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The caries continuum: Opportunities to detect, treat and monitor the re-mineralization of early caries lesions

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ABSTRACT

The aim of this review is to discuss dental caries as a dynamic process of de-mineralization and re-mineralization with progression, arrest or reversal of lesions reflecting the balance between them. The need for new clinical trial designs to assess oral care products which reflect and monitor these processes is highlighted and discussed.

The research evidence to support the use of two state-of-the-art methods that focus on re-mineralization of natural root caries lesions and natural enamel lesions is described. The use of the Electrical Caries Monitor (ECM) in combination with clinical scoring of lesions to assess the hardness of root dentin and the use of Quantitative Light-induced Fluorescence (QLF) to measure enamel lesions are described together with a number of studies that have employed the methods to assess the efficacy of oral care products.

It can be concluded that quantification of the re-mineralization provided by oral care products assessed using both buccal caries and root caries study designs is a valid approach to developing understanding of the mechanism of action of a new technology and to establishing its clinical efficacy in respect of arresting and reversing early caries lesions, and it complements, enhances and may ultimately supplant the information from a conventional two- to three-year clinical trial measuring effects at the cavitation level.

1. Introduction

During the last three decades, the prevalence and severity of dental caries in many populations across the world has improved significantly, declining to a fraction of the levels seen 30 years ago.[1] It is believed by most experts that the widespread introduction of fluoride toothpastes has been the most important factor in this decline,[2] and this view is supported by some of the strongest clinical trial data available in preventive dentistry.[3]

However, this general decline in mean dental caries prevalence and severity hides a significant burden of disease that remains in many populations. Often economically and socially deprived communities have unacceptable levels of dental caries, and the differences between deprived and non-deprived communities may have actually increased resulting in significant oral health inequalities.[4] In addition to inequalities between communities, there are also significant inequalities within communities; with a small proportion of the population bearing the significant burden of the disease.[5]

In addition, the improvements in dental caries seen in the developed world have not always been mirrored in the developing economies.[6] Changes in diet that occur with increased wealth and aspiration have the potential to increase caries levels,[7] and this is clearly the cause for some concern. It is also apparent that with increasing retention of teeth by older populations, their caries risk and potential treatment burden have increased dramatically. Root caries is a now a significant problem[4] which is difficult to treat restoratively

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and likely to increase into the future.[8,9] Therefore, whilst current fluoride products, such as toothpastes and mouth rinses, are efficacious,[3] there is a clear opportunity to continue to develop new and improved oral care products to address what still remains a significant disease globally.[10,11]

Conventional caries clinical studies, currently regarded as a 'gold' standard, are typically randomised controlled, two cell, parallel designs of two- to three-year duration, involving approximately 2–4000 participants, usually children. Currently, for ethical reasons, the majority of studies compare an experimental toothpaste to a conventional fluoride-containing positive control. The usual study outcome is the incremental change in the number of new surfaces (or teeth) developing dental caries at the cavitation level of diagnosis.[12] This design of studies is becoming increasingly difficult to implement. Firstly, caries levels have declined to the extent that it is challenging to find populations in which to conduct studies. Secondly, greater methodological sensitivity is required today than historically, because it is now necessary to detect differences between experimental and positive control products, whereas historically differences between experimental and negative control products were the norm.[13]

During the last two decades, there has been widespread acceptance that the methods currently employed to evaluate the efficacy of oral care products in caries clinical trials have not kept pace with either the advances in our understanding of the disease process, or the development of new caries detection and measurement technologies.[14,15] Perhaps most importantly, there has been a paradigm shift in our understanding of the caries process and the opportunities for prevention and treatment. The latest scientific evidence supports the concept that dental caries is a dynamic process, which is affected by numerous factors that can push the dynamic equilibrium to either re-mineralization or de-mineralization of tooth mineral. This process takes place at the interface of the complex biofilm overlaying the tooth surface comprising the pellicle and plaque micro flora[16–18] and, if left unchecked, can progress through a continuum that begins with the first episode of de-mineralization, through development of a reversible early lesion, to an irreversible cavity.[10,11] This new understanding of the disease opens up the possibility to promote therapies that encourage the re-mineralization of non-cavitated lesions and the preservation of tooth structure, function and aesthetics.[10,11] Indeed, it might now be argued that it is increasing less ethical to conduct clinical trials that detect and monitor dental caries using diagnostic methods that are focussed on irreversible, cavitated lesions. As it is an undisputed fact that all cavitated lesions began their natural history as early lesions, increased focus on early lesions for the evaluation of therapies for the prevention and treatment of caries is both scientifically well founded and highly appropriate.

