF correlated with SMH (r=0.67). **Conclusions:** Both the SMH and QLF methods demonstrated a significant F dose response for toothpaste in this *in vitro* remineralisation model and both methods were able to distinguish treatments with different F levels.

Key words: Remineralisation, Fluoride, Quantitative Light-induced Fluorescence, Surface Microhardness

Introduction

There has been an overall decline in the prevalence, extent and severity of dental caries in children and young adults around the world, particularly in developed countries (1). The evidence supporting the use of fluorides to prevent dental caries by reducing demineralisation and enhancing remineralisation is unequivocal and has contributed significantly to this decline (2, 3)

In vitro de- and re-mineralization models of enamel caries lesions have been developed to assess the anti-caries potential of fluoride and other factors influencing caries lesion progression and repair (4). The slower rate of progression of caries today, and the development of more sensitive methods of detection, have prompted caries researchers to examine smaller, initial mineral changes in *in vitro* and *in vivo* studies (5). Recently, researchers have shown an increased interest in non-destructive methods, such as Quantitative Light-induced Fluorescence (QLF), for the quantitative assessment and longitudinal monitoring of mineral changes in the early stages of caries (6). A consensus meeting (7) and a recent review (8) both concluded that QLF may help to reduce the subject numbers and trial duration when assessing efficacy of new anti-caries treatments.

QLF is a system based on the measurement of fluorescence loss following enamel demineralisation (6). This method has been employed in pH cycling experiments (9), and in monitoring *in vivo* remineralisation of white spot lesions (10-13). The purpose of this study was to determine the ability of QLF to detect differences in remineralisation of artificial caries lesions in a pH-cycling model using three types of silica-based NaF toothpastes (0 ppm, 550 ppm, 1100 ppm) and compare changes to those measured using surface microhardness.

Methods

Extracted human molar teeth were collected from dental surgeries located in the state of New Jersey, USA. Informed consent was obtained from the patients prior to the extractions. The teeth were stored in 10% (v/v) neutral phosphate buffered formalin for a minimum of two weeks. The selected teeth did not have any developmental defects, cracks or white spot lesions. Figure 7.1 illustrates the study design employed.

Enamel Specimen Preparation

Human extracted teeth were cut into three or four parts with a water-cooled diamond saw. Thirty-six slices were obtained, ground flat and polished using 3 retaining rings and 15μm Diamond polishing disk (Buehler, Illinois, USA). QLF images were taken before the creation of the lesions and used as reference area for the analysis. Specimens were selected based on their sound Surface Knoop hardness number (KHN). The KHN mean of the enamels blocks selected for this study was of 343.1 ± 30 kg/mm^2

Two-adhesive strips were attached to both sides of the sample so that a central area of 6 mm2 (approx.) was exposed. During the evaluations, specimens were kept in 100% relative humidity at 4°C. The specimens were air-dried for 5 seconds with compressed air fixed at 10 cm from the teeth before QLF and SMH assessment.

Lesion preparation

Caries-like lesions were formed in the exposed enamel after immersion for 32 hours (14) at 28°C in a pH 4.6 solution of 0.1 mol/L acetic acid containing 800 mg/L dissolved hydroxyapatite and 5g/L of Carbopol 981 (4). SMH assessment and QLF measurements were acquired and samples were randomly assigned to three groups based on the value of the Knoop Hardness Number after lesion creation. Lesions were stratified and assigned to three treatment groups (n =12 per group). Lesion average baseline values were 93.99 ± 27.87, 92.48 ± 25.95 and 92.1 ± 20.83 for SMH and average fluorescence loss values were 28.6 ± 3.3, 20.2 ± 4.4 and 24.3 ± 4.5 for the 0, 550 and 1100-ppm F treatments, respectively.

pH-Cycling

The pH-cycling model (Table 7.1) was performed by a custom-made robot system for 14 days. The samples were consecutively subjected to a demineralising solution for 20 minutes, then to one of three treatments under agitation for 1 minute and to a remineralising solution for 7 hours and 39 minutes, three times a day. After each demineralisation, treatment and remineralisation period, the samples were rinsed with deionised water for 6 seconds. Demineralisation and remineralisation solutions were prepared according to the compositions shown in Table 7.2 (15).

The treatments consisted of three silica-based sodium fluoride (NaF) dentifrices (0 ppm F-Group I, 550 ppm F-Group II, 1100 ppm F- Group III). Specimens were treated for a period of 1 minute with dentifrice and water slurries (1 part dentifrice, 3 parts deionized water) to represent the level of dilution that occurs during routine use of toothpaste products. All the solutions were changed daily. After 14 days of cycling, QLF measurements and SMH assessments were performed.

QLF customised system

After treatment, the tape was removed from the specimens which were then washed and dried for 5 seconds before QLF images were captured. A custom QLF set up was employed consisting of blue light-emitting diodes in a ring illuminator emitting light with peak source at 405-nm and a 3-charged coupled device (CCD) colour camera installed with a long-pass yellow filter (495 nm, Schott, Stafford, UK). A 35 mm focal length-imaging lens was used to capture a field of view of approximately 330 mm by 450 mm. The images were captured in a lightproof enclosure using custom software. Video-repositioning software was used to ensure that images were automatically captured when the correlation was higher than 0.90 to ensure consistent capture areas. The difference between the green pixel values on the reference area and the lesion area was divided by the reference area (green pixel values) at baseline and post-treatment. This difference was expressed as a change in fluorescence ΔF %.

Surface Microhardness

SMH measurements were taken with a Knoop diamond at a constant load of 50g applied for 15 seconds using a Buehler Micromet 5105 tester (Buehler, Illinois,

USA). The teeth were placed flat on the translation stage and fixed at a reproducible position within the micro-indentor. Four indentations were made on each specimen during each measurement time point at spacing of approximately 100 microns apart. The Knoop numbers were calculated and averaged at each time point. The outcome of surface microhardness change (ΔHV) was calculated based upon the differences between the Knoop hardness number values at baseline (lesion area) and after treatment.

Statistical analysis

Data were analysed using SPSS-PC (version 19). The variables analysed were:

- Change from baseline in surface hardness (ΔHV)

- Change from baseline in fluorescence (ΔF)

Differences between different treatment groups were tested for significance at the $p<0.05$ level using an analysis of covariance (ANCOVA) using the baseline measurement as a covariate. All three pair-wise comparisons were assessed using a Bonferroni correction for multiple comparisons. The strength of the association between QLF and SMH was evaluated with a Spearman's correlation coefficient.

Results

SMH

There were no statistically significant differences in the baseline of the three groups ($p=0.98$). All groups showed a significant increase in SMH of enamel from baseline to post-treatment (Table 3). The differences between all pair- wise comparisons were statistically significant (I vs. II; $p=0.003$; I vs. III; $p=0.001$; II vs. III; $p=0.001$). The mean percentage mineral changes found in the specimens treated with the three dentifrices are given in Table 7.3. The placebo treatment resulted in 14.9±2.1% remineralisation, the 550-ppm-F dentifrice produced 56.6±9.6% remineralisation, and the 1100-ppm-F dentifrice produced 103.9±9.6% remineralisation with respect to the enamel lesion.

QLF

The results of the QLF measurements are summarised in Table 7.4. There were no statistically significant differences in the baseline of the three groups (p=0.72). Statistically significant differences were detected between all pair- wise comparisons (I vs. II; p=0.002; I vs. III; p=0.001; II vs. III; p=0.006). As expected, specimens in the fluoride groups showed an increase in enamel fluorescence (ΔF values) between baseline and after treatment. Figure 2 shows examples of QLF images at baseline and after treatment. The percentage fluorescence change resulted in increases of 15.6±7.1% for the 0 ppm F, 59.8±11.9% for the 550 ppm F and 85.1±13.2% for the 1100 ppm F dentifrice (p<0.05).

Figures 7.2 show baseline and post-treatment values for QLF. The QLF changes were correlated with the SMH changes (r=0.67) (Fig.7.3).

Discussion

The aim of this study was to compare the ability of QLF and SMH to show differences between toothpastes of different F levels in a remineralisation pH-cycling model. Both systems detected statistically significant differences between both fluoride-containing and non fluoride-containing products within 14 days. The results showed a clear dose response among the dentifrices. To a lesser extent than the F toothpastes, the non-fluoride placebo group also showed mineral gain due to the exposure to the remineralising solution, supersaturated with respect to the enamel.

Results of the SMH clearly demonstrate the ability of the two fluoride-containing dentifrices to significantly harden softened enamel relative to the negative control in a pH-cycling model. QLF was also able to detect mineral changes and correlate well with the increase of surface hardness. The results showed that the percentage of fluorescence change and surface hardness increased linearly with the concentration of fluoride. The analysis reported in this study compared the change in fluorescence intensity of pre- and post-intervention images. Those images can be recorded and repositioned after months suggesting the possibility of longitudinal monitoring of mineral changes as seen *in vivo* (16).

The current results, while preliminary, suggest that QLF can be used in pH-cycling models to evaluate fluoride effect in artificial caries lesions using human enamel. QLF is based on the principle that demineralized enamel scatters both the light entering the lesion and the fluorescence emitted from the dentine. Hence, the lesion is observed as a dark spot (17). QLF will detect any mineral loss but cannot make a differential diagnosis; in such cases the clinical assessment is crucial. The presence of a dentine layer influences the light scattering and the absorption properties of the tooth (18). Therefore, in this study the samples were prepared including a dentine layer beneath the enamel. The demineralisation period (20 minutes) used in this study was designed to simulate the decreased pH occurring after meals. Fluoride treatments were given before and after demineralisation periods. The pH-cycling models attempt to simulate the dynamic conditions that occur in the oral cavity over an extended period of time (19). QLF has the advantage of being a non-destructive method that allows longitudinal analysis of tissues *in vitro*, *in situ* or *in vivo* (20). QLF has also shown the ability to detect and quantify changes of mineral content and size of lesions by demonstrating a dose response between F and non-F dentifrices in short-term clinical trials (11, 13).

In conclusion, the model employed in this study has demonstrated that a system based on fluorescence loss of enamel can detect remineralisation as part of a pH-cycling model comparing different concentrations of fluoride. In future investigations, it might be valuable/informative to compare different fluoride concentrations in a demineralisation pH-cycling model.

Acknowledgements

Authors' contributions

JG contributed to the protocol, experimental design, undertook the study, acquisition of data, analysis and interpretation of data and wrote the manuscript. RPS, BC, AR, contributed to the experiment. IAP contributed to the protocol and to the manuscript. RE contributed to the protocol, experimental design and to the manuscript.

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Table 7.1. pH-Cycling regime

Treatment	Time
Rinse	6 seconds
Demineralisation	20 minutes
Rinse	6 seconds
Treatment	1 minute
Rinse	6 seconds
Remineralisation	7:39 hours

Conduct 3x/day

Repeat for 13 additional days

Table 7.2. Composition and elements used in the pH-cycling model

Samples	Human enamel
Size per group	12
Groups	0 ppm NaF, 550 ppm NaF, 1100 ppm NaF
Demineralising Solution	Calcium: 2.0 mmol/L $\quad$ Ca(NO$_3$)$_2$ 4H$_2$0 $\quad$ 0.47 g/L Phosphate: 2.0 mmol/L $\quad$ KH$_2$PO$_4$ $\quad$ 0.27 g/L Acetic Acid: 75 mmol/L $\quad$ CH$_3$COOH $\quad$ 4.50 g/L pH 4.4 (adjusted with 50% NaOH)
Remineralising Solution	Calcium: 1.5 mmol/L; $\quad$ Ca(NO$_3$)$_2$ 4H$_2$0 $\quad$ 0.35 g/L Phosphate: 0.9 mmol/L; $\quad$ KH$_2$PO$_4$ $\quad$ 0.12 g/L KCl: 130 mmol/L; $\quad$ KCl $\quad$ 9.69 g/L PBS: 100 ml/L pH 7.0 (adjusted with concentrated HCL)
Diluent	Deionized Water
Treatment	1 minute 3x/day for 14 days
Evaluation	QLF SMH

Table 7.3. Change from baseline in Surface Microhardness and mean differences

Groups	Baseline (KHN)	Final (KHN)	ΔHV	% Change
0 ppm F	93.9±8	107.6±8.8	13.6±1.9[a]	14.9±2.1*
550 ppm F	92.5±7.5	138.8±7.56	46.4±5.6[a]	56.6±9.6*
1100 ppm F	92.1±6	181.7±10.6	89.6±9.2[a]	103.9±14.6*

Data is described as means ± standard errors
KHN: Knoop Hardness number
[*]Statistically significant difference compared with baseline (p=0.001).