Central to this new vision is the ability to perform detailed monitoring of the caries process and the ability to detect and quantify small changes in lesion mineralization.[14] Fortunately, in tandem with a greater understanding of the disease process, there have been significant improvements in our understanding of the methods that might be employed to detect and measure the early stages of dental caries.[19] Methods that can be used to improve the detection and monitoring of dental caries can be broadly divided into three groups: enhanced visual, instrumental and imaging methods.

2. Enhanced visual methods

The vast majority of caries epidemiology and clinical trials conducted during the last five decades have assessed coronal caries at a threshold of cavitation that requires professional intervention and restorative treatment. This approach is consistent with the historic surgical-based philosophy of restorative care, but not with contemporary concepts of preventive or therapeutic management of dental caries today. It has been suggested that this cavitation threshold approach to measurement helped to ensure reproducibility and comparability of data, as it was believed that detection and assessment of enamel lesions was difficult to achieve consistently. During the last decade, there has been considerable research relating to visual assessment of coronal caries and this has culminated in the International Caries Detection and Assessment System (ICDAS) system.[20] This system records lesions at the surface level, after they have been cleaned and dried (Fig. 1), and allows the detection of early white spot caries with a good degree of reproducibility.[21]

Lesions are staged using the criteria summarised below:

0. No lesion
1. Lesion seen only when dry
2. Lesion seen wet
3. Localised enamel breakdown
4. Localised enamel with dentin shadow
5. Distinct cavity with dentin shadow
6. Extensive distinct cavity

An earlier version of this method was employed in a caries clinical trial that evaluated whether the difference in efficacy between 1000- and 2500-ppm-fluoride dentifrices, which has been already been established in a number of clinical trials, could be detected with greater sensitivity when enamel lesions were considered.[22] After 12 months, statistically significant differences between the two groups were observed at the enamel lesion threshold, whereas differences were only seen at

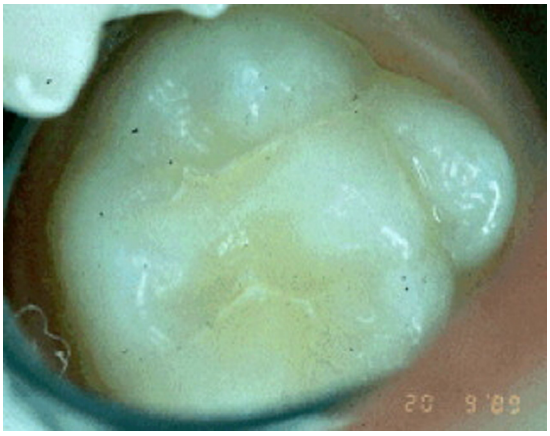

Fig. 1 – Initial caries lesion detected after cleaning and drying.

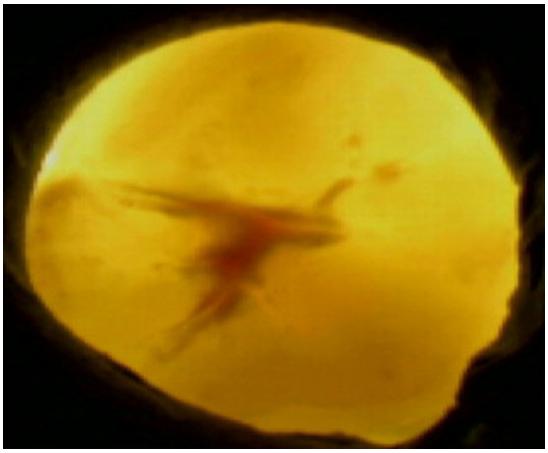

Fig. 2 – Enamel caries with initial dentin lesion as seen using FOTI.

the conventional dentin threshold after 24 months. This study clearly demonstrated the potential improvements in sensitivity that might be achieved in clinical trials by employing more sophisticated detection and monitoring methods.

Fibre Optic Trans-Illumination (FOTI) has also been employed to aid in the detection of dental caries at different stages of progression. This method utilizes the principle that light is scattered or absorbed in areas with greater porosity, resulting in dark patches that can be visually observed (Fig. 2). Caries in dentin often appears orange, resulting from chromophores in carious dentin, aiding the differential diagnosis of larger enamel lesions and early dentin caries. Comparison of the ICDAS and FOTI approaches as used by experienced examiners suggests similar levels of diagnostic utility for the two methods.[23]

The ICDAS, FOTI and other enhanced visual approaches represent a significant step forward in our ability to detect and monitor dental caries and their use should be encouraged in clinical practice. However, for the purposes of clinical trials and, in particular, the validation of efficacy of oral care products on reversible pre-cavitated lesions, their use is limited in a number of significant ways:

1. Criteria are subjective and open to interpretation.
2. Lesion stages represent a wide variety of lesion presentations.
3. In order to progress from one lesion stage to another, significant potentially irreversible changes may occur.

Ideally, methods for use in clinical trials should be objective and have the ability to detect small changes in lesion mineralization between identified points in time. A number of new instrumental detection and assessment methods that can facilitate this task are discussed below.

2.1. *Instrumental (point) methods of assessing dental caries*

The two most widely used instrumental methods of assessing dental caries are the Diagnodent caries detector[24] and the electrical caries monitor (ECM).[25]

2.1.1. *Diagnodent*

The Diagnodent instrument, manufactured by KaVo (Zurich, Switzerland), is perhaps the most widely known and employed caries diagnostic aid (Fig. 3). It works by illuminating the tooth at 655 nm (red light) to stimulate fluorescence in the near infrared by altered tooth substances and bacteria. Clean healthy tooth structure exhibits little or no fluorescence. Carious tooth structure exhibits fluorescence, proportionate to the degree of caries.[26] Red light, as well as infrared fluorescence, is less-absorbed and scattered by enamel than shorter wavelengths, such as those used by QLF (*see later*). Therefore, deeper penetration into the tooth occurs and it is possible for fluorescence to be measured from underlying carious dentin. The instrument generates a peak value for the point of application, which is then used to interpret the size of the lesion. For example, scores of 1–10 might be interpreted as healthy and scores of 30 or more might represent lesions that require restorative intervention.

The Diagnodent instrument is more sensitive than traditional diagnostic methods. However, the increased likelihood of false-positive diagnoses compared with visual methods limits its usefulness as a principal diagnostic tool.[27] Although it is generally acknowledged that the Diagnodent instrument has good performance for the detection of lesions at the dentin threshold, it does have significant disadvantages for use in clinical trials. As it is a single point or area measurement, the comparability of measurements taken at different examination periods is problematic. The method is also confounded by the presence of stain, and increases in tooth staining over time might be interpreted as lesion progression when, in fact, reversal has occurred. In addition, the mechanism of action for the detection and monitoring of enamel lesions is obscure. These early lesions are unlikely to present with significant levels of fluorophores and, hence, the use of this instrument for monitoring early carious lesions is unlikely to be optimal, if only differences in light scattering are to be quantified. For these reasons, it is unlikely that the Diagnodent instrument would provide optimum performance for use in caries clinical trials to detect and monitor the progression or reversal of early carious lesions.

Fig. 3 – The Diagnodent caries detection instrument.

2.1.2. *Electrical Caries Monitor (ECM)*

Detection systems employing electrical resistance are based on the principle that materials can be characterised by their ability to conduct electricity to different degrees. Further, changes in a material, for example due to increased porosity, fluid content or the balance of electrolytes, will also affect resistance. Enamel generally has a very high resistance. However, when it becomes more porous as a result of the presence of dental caries it contains more water and so the resistance is reduced. Dentin generally has much lower resistance than enamel, but it also increases in porosity due to dental caries, again resulting in a reduction in resistance.

The Electrical Caries Monitor (ECM) (*Lode, The Netherlands*) employs a single, fixed-frequency alternating current to measure the 'bulk resistance' of tooth tissue (Fig. 4).[25] Measurements can be taken from both enamel or exposed dentin surfaces at either a site or surface level. The measurement system consists of a probe to pass current through the tooth and body to a counter-electrode, usually held in the patient's hand. As the body has a low resistance compared to the tooth tissue, the measurement of the resistance generally closely reflects that of the tooth around the point of contact of the probe. It can be readily appreciated that, if the degree of porosity can affect the resistance of either enamel or dentin, treatments that promote re-mineralization could be detected as an increase in resistance using the instrument.