Table 7.4. Change in fluorescence values and mean differences

Groups	Baseline	Final	ΔF	% Change
0 ppm F	28.6±3.3	25.7±3	2.9±1.7	15.6±7.1*
550 ppm F	20.2±4.4	6.5±4.8	13.8±2.4	59.8±11.9*
1100 ppm F	24.3±4.5	0.96±4.6	23.2±3.2	85±13.2*

Data is described as means ± standard errors

*Statistically significant difference compared with baseline (p=0.001)

Figure 7.1. Flowchart of the study design
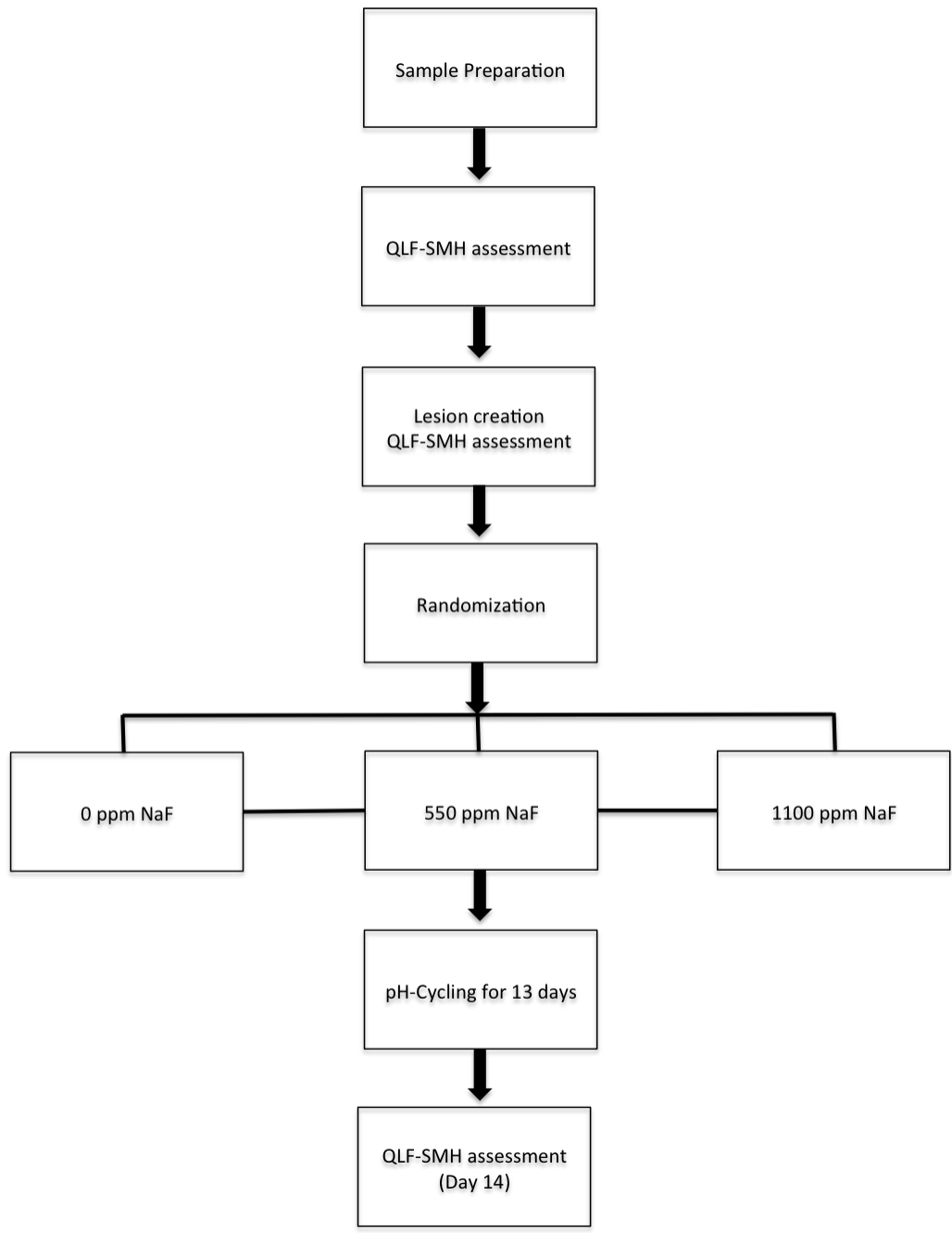
Figure 7.2. Examples of QLF images at Baseline and after treatment
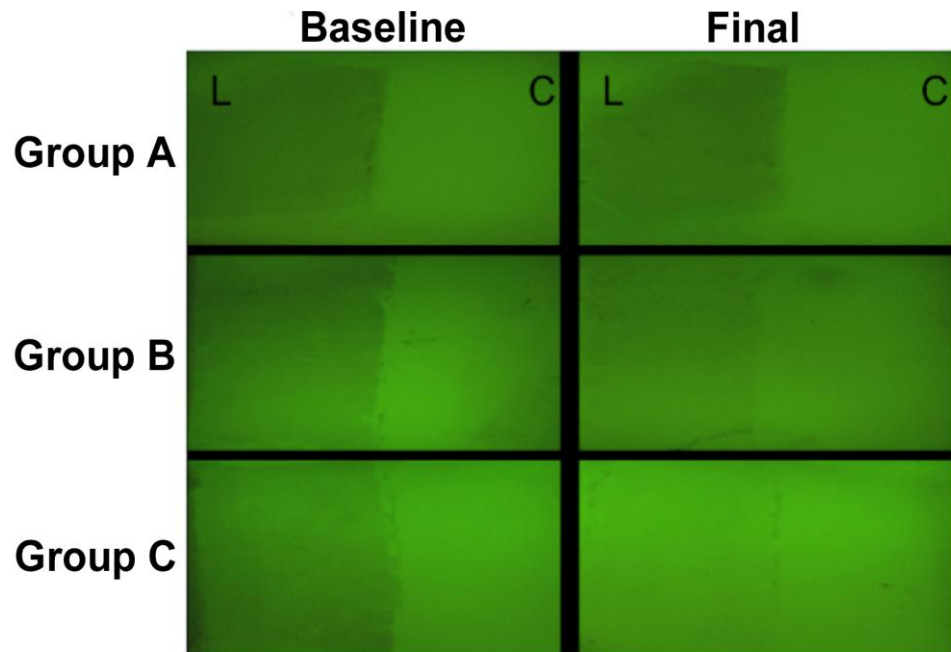
Figure 7.3. Plot of SMH values versus mean change (%) in fluorescence
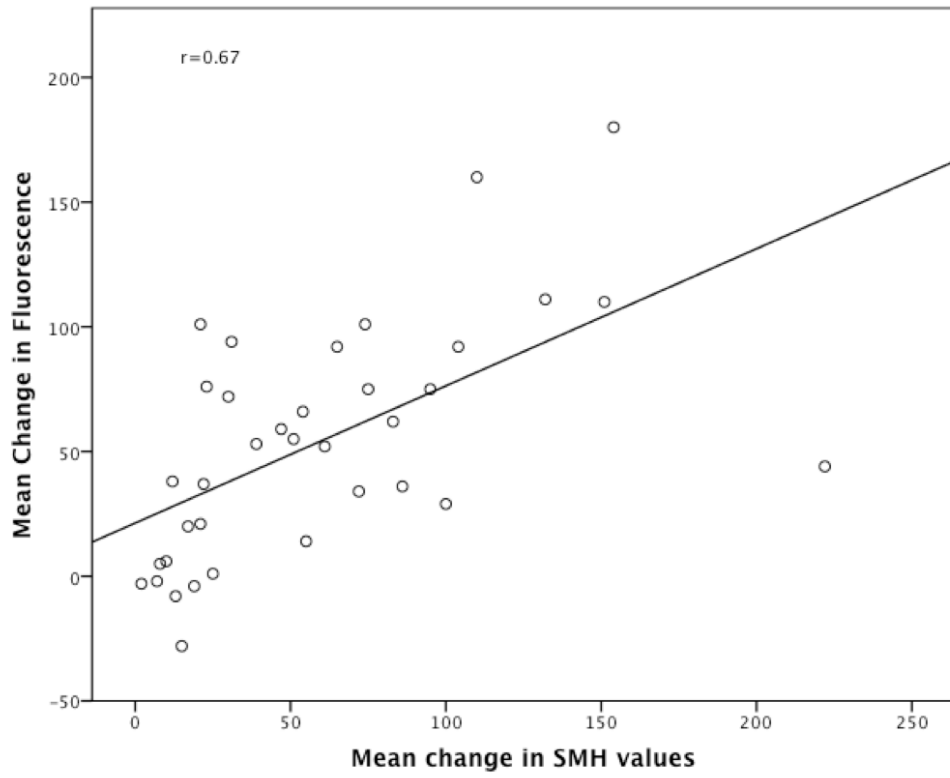
CHAPTER 8

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Use of QLF to Assess Enamel Mineral Changes in a pH Cycling Study

Use of QLF to assess enamel mineral changes in a pH cycling study

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Rationale Paper VII

As explained in the rationale of the previous chapter, pH-cycling models can be classified into reversal (remineralising) or progression (demineralising). This second pH-cycling experiment consisted on a demineralising model using sound substrate and the response was the potential of the dentifrice to reduce loss of mineral. Therefore, the purpose of this study was to test the ability of QLF to measure mineral changes after a demineralisation model.

Abstract

Objectives: This study assessed the ability of Quantitative Light-induced Fluorescence (QLF) and Surface Microhardness (SMH) to measure mineral changes after a pH-cycling model comparing two NaF toothpastes (550-ppm F and 1100-ppm F) and a fluoride placebo. **Methods:** Human sound enamel specimens (n=45) were randomly divided into 3 groups and submitted to a pH-cycling model for 14 days consisting of 6 hours of demineralisation, 16 hours of remineralisation and two treatments (1 minute) per day. The treatments consisted of three silica-containing dentifrices (0 ppm F, 550 ppm F, 1100 ppm F). Enamel mineral loss or gain was assessed by QLF and SMH. The outcome variables were: change from baseline in surface hardness (ΔZ) and percentage change from baseline in fluorescence from baseline ($\Delta F\%$). An analysis of covariance (ANCOVA) explored differences between different treatment groups ($p<0.05$ level). Associations between QLF and SMH were evaluated using Spearman's correlation coefficient. **Results:** The pH-cycling model showed a fluoride dose response reducing enamel demineralisation. The percentage SMH changes were $90.5\pm0.77\%$, $72.2\pm1.8\%$ and $62.8\pm2.6\%$ for the 0, 550 and 1100-ppm F dentifrices, respectively. The percentage fluorescence changes were $28.5\pm4.6\%$, $5.9\pm3.2\%$ and $-14.2\pm7.8\%$, respectively. The differences between all pair-wise comparisons were statistically significant for both methods at 14 days ($p=0.001$). QLF correlated with SMH (0.76). **Conclusions:** It was concluded that both techniques demonstrated a significant F dose response and they can be used to measure mineral changes after a pH-cycling demineralisation model. **Clinical significance:** The results of this study suggest that using QLF may facilitate the detection and quantification of early caries lesions in clinical practice.

Key words: Fluoride, Demineralization, Quantitative Light-induced Fluorescence, Surface Microhardness,

Introduction

The changes in the incidence and progression of dental caries and the biological understanding of the caries process have encouraged new strategies to control and prevent the disease at an early stage. Most clinical trials evaluating oral care products effectiveness, typically only use cavitated lesions as the primary outcome (1). However, non-invasive methods have been developed as potential detection aids for clinicians by facilitating the detection and quantification of early caries lesions (2). One of those systems, Quantitative light-induced fluorescence (QLF) is based on the measurement of fluorescence loss following enamel demineralisation (3). One of the major advantages of QLF over other technologies such as TMR or SMH is the ability of monitoring lesion progression and reversal of caries lesions using a non-destructive methodology (4). QLF also confers other benefits including remote analysis, repeated analyses, and archiving of image data.

In vitro protocols assessing anti-caries treatments are still widely used (5) and have the ability to show a dose response to different levels of fluoride inhibiting demineralisation or promoting remineralisation (6). The ability to carry out experiments under controlled conditions provides an advantage in testing fluoride efficacy (7) and these approaches can also be useful to assess the ability of caries detection instruments to detect mineral changes.

With pH cycling models, samples are cycled between a demineralising and a remineralising solution that mimic intraoral conditions and treated daily with oral care products. In principle, in vitro pH-cycling models can be classified into progression (demineralising) or reversal (remineralising) (7). Demineralisation models usually employ sound substrate and the response is the potential of the dentifrice to reduce the loss of mineral from the substrate to the demineralising solution or the gain of mineral from the remineralising solution. In remineralising models artificial carious lesions are formed and the response variable will be the gain of minerals (8).

The aim of this study is to build on previous findings on the dose response of two fluoride treatments 550-ppm, or 1100 ppm NaF and a fluoride placebo dentifrices

and to test the ability of Quantitative Light-induced Fluorescence (QLF) and Surface Microhardness (SMH) to measure mineral changes after a 14 days pH-cycling model.

Methods

Human extracted teeth were collected from dental surgeries located in the state of New Jersey, USA. Informed consent was obtained from the patients before the extractions prior to tooth collection. The teeth were stored in 10% (v/v) neutral phosphate buffered formalin for a minimum of two weeks. The selected teeth did not have any developmental defects, cracks or white spot lesions. Figure 8.1 illustrates the study design employed.

Human extracted teeth were cut into three or four parts with a water-cooled diamond saw. Forty-five slices were obtained and ground flat with a 15μm Diamond polishing disk (Buehler, Illinois, USA). QLF images were taken at baseline and used as reference area for the analysis. Specimens were randomised based on the Surface Knoop hardness number (KHN) to achieve balanced groups. The KHN mean of the sound enamel blocks was 375.8±55.8 KHN.

One-adhesive strip was attached to one side of the sample so that an area of 12 mm2 (approx.) was exposed. During the evaluations, specimens were kept in 100% relative humidity at 4°C. The specimens were air-dried for 5 seconds with compressed air fixed at 10 cm from the teeth before QLF and SMH assessment.

pH-Cycling

The forty-five specimens (15 per group) were exposed to a pH-cycling regimen as follows (Table 8.1): - Demineralisation for 6 hours in a solution containing 2 mM $Ca(NO_3)2 \cdot 4H_2O$, 2mM KH_2PO_4, 75 mM CH_3COOH. The pH was adjusted to 4.4 with with 50% NaOH; - Remineralisation for 16 hours overnight in a mineralising solution containing 1.5 mM $Ca(NO_3)2 \cdot 4H_2O$, 0.9 mM KH_2PO_4, 130 mM KCl and 20 mM $NaC_2H_6AsO_2 \cdot 3H_2O$ at 37°C (pH was adjusted to 7 with concentrated HCL) and two treatments per day in each per group. The treatments consisted of three silica-based sodium fluoride (NaF) dentifrices (0 ppm F, 550 ppm F, 1100 ppm F).