The performance of ECM was reviewed extensively by Huysmans and overall the studies considered demonstrated good to excellent performance.[28] For site specific measurements, the sensitivity was 74.8(±11.9) and specificity 87.6(±10) and for surface specific measurements, 63(±2.8) and 79.5(±9.2). The reproducibility of the device has also been assessed in a number of publications and has been rated as good to excellent for site and surface specific measurement techniques.[19]

Overall the ECM method represents a practical, objective and sensitive method of monitoring dental caries and has been proven to have significant utility in caries clinical trials.

2.2. *Imaging methods of caries detection and monitoring*

Imaging approaches to the detection and monitoring of caries lesions are also a well founded approach to increasing the sensitivity of caries clinical trials and enabling the monitoring of small changes in lesion mineralization over short periods of time. Images provide significant advantages over enhanced visual and instrumental methods. Most importantly, the status of lesions seen on paired images of the same site, captured at different points in time, can be compared so that even small differences between lesions can be visualised. In addition, quantitative assessment of images, using various image processing techniques, can provide high quality objective data.

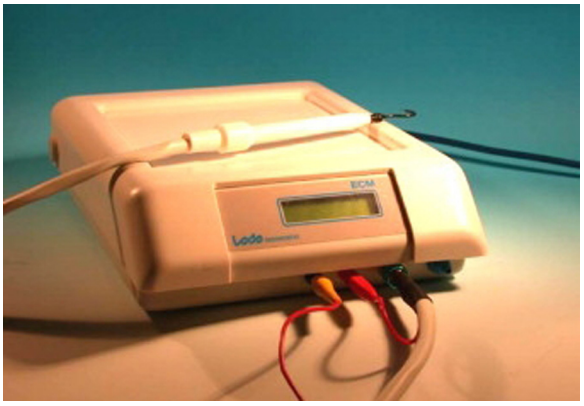

Fig. 4 – The Electrical Caries Monitor (*Lode, The Netherlands*).

Four techniques will be briefly considered in this overview: white light digital imaging, Digital Imaging Fibre Optic Trans-Illumination (DIFOTI), radiographs and Quantitative Light-induced Fluorescence (QLF).

White light digital imaging, using intra-oral cameras, is becoming increasingly common in general dental practice. Image quality has increased significantly and it is now possible to capture diagnostic quality images. These images might be further improved by using polarising filters to remove specula reflection that can obscure or mimic early caries lesions. From images of this type, caries can be scored using enhanced visual systems, such as ICDAS, and the approach also allows side-by-side comparison of images taken at different points in time to assess lesion progression and regression subjectively.

DIFOTI is an imaging implementation of the FOTI method previously described.[29] It has similar advantages to the white light digital imaging approach, but also has the potential to provide objective quantitative data. Unfortunately, it is not widely available currently and so will not be discussed in further detail.

Radiographs have been widely used in dentistry for many decades but, due to concerns about ionising radiation, it has become difficult to justify their routine use in caries clinical trials. In the future, with reductions in exposure achieved using digital radiographic imaging methods and the potential for image processing to enhance lesions, the use of methods, such as subtraction radiography, may become viable again.

2.2.1. *Quantitative Light-induced Fluorescence (QLF)*

Quantitative Light-induced Fluorescence (QLF) is a visible light system that offers the opportunity to detect early caries and then longitudinally monitor its progression or regression.[30] Fluorescence is a phenomenon by which an object is excited by a particular wavelength and then emits light at higher wavelength. When the excitation light is in the visible spectrum, the fluorescence will be of a different color. In the case of the QLF system, the excitation wavelength (λ) is around 370 nm (in the blue region of the spectrum) and emitted lighted is in the red and green region. This auto-fluorescence is then detected by filtering out the excitation light using a bandpass filter at $\lambda > 540$ nm attached to a camera and a red and green image is then produced.[31]

The source of the fluorescence is widely believed to be the dentin and the enamel–dentin junction. Studies have shown that when underlying dentin is removed from the enamel, fluorescence is lost, although only a small amount of dentin is required to produce the fluorescence seen.[32] Decreasing the thickness of enamel results in a higher intensity of fluorescence, as less light scattering occurs. The presence of an area of de-mineralised enamel reduces the fluorescence in two

ways. Firstly, if a lesion is present, it blocks the excitation light and, hence, less fluorescence occurs; secondly, any fluorescence from the dentin is back scattered as it attempts to pass through the lesion. Hence, de-mineralization of enamel results in a reduction of this auto-fluorescence. This loss can be quantified using proprietary software and has been shown to correlate well with actual mineral loss; $r = 0.73–0.86$.[32]

QLF equipment is comprised of a light source with a band pass filter to produce a blue light and a camera with another band pass filter to exclude the blue light and allow green and red light to pass into it. Live images are displayed via a computer and accompanying software enables patient's details to be entered and individual images of the teeth of interest to be captured and stored. In principle, QLF can image all tooth surfaces, except inter-proximally. When examining lesions longitudinally, the QLF method employs a video repositioning system that enables the precise geometry of the original image to be replicated on subsequent visits. Once an image of a tooth has been captured, the next stage is to analyse any lesions and produce a quantitative assessment of the de-mineralization status of the tooth. This is undertaken using proprietary software and involves using a patch to define areas of sound enamel around the lesion of interest. Following this, the software uses the pixel values of the sound enamel to reconstruct the surface of the tooth and then subtracts those pixels which are considered to be a lesion. This is controlled by a threshold of fluorescence loss, and is generally set to 5%. This means that all pixels with a loss of fluorescence greater than 5% of the average sound value will be considered to be part of the lesion. Once the pixels have been assigned "sound" or "lesion", the software then calculates the average fluorescence loss in the lesion, known as ΔF (%), and the total area of the lesion in mm^2. From the area and loss of fluorescence, a metric (ΔQ) representing lesion "volume" (or "size") can be calculated (Fig. 5).

QLF has been used to detect a range of lesion types including: occlusal caries, smooth surface caries, secondary caries, and de-mineralization adjacent to orthodontic brackets. For occlusal caries, sensitivity has been reported at 0.68 and specificity at 0.70, and this compares well with other systems. For lesion depth and QLF metrics, correlations of up to 0.82 have been reported and the reliability of both stages of the QLF process, i.e. the image capture and the analysis, has been examined and shown to be substantial.[19] The method is less appropriate for monitoring initial lesions at approximal sites, due to constraints in accessing and imaging the sites.

For clinical research use, the ability to analyse QLF images any time after their capture increases legitimacy in trials,