Specimens were treated for a period of 1 minute under agitation with dentifrice and water slurries (1 part dentifrice, 3 parts deionized water) to represent the level of dilution that occurs during routine use of toothpaste products. The samples were rinsed with deionized water for six seconds after each demineralisation, treatment and remineralisation period. The model used in this study was similar to the one proposed by ten Cate (1988) and Stookey (2011) (9, 10). All the solutions were changed daily. Assessments were performed at day 5 for QLF and at day 14 for QLF and SMH.

QLF Measurements

The samples were washed with deionized water and dried for 5 seconds before the QLF images were captured. A custom QLF set up was employed consisting of blue light-emitting diodes in a ring illuminator emitting light with peak source at 405-nm and a 3-charged coupled device (CCD) colour camera installed with a long-pass yellow filter (495 nm, Schott, Stafford, UK). A 35 mm focal length-imaging lens was used to capture a field of view of approximately 330 mm by 450 mm. The images were captured in a lightproof enclosure using custom software. Video-repositioning software was used to ensure that images were automatically captured when the correlation was higher than 0.90 to ensure consistent capture areas. The difference between the green pixel values on the reference area (baseline) and the green pixel values on the following assessments area was divided by the reference area (green pixel values) at baseline and post-treatment (Day 5 and Day 14). This difference was expressed as a change in fluorescence ΔF %.

Surface Microhardness assessments

SMH measurements were taken with a Knoop diamond at a constant load of 50g applied for 15 seconds using a Buehler Micromet 5105 tester (Buehler, Illinois, USA). The teeth were placed flat on the translation stage and fixed at a reproducible position within the micro-indentor. Four indentations were made at 100 μm apart on each specimen. The four Knoop numbers were calculated and averaged at each time point. The outcome of surface microhardness change (ΔHV) was calculated based upon the differences between the Knoop hardness number values at baseline (sound enamel) and after 14 days.

Statistical analysis

Data were analysed using SPSS-PC (version 20). The variables analysed were change from baseline in surface hardness (ΔHV) and change from baseline in fluorescence (ΔF). The strength of the association between QLF and SMH was evaluated with a Spearman's correlation coefficient. Differences between different treatment groups were tested for significance at the $p<0.05$ level using an analysis of covariance (ANCOVA) using the baseline measurement as a covariate. All three pair-wise comparisons were assessed using a Bonferroni correction for multiple comparisons.

Results

It was found that QLF changes were correlated with the SMH changes (r=0.76) (Figure 8.2). QLF and SMH both showed that fluoride treatments were significantly more effective in preventing mineral loss ($p<0.001$) in a dose response manner. There were no statistically significant differences at baseline between the three groups (p=0.72).

For the QLF assessment at day 5 (Table 8.2) there were statistically significant differences between the 1100ppm F and 0ppm F (p=0.001) and the 550 and 0ppm F (p=0.002) but the difference between the two fluoride-containing toothpastes was not statistically significant (p=0.86).

For the QLF assessment at day 14 (Table 8.3) there were statistically significant differences between the 1000ppm F and 0ppm F (p=0.001), between the 550 and 0ppm F (p=0.02) and between the 550ppm F and the 1100ppmF (p=0.02). Specimens in the fluoride groups showed less loss of enamel fluorescence (ΔF values) between baseline and after treatment (Figure 8.3). The percentage fluorescence loss from baseline resulted of 28.5±4.6% for the 0 ppm F, 5.9±3.2% for the 550 ppm F and -14.2±7.8% for the 1100 ppm F dentifrice (p<0.05).

For the SMH assessment at day 14, all groups showed a significant difference in SMH of enamel from baseline to post-treatment (Table 8.4). There were no statistically significant differences in the baseline of the three groups (p=0.84).

Statistically significant differences were detected for all pair-wise comparisons (0 ppm F vs. 550 ppm F; p=0.0001; 0 ppm F vs. 1100 ppm F; p=0.0001; 550 ppm F vs. 1100 ppm F; p=0.001). The percentage (SE) of surface microhardness loss was 90.5±0.77, 72.2±1.8 and 62.8±2.6 for the 0 ppm F. 550 ppm F and 1100 ppm F, respectively.

Discussion

The present study used a pH cycling model in order to investigate the effect of fluoride dentifrice treatment on remineralisation and the ability of QLF and SMH to detect mineral changes in vitro. As evidenced in Tables 3 and 4, NaF dentifrices significant reduced enamel demineralisation and were effective in limiting caries progression in vitro. As expected, the enamel on the fluoride placebo group was the most demineralized. The final fluorescence difference with respect to the sound enamel was higher for the placebo group (37.1%) than for the 550 ppm F (11.2%) and for the 1100 ppm F group (4.2%). This results accords with Featherstone et al. (1988) and Walsh (2010) showing that inhibition of lesion progression responded in a linear response relationship to fluoride concentration (11, 12). Previous studies using similar demineralisation models have concluded that fluoride treatments had a marked effect on the inhibition of lesions formation (8, 9). Therefore, the results of this study showing little or no demineralisation for the fluoride dentifrice treatment groups.

The large standard deviation found for SMH values can be explained by the fact that human samples are often affected by fluoride history, conditions within the oral environment, time since extractions and age of the samples (13), despite this fact, the use of human samples implies a greater clinical relevance within an in vitro design. Surface microhardness assesses the amount of mineral loss or recovery at the enamel surface (6). This method has been used for the quantification of early caries lesions in vitro (14-16) but has not been recommended to use in deep lesions (17, 18). Change in hardness values is a function of variation in lesion surface resulting from progression or regression of carious lesions. SMH has been correlate with TMR (19) an with calcium loss, lesion depth and mineral content in early lesions (18) and typically in vitro studies deal with shallow lesions (20).

The data from this study support data from previous studies comparing QLF vs. TMR (4, 21) demonstrating the ability of QLF to measure mineral changes. Applications of QLF are found in the testing of products designed to inhibit demineralisation and promote remineralisation of caries in vivo, in situ and in vitro (5). This experiment is a variation of the Featherstone pH cycling model using SMH instead of CSMH. The Featherstone model was designed to produce similar results to those in a human lesion formation (10). It was surprising to find that fluorescence final values were very similar to sound baseline values for the 550-ppm F and the 1100-ppm F group. Despite the ability of QLF to detect very early mineral changes, and its use as a standard reference measure in clinical tests of the efficacy of preventive measures (22, 23), it is important to bear in mind that QLF will detect any demineralisation as a loss of fluorescence. In such cases the importance of clinician assessment is crucial (2). In conclusion, the present study has shown that QLF can be accurate measure mineral changes and can be a valuable tool in studying lesion de-remineralisation. However, the combination with other methods can be useful to understand better the properties of the lesions.

Acknowledgements

Authors' contributions

JG contributed to the protocol, experimental design, undertook the study, and acquisition of data, analysis and interpretation of data and wrote the manuscript. IAP and RE contributed to the manuscript.

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Table 8.1. pH-Cycling regime

TREATMENT	TIME
Rinse	6 seconds
Treatment	1 minute
Rinse	6 seconds
Demineralisation	6 hours
Rinse	6 seconds
Treatment	1 minute
Mineralizing solution	16 hours

Repeat for 14 days

Table 8.2. Change in fluorescence values and mean differences at 5 days

Groups	Baseline	5 days	Final Difference	ΔF% Change
0 ppm F	127.7±6.6	78.4±4.2	49.4±6.4	37.1±3.8*
550 ppm F	118.9±5.2	103.6±5.1	15.3±6.6	11.2±5.3*
1100 ppm F	120±5.5	113.1±7	6.8±6.3	4.9±5*

Data are described as Means ± standard errors
*Statistically significant difference compared with baseline (p=0.001)

Table 8.3. Change in fluorescence values and mean differences at 14 days

Groups	Baseline	Final	Final Difference	ΔF% Change
0 ppm F	127.7±6.6	88.2±4.2	39.5±7.53	28.5±4.6*
550 ppm F	118.9±5.2	110.2±3	8.6±4	5.9±3.17*
1100 ppm F	120±5.5	137.4±11.8	-17.5±9.7	-14.2±7.8*

Data are described as Means ± standard errors
 *Statistically significant difference compared with baseline (p=0.001)

Table 8.4. Change from baseline in Surface Microhardness and mean differences

Groups	Baseline (KHN)	Final (KHN)	Final Difference	% Change
0 ppm F	362.8±13.1	33.6±2.2	329.2±13.4	90.5±0.77*
550 ppm F	381±14.1	103.1±4.9	277.9±16.6	72.2±1.8*
1100 ppm F	371.9±15	135.8±8.9	236±18.2	62.8±2.6*

Data are described as mean (SE); KHN: Knoop Hardness number
*Statistically significant difference compared with baseline (p=0.001)

Figure 8.1. Flowchart of the study design
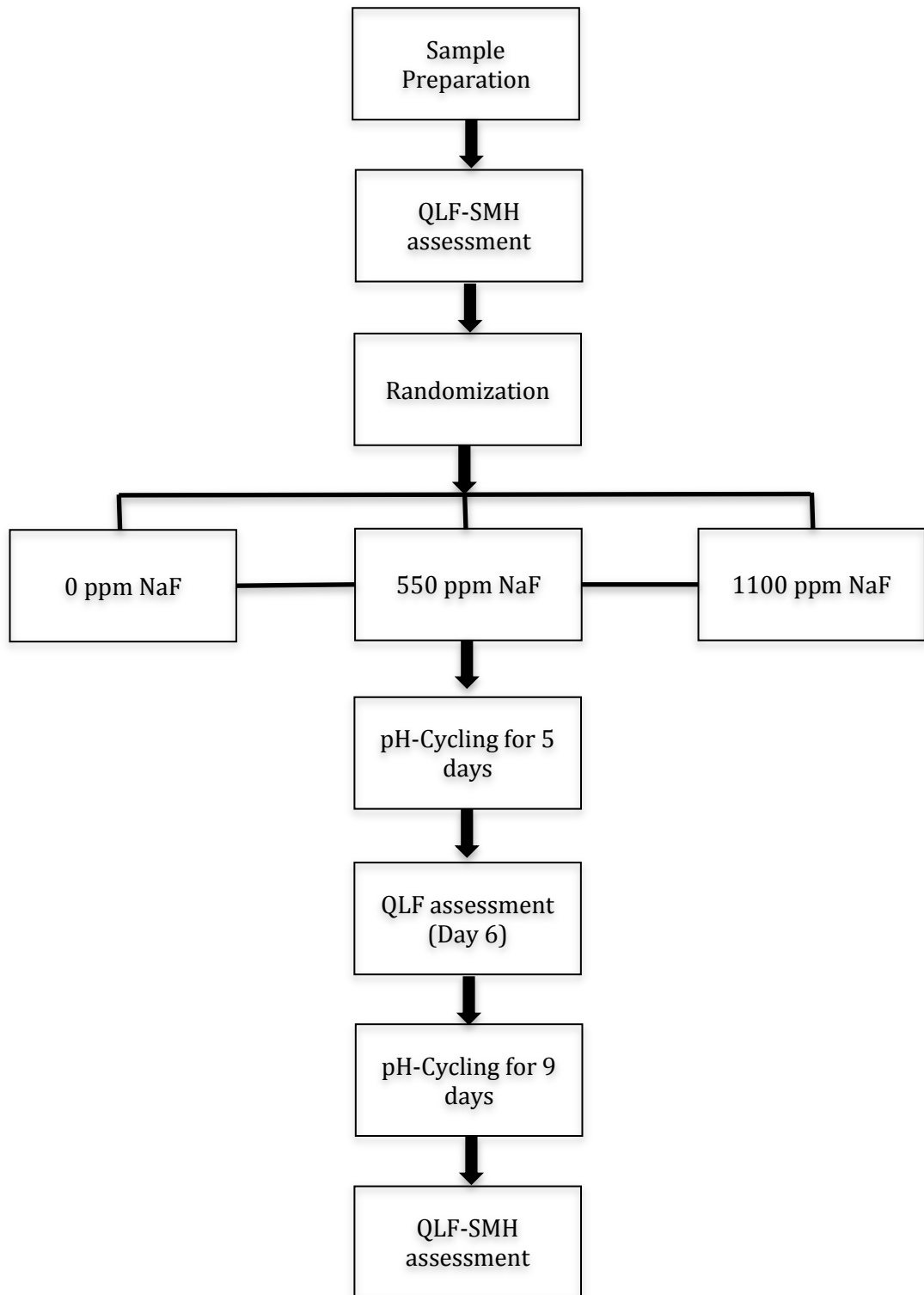
Figure 8.2. Scatter plot of SMH values and mean changes of fluorescence (%) (QLF)
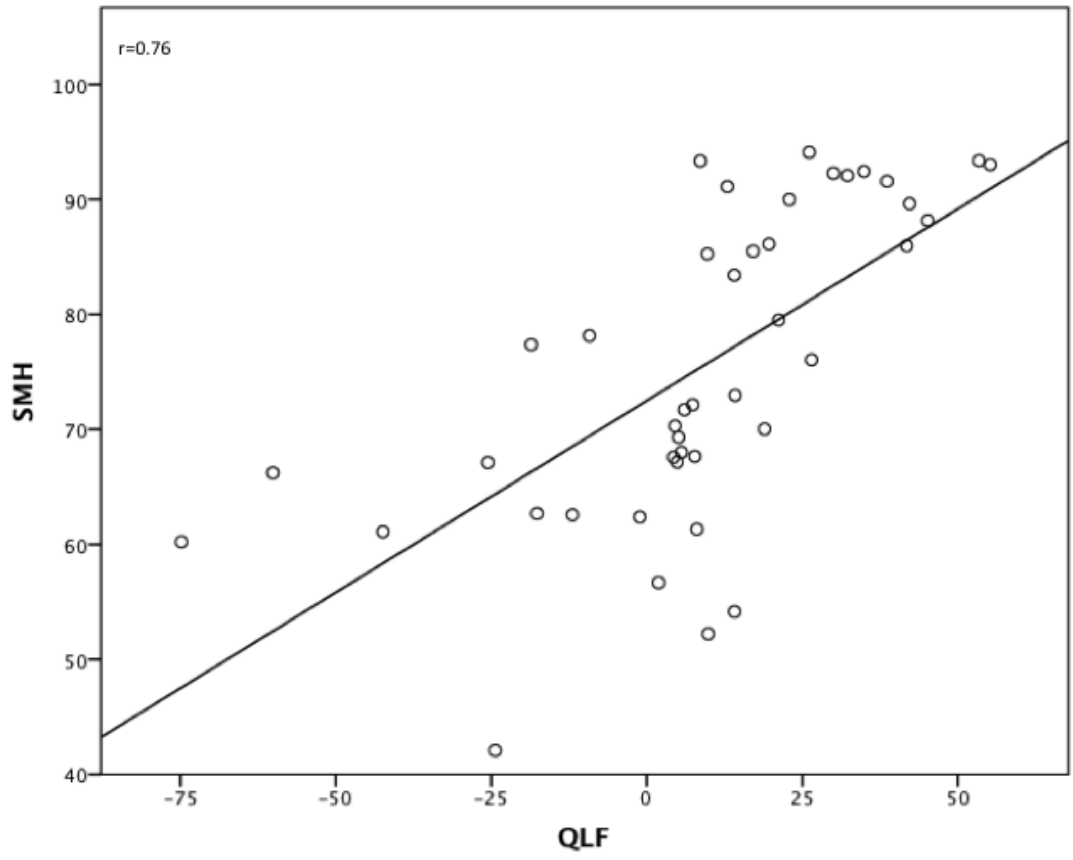
Figure 8.3. Examples of QLF images at Baseline and after 14 days
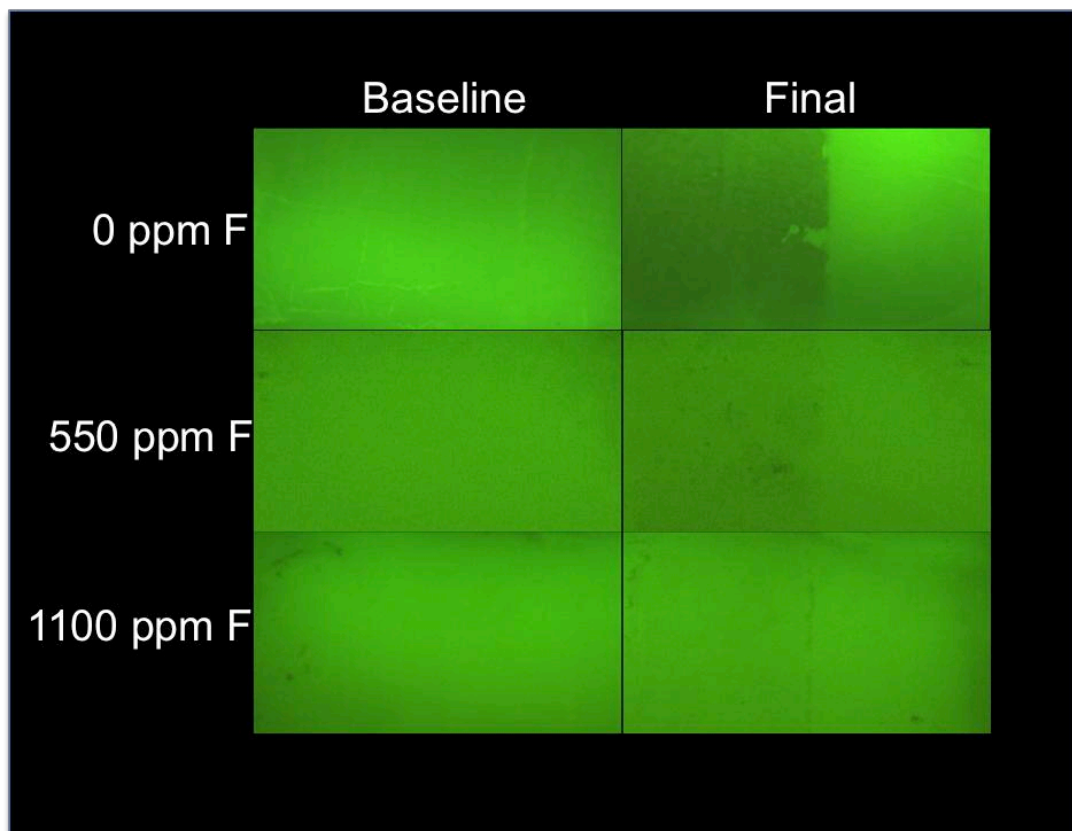
Group A=0 ppm F; B=550 ppm F; 1100 ppm F. (L= artificial carious lesion area; C=coated area)

CHAPTER 9

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Dentist's Perspectives on Caries-Related Treatment Decisions

Dentist's Perspectives on Caries-Related Treatment Decisions

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Rationale Paper VII

Are dentists doing what they should be doing? It was important to understand dentist's caries-related decisions in terms of: consideration of individual patient caries risk for the treatment decision; threshold and types of lesions dentists decide to treat (both preventive and operative) and monitoring of the treatment (recall interval). The purpose of this study was to determine if the biological basis of early caries is understood by practicing dentists and if so, is this translated in treatment decisions that reflect the medical model.

Abstract

The aim of this study was to assess Colombian dentists' caries related treatment decisions on early to intermediate caries lesions (ICDAS code 2 to 4). **Methods:** A web-based questionnaire to assess the views of dentists' caries related caries management of early/intermediate caries lesions was developed. The questionnaire included questions on demographic characteristics, five clinical scenarios with randomized levels of caries risk, and two questions on different Clinical (C) and Radiographic (R) thresholds images. **Results:** A total of 439 dentists answered the questionnaire. For the scenarios describing occlusal lesions ICDAS code 2 (Scenarios 1 and 2), dentists chose to provide a preventive option in 63.1% and 60.1% of the cases, respectively. For the approximal lesion ICDAS code 2 (Scenario 3) the majority of dentists chose to restore (81.1%). The main findings of the binary logistic regression analysis for the clinical scenarios suggest that for the ICDAS code 2 occlusal lesions, the odds of a high caries risk patient having restorations is higher than for a low caries risk patient. For the following questions describing different caries clinical thresholds images, the majority of dentists will restore at ICDAS code 2 (54.9%) and for the question showing different radiographic thresholds images, the majority of dentists will intervene operatively at the inner half of enamel (R2) (65.4%). No significant results were found for these questions with the logistic regression. **Conclusion:** The results of this study indicate that Colombian dentists have not yet fully adopted conservative treatment for early caries lesions.

Key words: Caries detection, Clinical decision-making, treatment thresholds, caries management.

Introduction

Current evidenced-based caries management strategies are based on a biological understanding of the disease process, new approaches in caries detection, assessment and therapeutic interventions targeted at early non-cavitated lesions. This paradigm requires changes in caries-related treatment decision-making within the dental workforce if the advantageous outcome of prevention is to be realised (1).

Previous systematic reviews have highlighted the inability to accurately identify early caries lesions and the need for a change in the system with respect to the non-surgical management of non-cavitated lesions (2-4). Unfortunately, this approach has not been universally adopted often due to remuneration and incentive systems based on rewards for restorative treatments and the inability for dentists to detect lesions at an early stage (5).

One of the most important activities in dental clinical practice is making decisions. However, a wide variation in management decisions among dentists has been reported. The decision-making process of how dentists choose the most appropriate therapeutic strategy is not well known and it is influenced by several factors, including learned concepts, years of experience, public and private practice among others (6).

The diagnosis process is based on how a clinician can unify diverse information into clinical pictures (7) using a specified memory structure leading to clinical elucidation (8). It has been suggested that during examination, dentists use caries scripts as a process of pattern recognition (9). In dentistry the decision-making process can be divided in three separate stages. The first is the detection phase where a disease is identified. The second stage involves a decision about intervention based on a previous diagnosis. The third phase is the selection of the treatment from among different options but mainly the choice between two types of treatment: operative and non-operative (10).

Based on the diagnosis and risk assessment, the clinician then considers various alternatives including patient and practitioner preferences (11). However, sometimes

the alternatives are not evidence-based but rather economical constraints (12). Evidently, clinicians want to provide effective treatments; patients want to be involved in the treatment decisions and health or insurance systems need to know for what are they paying for and if these measures are effective to reduce the costs of treatment (13). The clinical decision-making is a "social process", where the dentist, the patient and in some countries the insurers are involved (14).

The aim of this study was to describe the management decisions for early caries lesions among Colombian general dental practitioners (GDPs) in terms of: consideration of individual patient caries risk for the treatment decision; threshold and types of lesions dentists decide to treat (both preventive and operative) and monitoring of the treatment (recall interval). The influence of dentists' characteristics such as gender and date of graduation in the practitioners' treatment decisions was also explored.

Methods

A cross sectional, observational study was conducted among General dental practitioners in Colombia.

Questionnaire
A web-based questionnaire to assess the views of GDPs on management of early caries lesions was developed.

The photographs chosen for the questionnaire were scored using the International Caries Detection and Assessment System (15) by two trained ICDAS examiners (SM, JG). The questionnaire was validated in 2012 in terms of understanding, content, and language, first by the Preventive Dentistry Faculty from University of Manchester and subsequently by GDPs in Manchester. Then, the questionnaire was a forward translated from English into Spanish by two bilingual individuals, who worked independently of each other. Second, the two initial Spanish versions were compared and revised through a consultation process involving a review committee. After this process, the questionnaire was reviewed by the Caries Research Unit from Universidad El Bosque and tested in a target population using a convenience sample

of 59 GDPs to ensure that it was comprehensible and acceptable. After the piloting process, specific details on the questionnaire were adjusted based on outcomes of the feedback provided by the practitioners. The revision included easing the interpretation of the questions, summarizing treatment options, offering fewer options and removing two clinical scenarios.

In Colombia there were 28.310 dentists in 2000 and a reported relationship of 0,69 dentists for 1.000 inhabitants in 2000 (16). Taking into account that in Colombia there is a constitutional right for people to be asked and give permission to be included in database systems (Law 1581, 2012) (17) there are no public data bases to access dentists. Thus, a convenience sample was selected from the Colombian GDPs Colgate Database, which is composed of 8725 dentists distributed among 6 cities. A convenience sample was selected from the Colombian GDPs Colgate Database, which is now the biggest dentist's database in Colombia. The obtained sample was compared to the Colgate GDPs Database (Table 9.1). convenience sample was selected from the Colombian GDPs Colgate Database. The obtained sample was compared to the Colgate GDPs Database (Male (30.7%)/Female (69.3%), Date of graduation: <2000 (60.9%) or ≥2001 (39.1%) and Type of practice; public (10.2%) or private (89.8%). The sample was weighted to get and increase in the number of older dentists. The GDPs were approached by the Colgate Oral Care Consultants (OCCs) and were explained the objectives and the voluntary and anonymous nature of the study. GDPs, who were willing to participate, were asked to record on an iPad, preventive and/or restorative treatment options for different clinical scenarios and recall intervals. This descriptive study was limited to a single visit that lasted no more than 10 minutes.

The questionnaire consisted of three sections. The first section consisted of information on demographic characteristics of the dentists, including city, graduation year, university, gender and type of practice. The second section contained five clinical scenarios represented by photographs with two different levels of risk (Figure 1A): -'Low risk' defined as no new caries lesions or a recent history (within 3 years) of restorations without any risk factor associated or -'High risk' described as one or more new caries lesions at any severity and 2 or more risk factors associated: i.e. white spots on smooth surfaces, visible heavy plaque, frequent snacks (> 3x daily

between meals), inadequate saliva flow. Scenario 1, 2 and 3 (ICDAS code 2), involved demineralization in the inner half of enamel. Scenario 4 (ICDAS code 3) and Scenario 5 (ICDAS code 4) involved demineralization in the outer third of dentine. The first question of the Clinical Scenarios referred to treatment options: - Watch and wait until the next control; - Enhanced oral health instructions; - Fluoride varnish; - Seal and follow-up; - Open fissure and place a sealant restoration; Provide resin-based composite; - Provide amalgam. For the Scenario 3 the option 'Open fissure and place a sealant restoration' was not available. The second question consisted on recall intervals where practitioners were asked when they would like to see the patient again (less than 3 months, 3 months, 9 months or 12 months). The third section consisted of photographs (Figure 1B) and radiographs (Figure 1C) at different caries thresholds. The clinical thresholds were: C1-Sound; C2-ICDAS code 2: C3-ICDAS code 2; C4-ICDAS code 3, and C5-ICDAS code 4. The radiographic thresholds were radiolucency at: R1-outer half of enamel; R2-inner half of enamel until the EDJ (enamel-dentine junction); R3-external third of dentine; R4-middle third of dentine. The treatment options for this section were divided into Preventive (Topical fluoride or Sealant) and Operative (Resin-based composite or Amalgam) and an open space for 'Other options' where the participants were able to express other preferences. For the clinical scenarios and for the radiographic and clinic thresholds, respondents were asked to choose from preventive or/and restorative options.

The total pool of dentists in the sample frame was 8725. A sample size of 385 would be needed assuming response prevalence of 50% in the population with a 95% level of confidence. To calculate the standard error, we have divided the confidence interval by 1.96 (approximate value of the 97.5 percentile point of the normal distribution). We have estimated the proportion of responders to each question at 50% and calculated the sample size using $N= P (100\% - P)/(SE)^2$. Where N is the sample size, P is the population prevalence and SE is the standard error.