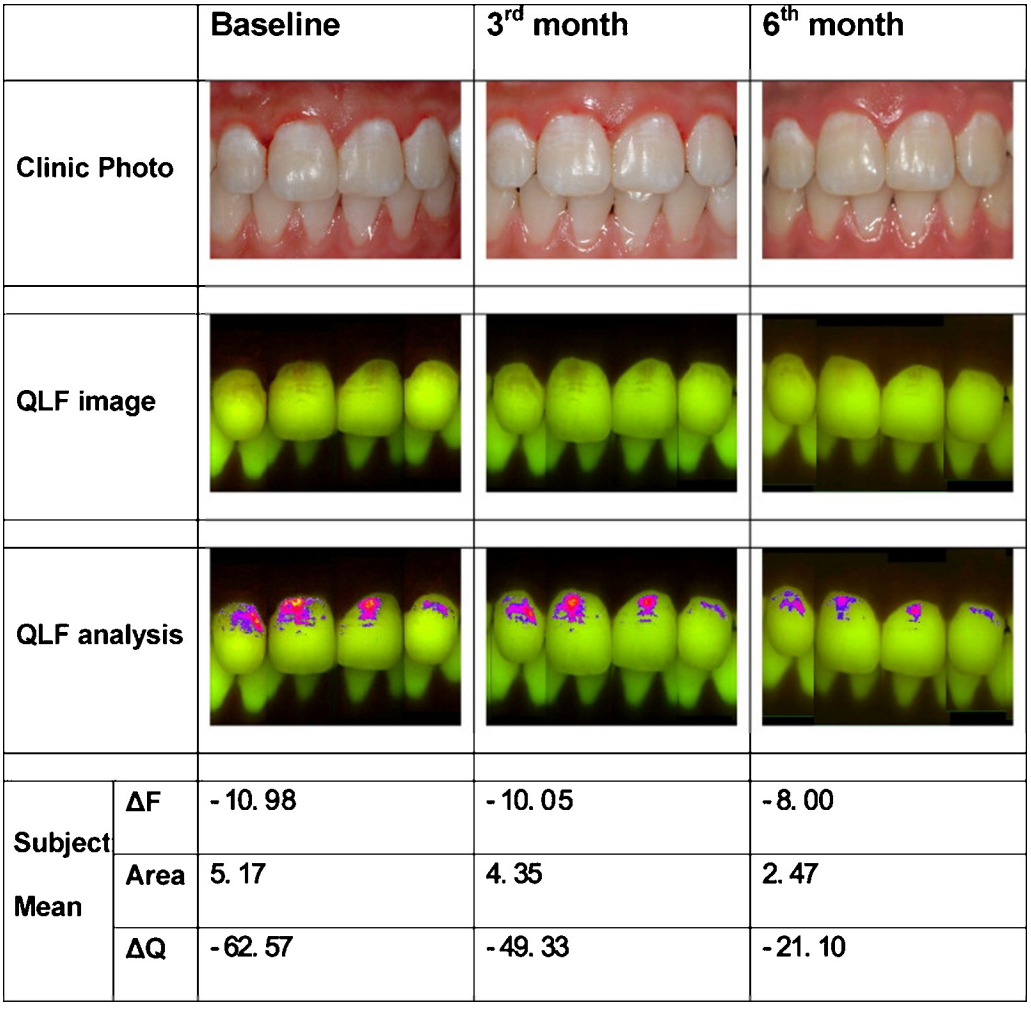

Fig. 5 – Example of QLF images of teeth and their analysis with accompanying clinical photographs.

permitting independent scoring of lesions. QLF is one of the most accurate and reliable caries detection and monitoring technologies available at present.

2.3. Validation of new assessment methods with clinical trials

The validation of new assessment methods for use in clinical trials was the subject of an extensive review as part of the International Consensus Workshop on Caries Clinical Trials.[14]

At this workshop it was concluded that 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. Specifically:

1. New caries assessment methods should have the ability to measure de-mineralization and also re-mineralization of non-cavitated lesions.
2. While there are many other ways in which the design of caries clinical trials (CCTs) might be improved further, through better diagnostic, design, and analytical techniques, the overriding principle behind validation of new CCT designs must be that the results and conclusions from any new design are in line with those shown previously by 'conventional' CCTs.
3. Any new design of CCT must not compromise the standard of proof of either efficacy or safety.

An extensive review of fluoride toothpastes considered 70 studies involving 42,300 children and concluded that

> ''Supported by more than half a century of research, the benefits of fluoride toothpastes are firmly established. Taken together, the trials are of relatively high quality, and provide clear evidence that fluoride toothpastes are efficacious in preventing caries.''[3]

Accordingly, it would seem prudent that any new method of evaluating oral care products should be evaluated using fluoride as the benchmark by either comparing products with and without fluoride or products containing different levels of fluoride. This approach has been taken in the development and clinical validation of the superior anti-caries efficacy of a new toothpaste containing 1.5% arginine, an insoluble calcium compound and 1450 ppm fluoride as compared to toothpastes with 1450 ppm fluoride alone, some details of which are provided in Section 2.4 below.

2.4. The clinical validation of two new approaches for the assessment of oral care products

The validation of two state-of-the-art approaches for the assessment of oral care products will now be described:

1. Assessment of the ability to re-mineralize and prevent further de-mineralization of naturally occurring root caries lesions using conventional clinical assessments of lesion hardness supplemented by Electrical Caries Monitor (ECM) measurements.
2. Assessment of the ability to re-mineralize and prevent further de-mineralization of naturally occurring buccal caries lesions using Quantitative Light-induced Fluorescence (QLF).