Statistical Analysis

The data obtained from the answers of the questionnaires was exported into an excel file and exported to SPSS (version 19) for analysis. Binary logistic regression models were fitted to the data to calculate odds ratios (OR) and confidence intervals (95%

0The independent variables for the model were risk, gender and date of graduation. Date of graduation was dichotomised using the median date of graduation as the point of dichotomisation. The binary logistic regression model was used to calculate the association of the independent variables with the dependent variable (type of treatment). Chi-square test was used to test for significant differences between the recall intervals and the individual caries risk (p<0.05).

Results

Four hundred and ninety three practitioners were approached to participate in the study and 439 (89%) accepted to participate. They were distributed among six Colombian cities.

The majority of respondents were females (69.2%). The largest group of dentist were in private practice (68.1%), followed by mixed practice (24.1%) and public practice (7.7%). Most of the practitioners were located in medium socio-economic areas (73.1%) followed by high (21%) and low (5.9%). Regarding the groups by date of graduation, 52% graduated in 2001 or after and 48% before 2001.

For the Scenarios describing occlusal lesions ICDAS code 2 (Scenario 1 and Scenario 2), the dentists chose to provide a preventive treatment in 63.1% of the cases for the Scenario 1 and in 60.1% for Scenario 2, and for Scenario 3, they chose to restore the approximal lesions ICDAS code 2 in 81.1%. The results for the Scenarios 1 to 5 by risk are described in Table 1. For the question describing different caries clinical thresholds, the majority of dentists would restore at ICDAS code 2 (C3) (54.9%), and for the question on radiographic thresholds, the majority of dentists would intervene operatively at the inner half of enamel (R2) (65.4%) (Figure 2).

The main findings of the binary logistic regression analysis suggest that the odds of a high caries risk patient having restorations is higher than for a low caries risk patient with a pooled OR for ICDAS code 2 (Scenario 1) of 1.89; (95% CI 1.21-2.81; p=0.002), for ICDAS code 2 (Scenario 2) of 1.61 (95% CI 1.09-2.37; p=0.01), and for ICDAS code 3 (Scenario 4) of 1.92 (95% CI 0.43-0.96; p=0.001) (Table 2).

Logistic regression analyses, regarding influences of gender on treatment decisions are not significant. Date of graduation seems to have an influence only on the ICDAS code 3 (Scenario 4). The odds of a patient having a restoration is 1.55 times higher if the dentist was graduated before 2001. No significant results were found for the questions on clinical and radiographic thresholds using the regression analysis.

The results for the recall intervals by risk are described in Figure 3. The majority of dentists would see the patient again in 3 or 6 months. There were only statistical significant differences on the recall intervals by risk in the Scenario 5 (ICDAS code 4) (p=0.004). Further Chi-squared tests looking at differences between 3 and 6 months recall intervals revealed statistical significance for S5 showing a preference for a 6 months interval (p=0.01).

Discussion

The questionnaire used in this study described caries related treatment decisions among Colombian dentists. The results of this study showed that the majority of dentists did not always based their treatment decisions depending on individual caries risk. Only scenarios representing occlusal lesions ICDAS code 2, were found to have significant differences on treatment preferences depending on individual risk status. In this study, high caries risk scenarios were associated with an increase of tendency to restore. These results suggest that risk is not been taking into account when making decisions on approximal lesions (Scenario 3) where the only approach seems to be the operative intervention. Assessing a patient's risk of developing caries is a vital component of the caries management (18). Evidence suggests that assigning therapeutic regimens to individuals according to their risk levels should yield a significantly greater probability of success and better cost-effectiveness than applying identical treatments to all patients independent of risk (19).

For the occlusal ICDAS code 2 lesions, the majority of practitioners felt that the best options were preventive interventions. However, on the question of approximal lesions (clinically and radiographically), most of dentists would fill an approximal lesion whose radiolucency was confined to an ICDAS code 2 (Scenario 3) (79.3%) and at the EDJ in the radiographic images (65.4%). This finding supports previous

research showing that dentists would restore when there is evidence of radiolucency at the enamel-dentine junction (20-22). However, other preventive options such as fluoride varnish, proximal sealing and proximal infiltrants may be available for non-cavitated approximal lesions (23, 24).

Even if the majority of dentists would choose a preventive option for the occlusal ICDAS code 2 lesions (Scenario 1=63.1%; Scenario 2=60.1%), still a large number of dentists would undertake operative treatment when it could be considered inappropriate. When dealing with occlusal caries clinicians should follow the 'if in doubt seal' strategy [Deery, 2013 #2060] as part as a conservative management approach. Overtreatment was one of major issues found in this study; premature or unnecessary restoration eliminates the chance for remineralisation and does not necessarily reduce the caries risk of patients, entering them instead into a restorative cycle (19). The decision on when to intervene is crucial since any restoration is permanent and they all have a limited lifetime. For restorative treatment, a substantial amount of sound tissue needs to be removed; once the tooth is been restored for the first time, it will enter in circle of treatment, known as a 'death spiral of restorations' (25). Therefore, to ignore non-operative treatment can be considered biologically illogical and ethically unacceptable (26). For many years, dentists have been oriented to a restorative approach preferring to treat rather than control caries. Trends in recent decades have been trying to discriminate between early lesions that need preventive interventions and lesions where operative care is advised. Despite a better understanding of the caries process based on a biological approach, there has been a failure to implement comprehensive caries management into the clinical practice in many countries (27).

The recall interval results are complex; they seem not to be influenced by risk or by type of lesion. Routine six-monthly dental check-ups have been customary for many patients in the general dental services around the world by both patients and clinicians, however it appears□very little evidence to support this recall interval. Recall intervals of no longer than 12 months give the opportunity for delivering and reinforcing preventive advice and for raising awareness of the importance of good oral health (28). The use of longer recall intervals also enables greater capacity

within dental services, especially those where access is limited or which are state-funded.

It is interesting to note that only in one clinical scenario (ICDAS code 3), date of graduation had an influence in the decision to treat and older dentists were more likely to restore. The results of younger dentists not following a more preventive approach for all the scenarios corroborates with a previous study using sealants in non-cavitated caries lesions (29) showing no difference between younger and older dentists, suggesting that dental education has not yet fully adopted an evidence-based approach in their curriculum, confirmed by a questionnaire conducted among Latin American dentists in 2010-2011, where Colombian dentists refer to use ICDAS for the detection and classification of caries lesions, but tend mostly to only treat lesions in need of operative treatment, probably influenced by the reimbursement characteristics of the Colombian National Health System. More recently, the global initiative Alliance for a Caries Free Future, launched its first chapter in Colombia (2011) and a consensus on cariology curriculum for undergraduate students among Colombian dental schools has already been achieved and is now in the process of being adopted (30).

It is important to bear in mind the possible limitations of this study. First, one of the limitations of the study is that dentists may find it difficult to interpret what constitutes a lesion in terms of a simple visual description. Second, the low utilization of non-operative treatment in this specific population can be explained by different factors related to the health system incentives, patients demand and dentists' knowledge, among others (31). Third, most of the dentists surveyed are in private or mixed practice, where the patient may pay per procedure and prevention is not well remunerated, except for sealants. Another reason that may explain the interventionist attitude of the practitioners is the belief that restorations are a rapid and safe method to return the tooth to health (32).

The concept of 'caries scripts' described by Bader and Shugars (9) is demonstrated with the results of this study and corroborates with previous studies on treatment thresholds (20, 21, 31). The inherent attitudes and learned concepts (caries scripts) in dentists appear to have greater influence in the treatment decisions than the

biological understanding of the disease per se (32). Clinicians elaborate their scripts during their professional education and then they will modify them through their practicing careers. There are several experience-based feedbacks that can modify those scripts. Long-term outcomes of decisions of intervention and no intervention will modify subsequent intervention decisions. However, the mechanism of how feedback modifies intervention decisions is still unknown but is likely that changes in knowledge and increase in confidence may be part of this process (9). The gap between the cariology curriculum in the dental schools and what actually is done remains wide. The greatest improvement will be that the scripts based on biological factors are introduced at dental school, so appropriate scripts will be associated to appropriate treatment decisions (9).

Suggestions on how to minimize variations in the diagnosis and treatment should be based on the current evidence base (33). Questions have been also raised about how dentists can easily adopt new techniques but have difficulty with new concepts (34) and how they try to bring their own experiences and biases to particular treatment strategies (9). The lack of consensus among dentists about the diagnosis and treatment for the same or similar patients (6), has implications on the outcomes and costs for the patient (35). Evidence-based guidelines and recommendations have been developed but difficulties on how to disseminate this knowledge may be present (27). It seems that printed material has only a minor effect in change of clinician's behaviours. Intervention techniques such as participatory workshops, audit and feedback and educational outreach have greater evidence of effectiveness (36).

Clinical decision-making is a key element of clinical performance. In fact, it is maybe the one with greater importance in terms of health outcomes and patient safety. Therefore, for patient safety it seems essential to think critically, analyse, reason, decide, and diagnose effectively (37). The ultimate goal will be to promote conservation of tooth structure with surgical intervention as a last resort philosophy.

The practice of evidence-based (or evidence informed) dentistry requires the combination of research knowledge with provider experience. In normal circumstances this combination would happen as a result of lifelong learning but clinicians often fail to integrate current best evidence into their treatment decisions

(38). The implementation of research findings into practice can take more than 20 years – a lengthy translation process that disadvantages patients. It may be explained by the fact that health care practitioners do not change if the systems of care and payment are not aligned to help them to provide the level of evidence informed care (29).

The results of this study support the development of an evidence-based, standardized, less invasive management system of early caries lesions for the dental curriculum, practitioners and the responsible health system. There is abundant room for further progress in determining how to standardise dentist's management concepts. Further studies will be required in other settings and populations to determine if the findings of the current study are generalizable to other countries. It will be interesting to assess if national oral care plans and strategies, such as England's Delivering Better Oral Health, make an impact on decision-making with regard to caries management and recall interval.

Acknowledgments

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Table 9.1. Practitioner's characteristics (Colgate Database N=8725; Sample of the study N=439)

	Colgate DB	Sample Study
Gender	*%*	*%*
Male	30.7	30.8
Female	69.3	69.2
Date of graduation		
≤2000	60.9	48
≥2001	39.1	52
Type of practice		
Public practice	10.2	7.7
Private practice	89.8	93

Table 9.2. Results for the Scenarios 1 to 5 by risk (N=439)

Treatment		Scenario 1 ICDAS code 2- Occlusal				Scenario 2 ICDAS code 2- Occlusal				Scenario 3 ICDAS code 2- Approximal				Scenario 4 ICDAS code 3- Occlusal				Scenario 5 ICDAS code 4- Occlusal			
		High Risk		Low Risk		High Risk		Low Risk		High Risk		Low Risk		High Risk		Low Risk		High Risk		Low Risk	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Preventive	Watch and wait until next control	2	0.9	4	1.9	2	0.9	9	4.2	2	0.9	5	2.3	3	1.4	6	2.7	2	0.9	1	0.4
	Oral Hygiene instructions	9	3.9	9	4.3	9	4	5	2.4	4	1.8	4	1.9	3	1.4	4	1.8	0	0	0	0
	Fluoride Varnish	38	16.7	39	18.5	31	13.7	43	20.3	26	11.7	28	13	17	7.9	31	13.8	1	0.5	5	2.2
	Seal and follow-up	31	13.6	34	16.1	22	9.7	38	17.9	8	3.6	6	2.8	15	7	15	6.7	2	0.9	4	1.8
	Open fissure-sealant restoration	48	21.1	63	29.9	60	26.4	45	21.2	0	0	0	0	23	10.7	41	18.3	7	3.2	11	4.9
	Total	**128**	**56.2**	**149**	**70.7**	**124**	**54.7**	**140**	**66**	**40**	**18**	**43**	**20**	**61**	**28.4**	**97**	**43.3**	**12**	**5.5**	**21**	**9.3**
Operative	Provide resin-based composite	96	42.1	60	28.4	100	44.1	69	32.5	180	80.7	168	77.8	149	69.3	125	55.8	179	82.9	188	84.3
	Provide Amalgam	4	1.8	2	0.9	3	1.3	3	1.4	3	1.3	5	2.3	5	2.3	2	0.9	25	11.6	14	6.3
	Total	100	43.9	62	29.3	103	45.4	72	33.9	183	82	173	80.1	154	71.6	127	56.7	204	94.5	202	90.6

Table 9.3. Scenarios 1-5. Association between practitioner's characteristics and choice of treatment (preventive/operative) (N=439)

Variables	Scenario 1				Scenario 2				Scenario 3				Scenario 4				Scenario 5			
	ICDAS code 2- Occlusal				ICDAS code 2- Occlusal				ICDAS code 2-Approximal				ICDAS code 3-Occlusal				ICDAS code 4-Occlusal			
	OR	SE	95%CI	P value	OR	SE	95%CI	P value	OR	SE	95%CI	P value	OR	SE	95%CI	P value	OR	SE	95%CI	P value
Gender	1.1	0.22	0.71-1.69	0.67	0.9	0.21	0.6-1.37	0.63	1.29	0.26	0.78-2.15	0.32	1.21	0.22	0.79-1.86	0.38	1.22	0.39	0.57-2.6	0.61
Date of graduation	1.05	0.2	0.7-1.55	0.82	0.91	0.2	0.62-1.35	0.66	0.83	0.24	0.51-1.33	0.43	1.55	0.2	1.04-2.3	0.03*	0.96	0.36	0.47-1.95	0.9
Caries Risk	1.89	0.2	1.27-2.81	0.002*	1.61	0.2	1.09-2.37	0.01*	1.13	0.24	0.7-1.83	0.6	1.92	0.2	0.43-0.96	0.001*	1.8	0.37	0.86-3.75	0.12

Figure 9.1. Clinical Scenarios
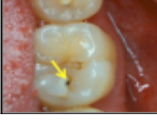
SCENARIO 1: This image is from a 20 year old woman who is a regular attender at your practice. Her caries risk based on caries experience, tooth brushing, attendance and plaque control is indicated by the traffic light. Assume that a radiograph of the tooth shows evidence of caries extending into the inner half of enamel.

SCENARIO 2: This image is from a 14 year old boy who is a regular attendant at your practice. During your routine examination you notice this spot un an upper premolar. His caries risk based on caries experience, tooth brushing, attendance and plaque control is indicated by the traffic light. Assume that a radiograph of the tooth shows evidence of caries extending into the inner half of enamel.

SCENARIO 3: This image is from a 30 year old woman who presents at your practice for the first time today. Her caries risk based on caries experience, tooth brushing, attendance and plaque control is indicated by the traffic light. Assume that a radiograph shows evidence of caries extending into the inner half of enamel.

SCENARIO 4: This sixteen-year-old girl presents to your practice for the first time today. Her caries risk based on caries experience, tooth brushing, attendance and plaque control is indicated by the traffic light. The radiograph of the tooth shows evidence of caries extending to the outer third of dentine. The clinical examination shows enamel breakdown.

SCENARIO 5: This image is from a 16 year old girl who is a regular attender at your practice. Her caries risk based on caries experience, tooth brushing, attendance and plaque control is indicated by the traffic light. Assume that a radiograph of the tooth shows evidence of caries extending into the outer third of dentine.

Figure 9.2. Clinical images with different stages of caries

C1	C2	C3	C4	C5
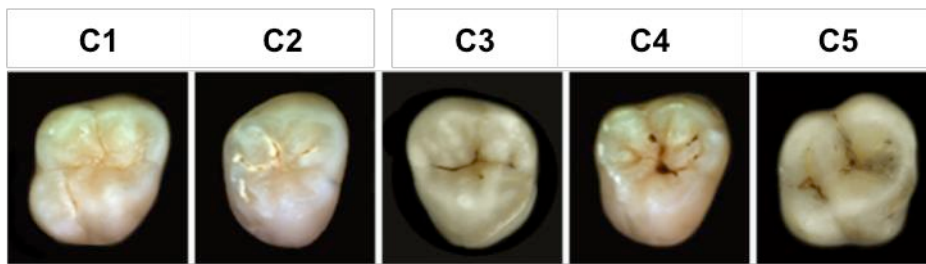
Figure 9.3. Radiographic images with different stages of caries progression
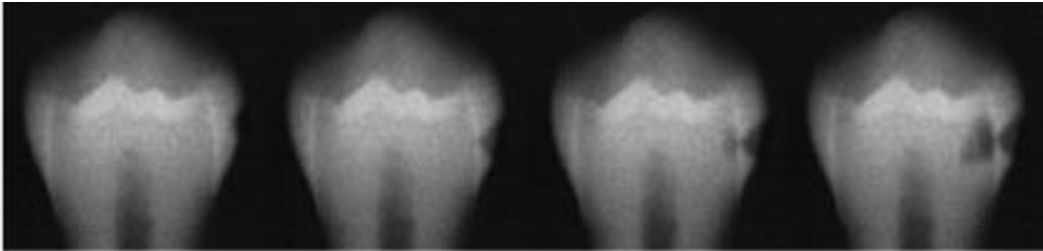
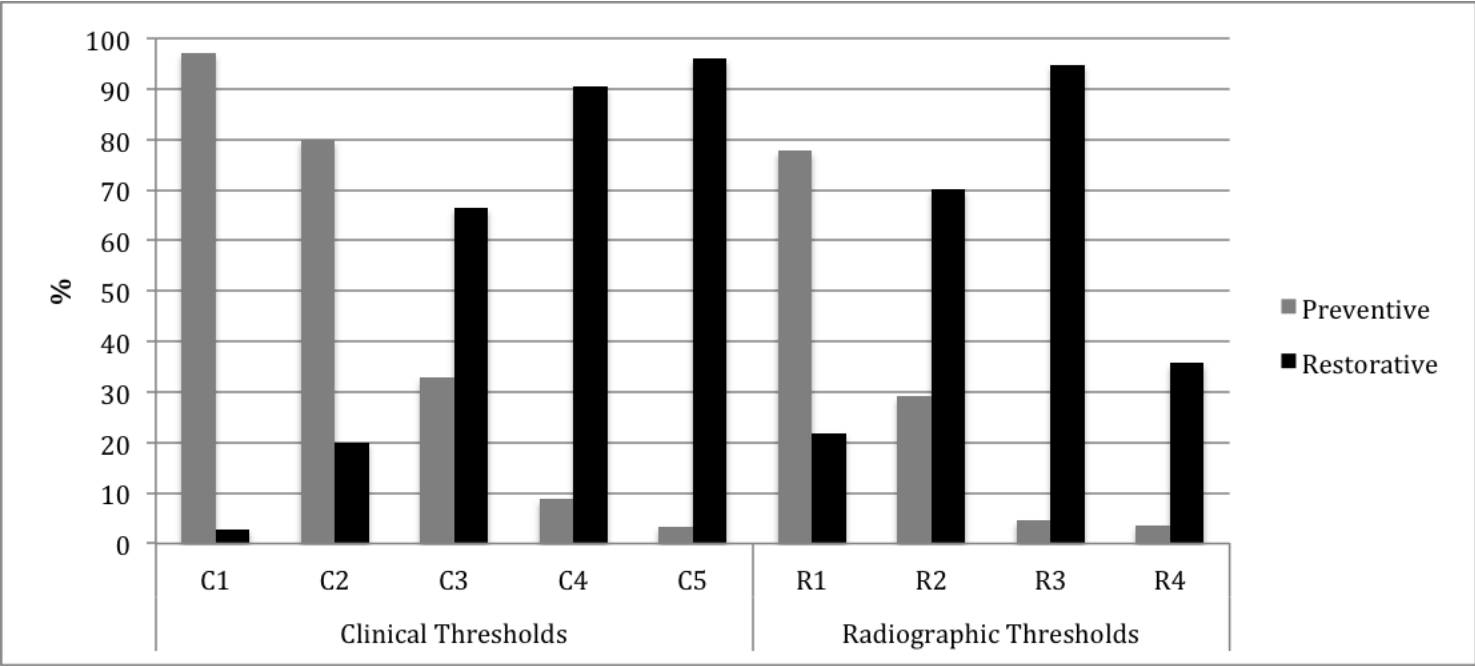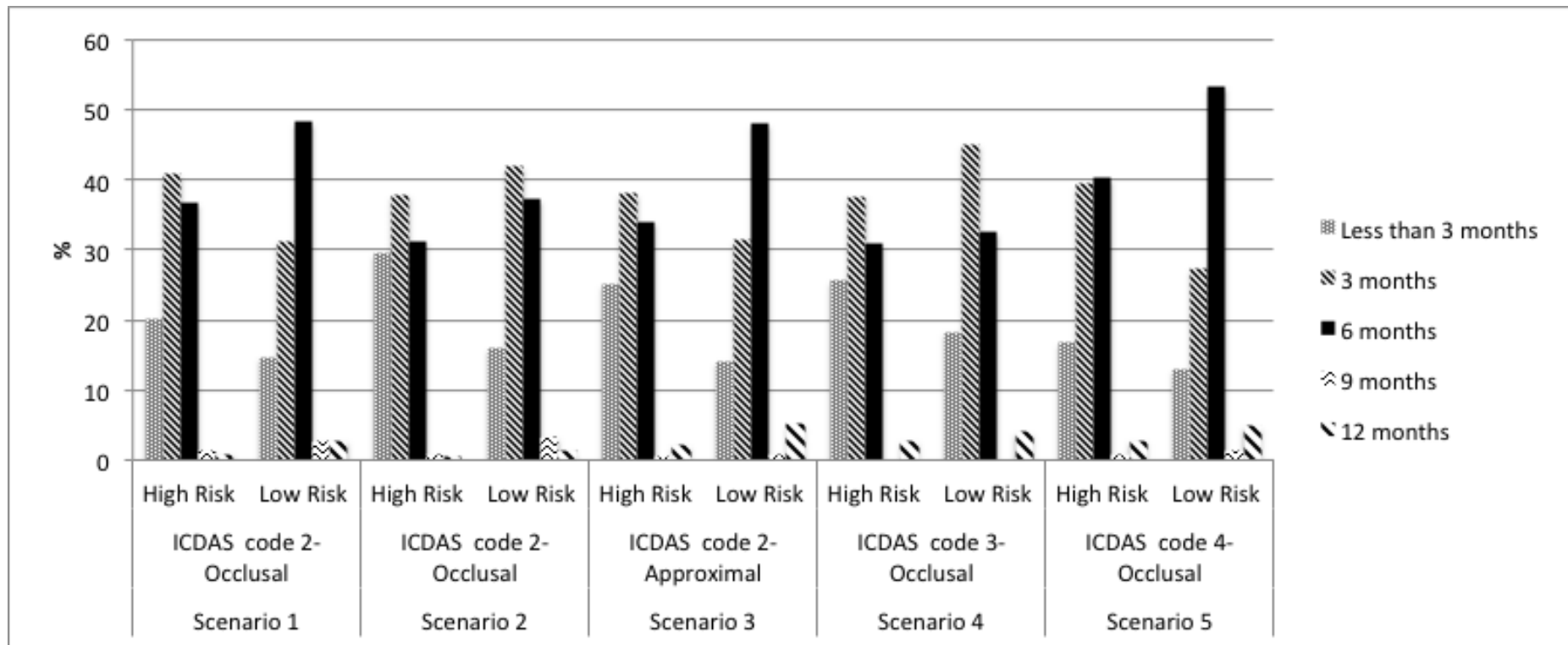**Figure 9.4. Results Clinical and Radiographic thresholds (N=439)**

Figure 9.5. Results of Recall intervals by risk (N=439)

CHAPTER 10

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SUMMARY

10.1. The Main Findings

The studies in this thesis have focused on understanding whether the caries paradigm shift has been reflected on the evidence of caries detection and management and on testing the ability of different caries detection methods, in particular QLF, in detecting mineral changes. The caries-related treatment decisions among dentists have also been investigated. The studies were conducted in three phases.

10.1.1. Conclusions of Systematic Reviews

The main findings of the Systematic Review on Detection Methods were large variations of sensitivities and specificities and the lack of consistency in defining caries disease at different thresholds. One important source of heterogeneity found within the studies examined is the inconsistent use of D1 and D2. For example, some studies reported D1 combining enamel and dentine or other collapsing sound and enamel. When Se and Sp were recalculated only for non-cavitated lesions, the values were usually lower than the ones reported initially. The results on NCCLs are inconclusive for some methods and it seems that the diagnosis can be improved in combination of visual assessment such as ICDAS and other quantitative methods. However, the review suggested serious limitations on the detection accuracy of caries detection systems.

The systematic review based on Caries Risk Assessment systems/guidelines aimed to find whether current systems are predictive of future caries and what are the outcomes of management based upon the use of these systems. There were large variations in terms of definition of caries risk categories, type and number of risk factors and disease indicators. Prospective studies have only been conducted for Cariogram to assess its performance. Cariogram showed good to moderate caries prediction in elderly adults. One retrospective study found the CAMBRA assessment to provide prediction for cavitated lesions only when extreme risk and low risk individuals were compared. The evidence concerning CRA systems is limited as they are based on cross-sectional studies establishing associations but not causal mechanisms. The findings from this review reflect a lack of evidence of the predictive ability of caries risk assessment systems.

For the Caries Management review, as expected, fluorides in different vehicles continue to be the most effective anti-caries intervention on NCCLs. However, the quality for more than a half of the studies assessed was found to be poor and had moderate to high risk of bias. These results do not agree with the last International Conference on Novel Anticaries and Remineralising Agents (1), which made recommendations for new approaches and products for caries prevention. It is possible, therefore that their suggestions were based on 'expert opinions' rather than a rigorous appraisal of the evidence.

The review on alternative clinical trials found that clinical trials using alternatives technologies seem to reduce the numbers of subjects required and the duration of the study; and therefore the costs of testing effectiveness of oral care products. Explanatory trials are carried out under ideal conditions, as they aim is primarily to further scientific knowledge. It is important to bear in mind that extrapolating the results of explanatory trials to the care of individual patients in the real world can be problematic. Pragmatic trials have implications for 'real world' settings and applying therapies in routine clinical practice usually results in a reduce effect size to due to the therapy being applied in a less than idea way. It is important that the methodological approach used (explanatory vs pragmatic trial) is matched to the aim of the study and the results are interpreted based on the context and the methodological approach that has been employed.

The result of the systematic reviews presented, agree with previous statements on caries detection including: 1. Different degrees of severity, involving enamel and dentine, are present. 2. The diagnosis and assessment become more accurately using the visual signs. 3. Treatment decisions do not only involve operative dentistry; they will be made according to a specific diagnosis and the individual caries risk (2).

10.1.2. *In vitro* studies

Practitioners have traditionally employed clinical visual assessment as a caries detection method. However, over the past years new quantitative technologies

detecting early carious lesions have been used in practice and in clinical trials. Quantitative methods may allow clinicians to revaluate the effectiveness of therapies and treatment decisions and may reduce the duration and the subjects of the clinical trials measuring small changes.

The first in vitro study presented in this thesis compared the in vitro performance of ICDAS, digital photographs scored with ICDAS, FOTI, QLF (Custom and Inspektor), OCT and Soprolife camera to detect early/intermediate occlusal lesions. The findings of the detection methods were compared with the gold standard (histology) to find the degree of correctness of the diagnostic method. The results of this study showed better performance for the visual assessment using ICDAS. All the methods were strongly correlated with histology except for OCT, which showed a moderate correlation (0.65). The sensitivities at the enamel level were high for ICDAS, FOTI and OCT and the specificities at the same level were high for all methods except for OCT (0.39). It was found that accurate caries detection could be achieved with visual examination using ICDAS. However, additional methods may improve detection performance and are helpful for monitoring purposes. Also, the fact that quantitative methods are able to measure small changes will allow much shorter duration trials and fewer subjects. The application of quantitative methods complement clinicians' interpretation of the severity and extension of the lesions. It is difficult to conclude whether a combination of methods will improve the performance of the caries diagnosis; the evidence on the effect of the combination of caries detection methods is inconclusive, with some studies showing that combining methods may decrease the reproducibility for both intra- and inter-examiner comparisons (3), while others report the opposite effect (4, 5).

Two further studies looking at the ability of QLF to measure mineral changes were conducted. The main advantage of this type of in vitro testing, despite its limitations, is the ability to perform experiments under controlled conditions. These two in vitro studies consisted in a remineralisation and a demineralisation pH cycling models. The remineralisation study started with artificial caries lesions and the aim was the gain of minerals through the model from the fluoride dentifrices. The demineralisation model consisted on sound enamel specimens in a demineralisation model. The major outcome of this model was to look at the ability of the fluoride

products to prevent or resist to demineralisation. The remineralisation of the artificial caries lesions for the fluoride groups was unequivocal. For the demineralisation model, sound enamel seems to produce little or no demineralisation in the fluoride groups. An important implication of these findings is the ability of QLF to show mineral changes of very early lesions. In the demineralisation model at 5 days, the difference between the fluoride placebo group and the two NaF toothpastes was significant. At 14 days QLF was able to show differences between all the products.

QLF was found to be able to detect and quantify small mineral changes, making it useful for evaluation of effectiveness of oral care products. However, the practicability of the use of QLF in regular practice has been questioned in terms of time-consuming imaging and analysis and costs. It has also been suggested that QLF should be combined with clinical visual assessment since QLF detects any demineralisation, including fluorosis, development defects and also stain; again it is a detection device. QLF has the advantage of being a non-destructive method that allows longitudinal analysis of tissues *in vitro*, *in situ* or *in vivo* (6). QLF has also shown the ability to detect and quantify changes of mineral content and size of lesions by demonstrating a dose response between F and non-F dentifrices in short-term clinical trials (7, 8). However, limita

The main limitation of the caries detection study was related to the fact that only one examiner assessed the lesions for most of the instruments; therefore, the performance of the methods can be over estimated. To overcome these issue, an ideal study would have consisted of a team of calibrated examiners collecting measurements of all different lesions.

The main limitation of the pH-cycling models is the inability to completely simulate the intraoral conditions including bacterial biofilm, surface area/solution ratios since different oral surfaces are bath in different volumes of saliva and they are not able to simulate clearance of products from the oral cavity (9).

10.1.3. Caries related treatment decisions

Early detection and risk-based preventive strategies can stop or reverse the progression of the caries process. Over the last century enough scientific evidence has been presented on the limitations of the caries management only based on a restorative approach. However, a large proportion of practitioners still prefer to prescribe operative options despite the many available preventive and remineralising alternatives. In this study, even if the majority of dentists would choose a preventive option for the occlusal ICDAS code 2 lesions (S1=63.1%; S2=60.1), still a large number of dentists that would undertake operative treatment when it could be considered inappropriate. Only for Scenarios 1 and 2 (ICDAS code 2 lesions) was risk found to influence the treatment decisions. For approximal lesions most of the dentists decided to intervene operatively in ICDAS code 2 lesions in the inner-half of enamel. This finding corroborates with other studies suggesting that dentists would restore when evidence of radiolucency at the enamel-dentine junction was present (10-12). The decision of when to intervene is crucial since premature or unnecessary restoration eliminates the chance for remineralisation and a restoration is permanent and will have a limited lifetime.

Many dentists in this study continue working with familiar techniques despite well-disseminated evidence concerning preventive treatments. They may be operating in their comfort zone under the notion of anecdotal success (13). New approaches have been accepted and adopted but they have not had a change in the reimbursement systems and consequently in dental education and dental practice. The focus on dental restorative care continues to drive the management approach and reimbursement or incentive systems all over the world (14). However, the findings of this study are somehow encouraging showing that approximately at least 60% of the dentists will manage occlusal lesions with preventive options such as fluoride varnish or sealants. The results of this study support the development of caries management system based on available evidence, standardized for the dental curriculum, practitioners and the responsible health system.

Some of the possible limitations of this study were the difficulty that may represent to interpret a simple vision description of a caries lesion and also that most of the

dentist surveyed are in private practice and are paid per procedure and preventive treatments are not well remunerated.

10.2. Implications of this Thesis for Policy, Practice and Further Research

Dental caries is a reversible disease that can be halted at any given point, as long as the biofilm can be removed. The very early changes in the enamel can be detected with traditional visual-tactile methods; other additional tools can be used for monitoring purposes in practice and in clinical trials. All caries detection methods are subject to errors with less than perfect reliability and validity (5). The detection of caries lesions should be focused on the exoneration of sound surfaces, instead on the detection of lesions biased towards the restorative approach. False positive diagnoses are more dangerous in terms of unnecessary invasive treatments (5). However, dentists normally are more focused on the detection of lesions than on the exoneration of sound surfaces, particularly to avoid overlooking deep lesions. It is at this moment that clinicians tend to use additional methods to complete the decision of when to intervene (5).

In terms of caries diagnosis, the main objective on the patient care should be to classify the lesions according to their biological representation and provide them with the best biological oriented treatment in order to preserve tooth structure. The biological rationale is that cavitated lesions will require a restoration, whereas non-cavitated active lesions can be controlled with preventive therapies such as plaque control and fluorides. This objective can only be achieved with the visual-tactile clinical examination.

Clearly, a restorative bias continues to influence how dentistry is practised today. This approach has been embedded in pre– and postgraduate education, licensing, insurance, finances and reimbursement systems and also in public opinion. Restorative treatment offers a tangible and well-defined service in contrast to the preventive strategies that become intangibles for both practitioners and patients. Financial constraints on how dentists are remunerated play a key role on how dentistry is practised. Dentist can be remunerated with a fixed salary, per capita or fee-for-item remuneration, being the fee more expensive for operative treatments.

Two different issues arise with these systems, under treatment for per-capita payments or overtreatment of fee-for-item. The focus should be placed on the individual dentist in relation to ethics, norms and quality control (15). The dental education has also an important role in the restorative bias in dentistry. Dental students often learn anecdotal concepts from their master clinicians based on a repetition of mechanical and technical procedures in order to achieve restorative excellence and far from a evidence-based comprehensive care (16).

The evidence presented in this thesis is not completely new, similar arguments have been presented before in previous published reviews. Thus, programmes for more effective dissemination and implementation of research findings are required. Nevertheless, the implementation of research into an optimal personalized caries management has been started with some initiatives as the WHO, FDI and the Alliance for a Cavity free future among others.

The World Health Organization (WHO) after an Assembly in 2007 adopted an action plan for health promotion and integrated disease prevention. The International Dental Federation (FDI) has also promoted minimally invasive dentistry and supported new classification systems such as ICDAS (17). The American Dental Association is also reviewing caries classification and is supporting therapeutic interventions such as sealants on non-cavitated lesions (18). The European Organisation for Caries Research (ORCA) formed a task force to work with the Association of Dental Education in Europe (ADEE) on a European Core Curriculum in Cariology (19). More recently, the global initiative Alliance for a Caries Free Future, launched its first chapter in Colombia (2011) and a consensus on cariology curriculum for undergraduate students among Colombian dental schools has already been achieved and is now in the process of being adopted (20).

In general, information gained from the studies presented in this thesis has helped to better understand the evidence regarding caries detection and management of non-cavitated lesions, caries risk systems and new technologies used in clinical trials, to identify detection methods able to detect mineral changes and finally to understand how dentists are taking caries related treatment decisions. However, further research is necessary in other settings and populations to determine if the results found in this

thesis are generalizable to other settings and countries. The following is a summary of the recommendations for further research:

- A methodological clinical study using Visual assessment (ICDAS) with QLF testing the effectiveness of anti-caries products.

- Further research in clinical trials using caries risk systems able to predict disease.

- Further research in short clinical trials using alternative methods with fewer subjects testing the effectiveness of anti-caries products.

- Further research in the use of QLF in general dental practices in terms of practicability, reliability and opportunity to expand the use of the method.

- Further research using surveys or focus groups with dental students and practitioners that may help clarify other significant factors that affect practitioner attitudes.

- Future research on education and training of dental students and practitioners and how this will improve their clinical decision-making.

- Further research about the impact of standardisation of curriculums across nations and educational programmes is also needed.

- Further research in epidemiological studies collecting data at non-cavitated level and cavitated level. Clinical data can then be recalculated for cavitated lesions to be able to compare with previous surveys.

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APPENDICES

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APPENDIX I: Cover pages of published papers

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Non-cavitated carious lesions detection methods: a systematic review

Unsolicited Systematic Review

Juliana Gomez[1,2]**, M. Tellez**[3]**, I.A. Pretty**[1]**, R.P. Ellwood**[1] **and A.I. Ismail**[3]

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Gomez J, Tellez M, Pretty IA, Ellwood RP, Ismail AI. Non-cavitated carious lesions detection methods: a systematic review. Community Dent Oral Epidemiol 2013; 41: 55–73. © 2012 John Wiley & Sons A/S. Published by Blackwell Publishing Ltd

Abstract – The aim of this study was to critically appraise the performance of detection methods for non-cavitated carious lesions (NCCLs). A detailed search of Medline (via OVID), the Cochrane Collaboration, Scielo and EMBASE identified 2054 publications. After title and abstract review by three investigators (JG, MT, AI), 124 publications were selected for further review. The final publications evaluated the following methods: Visual (V), Caries Lesion Activity Assessment (CLAA), Laser Fluorescence (LF), Radiographic (R), Fibre-optic Transillumination (FOTI), Electrical Conductance (EC) and Quantitative Light-induced Fluorescence (QLF). All included studies used histological assessment as a gold standard for *in vitro* studies or clinical/visual validation for the *in vivo* designs. They reported outcomes measures such as sensitivity (SE), specificity (SP), area under the receiver operating characteristic curve (AUROC) and reliability. Data were extracted from the selected studies independently by two reviewers and checked for errors. The quality of the studies was evaluated as described by Bader et al. (2002). Of the 124 articles, 42 were included that described 85 clinical assessments. Overall, the quality of evidence on detection methods was rated 'poor', except for EC that was rated 'fair'. The SE rates were as follows: V (0.17–0.96), LF or DIAGNOdent (DD) (0.16–0.96), R (0.12–0.84), FOTI (0.21–0.96), EC (0.61–0.92) and QLF (0.82). The SP rates were as follows: V (0.46–1.0), LF (0.25–1.00), R (0.55–0.99), FOTI (0.74–0.88), EC (0.73–1.0) and QLF (0.92). There is a large variation in SE and SP values for methods and a lack of consistency in definition of disease and analytical methods. EC and QLF seem to be promising for detection of early lesions. For both cost and practicality considerations, visual methods should remain the standard for clinical assessment in dental practice.

Dental caries is the process of dynamic interaction between the tooth surface and the plaque biofilm. The balance between mineral loss and gain can shift to favour either re- or demineralization (1, 2) so that early or non-cavitated carious lesions (NCCLs) can be arrested or remineralized (3). Recently, there has been an increased interest in this area of caries management, not least because of the changing disease severity observed in Western populations (4). Agreement on classification of lesions and interventions to conservatively manage

early lesions is necessary to promote this approach (5). Over the last decade, there were many attempts to develop protocols to achieve these goals (6).

Even though the importance of management of non-cavitated (NC) enamel lesions has been recognized since the early 1900s, dental caries has been traditionally detected at the cavitation stage, and its management has been strongly focussed on operative treatment. New methods of detection of early carious lesions have received significant research attention over the last 20 years. These

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Unsolicited Systematic Review

Evidence on existing caries risk assessment systems: are they predictive of future caries?

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Tellez M, Gomez J, Pretty I, Ellwood R, Ismail AI. Evidence on existing caries risk assessment systems: are they predictive of future caries?. Community Dent Oral Epidemiol 2013; 41: 67–78. © 2012 John Wiley & Sons A/S

Abstract – *Aim:* To critically appraise evidence for the prediction of caries using four caries risk assessment (CRA) systems/guidelines (Cariogram, Caries Management by Risk Assessment (CAMBRA), American Dental Association (ADA), and American Academy of Pediatric Dentistry (AAPD)). This review focused on prospective cohort studies or randomized controlled trials. *Methods:* A systematic search strategy was developed to locate papers published in Medline Ovid and Cochrane databases. The search identified 539 scientific reports, and after title and abstract review, 137 were selected for full review and 14 met the following inclusion criteria: (i) used as validating criterion caries incidence/increment, (ii) involved human subjects and natural carious lesions, and (iii) published in peer-reviewed journals. In addition, papers were excluded if they met one or more of the following criteria: (i) incomplete description of sample selection, outcomes, or small sample size and (ii) not meeting the criteria for best evidence under the prognosis category of the Oxford Centre for Evidence-Based Medicine. *Results:* There are wide variations among the systems in terms of definitions of caries risk categories, type and number of risk factors/markers, and disease indicators. The Cariogram combined sensitivity and specificity for predicting caries in permanent dentition ranges from 110 to 139 and is the only system for which prospective studies have been conducted to assess its validity. The Cariogram had limited prediction utility in preschool children, and a moderate to good performance for sorting out elderly individuals into caries risk groups. One retrospective analysis on CAMBRA's CRA reported higher incidence of cavitated lesions among those assessed as extreme-risk patients when compared with those at low risk. *Conclusion:* The evidence on the validity for existing systems for CRA is limited. It is unknown if the identification of high-risk individuals can lead to more effective long-term patient management that prevents caries initiation and arrests or reverses the progression of lesions. There is an urgent need to develop valid and reliable methods for caries risk assessment that are based on best evidence for prediction and disease management rather than opinions of experts.

Caries risk assessment (CRA) is one of the cornerstones in patient-centered caries management. CRA should be included in contemporary treatment plans in order to assist the clinician in the decision-making process concerning treatment, recall appointments, and need for additional diagnostic procedures. An ideal CRA system should have high validity and reliability, and it should also be easy to use in practice at a low cost (1).

Designing a CRA system has so far been based on findings either from cross-sectional studies, where various caries-related factors are identified using statistical models that identify the risk factors or indicators associated with caries status

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Unsolicited Systematic Review

Non-surgical management methods of noncavitated carious lesions

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Tellez M, Gomez J, Kaur S, Pretty IA, Ellwood R, Ismail AI. Non-surgical management methods of noncavitated carious lesions. Community Dent Oral Epidemiol 2013; 41: 79–96. © 2012 John Wiley & Sons A/S. Published by Blackwell Publishing Ltd

Abstract – *Objective:* To critically appraise all evidence related to the efficacy of nonsurgical caries preventive methods to arrest or reverse the progression of noncavitated carious lesions (NCCls). *Methods:* A detailed search of Medline (via OVID), Cochrane Collaboration, Scielo, and EMBASE identified 625 publications. After title and abstract review, 103 publications were selected for further review, and 29 were finally included. The final publications evaluated the following therapies: fluorides (F) in varying vehicles (toothpaste, gel, varnish, mouthrinse, and combination), chlorhexidine (CHX) alone or in combination with F, resin infiltration (I), sealants (S), xylitol (X) in varying vehicles (lozenges, gum, or in combination with F and/or xylitol), casein phosphopeptide amorphous calcium phosphate (CPP-ACP) or in combination with calcium fluoride phosphate. All included studies were randomized clinical trials, were conducted with human subjects and natural NCCls, and reported findings that can yield outcomes measures such as caries incidence/ increments, percentage of progression and/or arrest, odds ratio progression test to control, fluorescence loss/mean values, changes in lesion area/volume and lesion depth. Data were extracted from the selected studies and checked for errors. The quality of the studies was evaluated by three different methods (ADA, Cochrane, author's consensus). *Results:* Sample size for these trials ranged between 15 and 3903 subjects, with a duration between 2 weeks and 4.02 years. More than half of the trials assessed had moderate to high risk of bias or may be categorized as 'poor'. The great majority (65.5%) did not use intention to treat analysis, 21% did not use any blinding techniques, and 41% reported concealment allocation procedures. Slightly more than half of the trials (55%) factored in background exposure to other fluoride sources, and only 41% properly adjusted for potential confounders. *Conclusions:* Fluoride interventions (varnishes, gels, and toothpaste) seem to have the most consistent benefit in decreasing the progression and incidence of NCCls. Studies using xylitol, CHX, and CPP-ACP vehicles alone or in combination with fluoride therapy are very limited in number and in the majority of the cases did not show a statistically significant reduction. Sealants and resin infiltration studies point to a potential consistent benefit in slowing the progression or reversing NCCls.

The diagnosis of early carious lesions is essential for nonsurgical management of dental caries (1). The measurement of incipient or noncavitated carious lesions (NCCls) increases the sensitivity and efficiency of clinical trials (2). However, caries trials have often excluded initial lesions because of difficulties they pose for reliable detection (3). More recent studies have demonstrated that early carious lesions can be measured reliably (4) and detecting subtle changes in progressing incipient lesions

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What is This?

Caries Clinical Trial Methods for the Assessment of Oral Care Products in the 21st Century

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APPENDIX 1

REVIEW OF ALTERNATIVE CARIES CLINICAL TRIAL DESIGNS

Methods

We conducted a detailed literature search (not restricted to English) of manuscripts published between 1980 and March 2011, using MEDLINE, Ovid, Embase, the Cochrane Oral Health Group's Specialized Register, and the Cochrane Central Register of Controlled Trials. The initial search identified 614 citations. The inclusion criteria applied were: (1) clinical trials comparing preventive intervention with a fluoride test or control product reporting outcomes of up to 1 year's duration; (2) limited to humans and natural caries lesions; (3) primary coronal and root caries, including the primary and permanent dentition; (4) reported in peer-reviewed journals; and (5) outcomes expressed as mean ± standard deviation of the increment of caries or other measures, such as the percentage change in the prevalence of lesions.

Inclusion and exclusion criteria were applied by examining titles, abstracts, and, where necessary, full papers by dual independent reviews. In total, 32 papers were identified in the search. Three reviewers agreed on the inclusion status of 19 publications. Data were abstracted (single abstraction, subsequent independent review) from the studies.

Studies were identified that could be broadly divided into four methods of caries detection and assessment:

(1) Clinical visual and tactile assessment (Appendix Table 1)
(2) Electric Caries Monitor
(3) Diagnodent (Appendix Table 2)
(4) Quantitative Light-induced Fluorescence (Appendix Table 3)

## Clinical Visual and Tactile Assessment

Coronal Caries

Bailey *et al.* (2009). [NB: All references appear in the main paper.] This study assessed the remineralization of white-spot lesions following the removal of fixed orthodontic appliances over 12 wks according to the ICDAS criteria, supplemented with the Nyvad *et al.* (1999) criteria to take into account lesion activity. Forty-five individuals were randomly assigned to two groups. Both groups used fluoride toothpaste (1,100 ppm F), with one of the groups also applying CCP-ACP paste with their finger to lesions twice daily. For the group using the CCP-ACP paste, when all white-spot lesions at baseline were considered (ICDAS codes 1-3), 72% of lesions regressed compared with 59% in the control group (p = 0.16). When the ICDAS code 1 lesions were excluded from analysis, 77% reversed in the CCP-ACP group compared with 59% in the control group (p = 0.04). Quantitative Light-induced Fluorescence (QLF) and digital photography were also initially included as outcomes for the study, but, due to difficulties in the analysis of lesions at the gingival margin, these data were not reported in the manuscript.

Chesters *et al.* (2002). This study was one of the first modern abbreviated caries clinical trials assessing the progression and reversal of "white spot" caries. The 2-year study involved over 2,000 participants and compared toothpastes containing 2,500 and 1,450 ppm F. Participants were instructed to brush twice daily at home and also brushed in school under supervision. Significant differences between the groups were seen at both 12 and 24 mos for white-spot lesions (D1) when lesion progression and regression were assessed by transition matrices. A traditional assessment of caries increment at the D3 threshold did not detect a significant difference at 12 mos, but confirmed the outcome of the D1 threshold assessment at 24 mos.

Lima *et al.* (2008). In a one-year study conducted in Brazil, the mean numbers of lesions progressing for caries-active and -inactive (Nyvad criteria) children, using either a 500-ppm-F or 1,100-ppm-F toothpaste, were compared. All children (aged 2-4 yrs) brushed twice *per* day at home and had supervised brushing in the nursery setting. For the caries-inactive children, as might be expected, the rate of caries progression was low, and differences between the two toothpaste groups were not statistically significant. For the caries-active individuals (n = 43), the number of lesions progressing in the group using the 500-ppm-F paste was 3.0 compared with 1.5 in the 1,100-ppm-F group (p < 0.01).
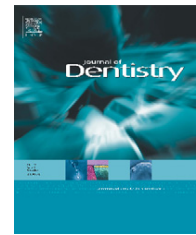
In vitro performance of different methods in detecting occlusal caries lesions

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ARTICLE INFO

ABSTRACT

Early caries detection is essential for the implementation of preventive, therapeutic and intervention strategies within general dental practice.

Objective: The aim of this study was to compare the in vitro performance of the International Caries Detection and Assessment System (ICDAS), digital photographs scored with ICDAS (ICDAS photographs), fibre-optic transillumination (FOTI), optical coherence tomography (OCT), SoproLife® camera and two implementations of quantitative light-induced fluorescence a commercial (QLF-Inspektor Research systems) and a custom (QLF-Custom) system, to detect early and intermediate occlusal lesions.

Methods: One hundred and twelve permanent extracted teeth were selected and assessed with each detection method. Histological validation was used as a gold standard. The detection methods were compared by means of sensitivity, specificity, areas under receiver operating characteristic (AUROC) curves for enamel and dentine levels and with the Spearman's rank correlation coefficient against histology.

Results: For any enamel or dentine caries detection, the AUROC curves ranged from 0.86 (OCT) to 0.98 (ICDAS and ICDAS photographs, SoproLife® camera) and at the dentine level from 0.83 (OCT) to 0.96 for FOTI. The correlations with histology ranged between 0.65 (OCT) and 0.88 (ICDAS and FOTI). Under in vitro conditions, the assessed detection methods showed excellent intra-examiner reproducibility. All the methods were strongly correlated with histology ($p < 0.01$) except OCT which showed a moderate correlation (0.65).

Conclusion: Even though all methods present similar performance in detecting occlusal caries lesions, visual inspection seems to be sufficient to be used in clinical practice for detection and assessment of lesion depth. Other methods may be useful in monitoring caries lesion behaviour.

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APPENDIX II: Commentary Limited evidence for existing caries assessment systems. Abstracted from Tellez M, Gomez J, Pretty I, Ellwood R, Ismail A. Evidence on existing caries risk assessment systems: are they predictive of future caries? *Community Dent Oral Epidemiol* 2012; Sep 15. doi: 10.1111/cdoe.12003.

Limited evidence for existing caries assessment systems

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Question: Are current caries risk assessment systems predictive of future caries?

Data sources   Data were sourced from the Cochrane Oral Health Groups Specialised Register, Cochrane Central Register of Controlled Trails, Medline, bibliographic references of identified systematic reviews, prospective cohort studies and clinical trials, textbooks and review articles.

Study selection   The studies included presented validating criteria for caries incidence/ increment and were limited to those with human subjects and natural carious lesions. Only studies published in peer reviewed journals were included. Excluded were studies which gave an incomplete description of sample selection, or of outcome, or had a small sample size. Studies which did not meet the Oxford Centre for Evidence Based Medicine prognosis category criteria for best evidence were also excluded.

Data extraction and synthesis   Data were extracted by the first review author and were independently checked by a second author. The criteria reported in the ADA Clinical Recommendations Handbook[1] were used to assess the quality of the studies. Adjustments made for potential confounders were considered as a means to evaluate the internal validity of each study.

Results   One hundred and thirty-seven study reports remained for review following systematic strategic search and title review. Of these, six studies of existing caries risk assessment models were selected for inclusion. Of the six studies reviewed four were deemed 'fair' by the ADA criteria and two 'poor'. The authors found variation in the parameters used for caries risk assessment and the population groups studied. No study found the risk assessment systems to have reliable prediction utility in children. One prospective study found Cariogram to give good to moderate caries prediction in elderly adults and one retrospective study found the CAMBRA assessment to provide prediction for cavitated lesions, but only between low risk and extreme risk individuals over the age of six.

Conclusions   This systematic review suggests that evidence available on the validity of a number of existing systems for caries risk assessment is limited and weak.

Commentary

The identification of high risk individuals to allow both prevention and intervention based on susceptibility to disease is commonplace in contemporary treatment planning. A systematic review of the literature by Harris *et al* in 2004 found '106 risk factors significantly related to the prevalence or incidence of caries'[2]. In general caries risk assessment systems standardise the risk factor information collected in order to predict potential caries outcome for the patient.

This systematic review examines the evidence on whether existing caries risk assessment systems are predictive of future caries. In addition, a second research question: 'What are the outcomes of management based on the use of these systems?' is presented within the introduction to the review. The authors searched three relevant databases and appropriate reference lists. The search was restricted to articles where one of four specific caries risk assessment models was used. It is possible that additional caries risk assessment models such as the recently published Dundee Caries Risk Assessment (DCRAM)3 may have been found by including further databases and, or extending the search to include unpublished literature. No restrictions were put on the population group to be studied in terms of age or stage of dental development. Limited evidence to answer either of the proposed research questions was found.

The inclusion of prospective and retrospective cohort studies allowed the predictive capability for of each of the caries risk assessments to be assessed in terms of an increase in the clinical caries incidence over time. Both cohort and randomised control trial studies which met the inclusion criteria were included for review. Randomised control trials would generally be included within a review where a specific intervention is being tested. Only one randomised control trial which met the inclusion criteria was included. This significantly limited the evidence available to review with regard to the second additional research question.

Six studies were reviewed by the authors. A narrative review of each individual study is provided alongside a table of result characteristics. Summary statistics from each study were described and discussed. Meta-analysis was not carried out for this review. The authors found variation in the parameters used for caries risk assessment and the population groups studied. Published evidence was found for only two of the four selected caries risk assessment systems. The same caries risk assessment program was used in five of the six articles which met the search criteria. These five studies were all carried out in Sweden, with three performed on the same

sample of children. A quality assessment was performed and found two of the six studies of poor quality, the remaining four studies were deemed to be fair. One study included in the review looked at caries risk assessment in an adult population. The results of this describe good to moderate caries prediction for extreme risk adult subjects but should be interpreted with caution given the quality of the study. Eight predictive models in longitudinal studies were also tabled for discussion within the article but were not reviewed in full.

The authors of this article have provided a structured review. There are limitations with regard to the quality of the evidence retrieved and the content of the review. Nevertheless, the authors bring to the attention of the dental research community the difficulties and limitations of caries risk assessment.

This is an area which warrants research development and further systematic review.

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1. Center for Evidence Based Dentistry American Dental Association. ADA Clinical Recommendations Handbook. October 29, 2009.
2. Harris R, Nicoll AD, Adair PM, Pine CM. Risk factors for dental caries in young children: a systematic review of the literature. *Community Dental Health* 2004. **21** (Suppliment), 71–85.
3. MacRitchie HM, Longbottom C, Robertson M, Nugent Z, Chan K, Radford JR, Pitts NB. Development of the Dundee Caries Risk Assessment Model (DCRAM) – risk model development using a novel application of CHAID analysis. *Community Dentistry and Oral Epidemiology* 2012. Feb; **40:** 37–45