Assessment of the ability to re-mineralise and prevent further de-mineralization of naturally occurring root caries lesions using conventional clinical assessments of lesion hardness supplemented by Electrical Caries Monitor (ECM) measurements

The assessment of the mineralization status of root caries lesions by measuring their hardness, using clinical probing assessments, has been supplemented by the use of the Electrical Caries Monitor (ECM) in a number of studies. The first study to use the combination of methods was reported by Baysan et al.[33] A total of 201 subjects with at least 1 primary root caries lesion took part in a study to assess the efficacy of a high fluoride toothpaste (5000 ppm) compared to a conventional fluoride toothpaste (1100 ppm). At the 3-month examination, 38.2% of the subjects using the high fluoride paste had one or more lesions becoming hard compared to 10.7% of subjects using the conventional fluoride toothpaste. After 6 months, the corresponding percentages were 56.9% and 28.6%. Both the differences at 3 and 6 months were statistically significant. For the ECM results at 3 months, the subject log mean resistance was reduced by 0.06 for the conventional fluoride toothpaste compared to an increase of 0.40 for the high fluoride toothpaste. After 6 months, there was little change in the mean log resistance for the conventional fluoride toothpaste compared to an increase of 0.56 for the high fluoride toothpaste.[33] The results of this study, which are consistent with expectation from conventional caries clinical trial, indicate that the high fluoride toothpaste is more effective than the conventional fluoride toothpaste.

Two clinical studies were also conducted comparing commercially available fluoride dentifrices to a fluoride-free negative control dentifrice. In the first study a toothpaste containing 1000 ppm fluoride, as sodium monofluorophosphate (MFP), was tested[34] and in the second study a toothpaste containing 1450 ppm fluoride, as a combination of sodium fluoride (NaF) and MFP, was evaluated.[35] Clinical probing measurements of the hardness of primary root caries lesions and their electrical resistance using the Electrical Caries Monitor (ECM) were used for the efficacy assessment. Examinations of root caries lesions were conducted at baseline, and after 3 and 6 months of product use.

For the study evaluating 1000 ppm fluoride, a total of 286 subjects completed the study. For subjects using the fluoride toothpaste, 33.3% of subjects exhibited at least one root caries lesion which became hard during the 6-month period of product use. This was significantly greater than the corresponding 19.3% for subjects who used the fluoride-free control toothpaste.[34] For the study evaluating 1450 ppm fluoride, 283 subjects completed the study. For subjects using the fluoride toothpaste, 42.1% of subjects exhibited at least one root caries lesion which became hard during the 6-month study. This was also significantly greater than the corresponding 19.6% for subjects who used the fluoride-free control toothpaste.[35] For both studies, the difference in the improvement in ECM scores between the fluoride and

fluoride-free products attained statistical significance at the 6-month time point.[34,35]

The clinical effect of brushing with amine fluoride toothpaste and rinsing with either a mouthrinse containing 250 ppm fluoride, as amine fluoride, or a control rinse without fluoride were also compared using similar methods.[35] After 12 months, for the fluoride rinse group, 67% of lesions became hard compared to only 7% in the control rinse group. This difference was statistically significant as were the differences seen between the two groups for ECM resistance values at the same examination.[36]

Taken together, these root caries studies demonstrate that this clinical design is able to distinguish products of known differences in anti-caries efficacy after 6 months of product use, with sample sizes of approximately 150 subjects per group. Moreover, use of the root caries study design enables the assessment of oral care products that re-mineralize and prevent further de-mineralization of naturally occurring lesions more rapidly and with greater sensitivity than conventional caries clinical trials.

In a recent study employing this method, a new toothpaste containing 1.5% arginine and 1450 ppm fluoride, as MFP, in a calcium base was compared to a positive control toothpaste containing 1450 ppm fluoride and a negative control fluoride-free toothpaste.[37] A total of 412 subjects completed the study. After 3 months product use, 27.7%, 24.6% and 13.1% of lesions had improved in the arginine-containing toothpaste, positive control and negative control toothpaste groups, respectively, and 0.7%, 4.5% and 16.8% had become worse. The differences in the distribution of lesion change between the negative control group and both the arginine-containing toothpaste and positive control groups were statistically significant. In all three groups, the mean Electrical Caries Monitor end values increased from the baseline to 3-month examinations, but none of the differences between the groups attained statistical significance. After 6 months, only one lesion (0.7%) was worse than at the baseline examination in the arginine-containing toothpaste group compared to 9.0% and 18.2% in the positive and negative control groups, respectively. In addition, 61.7%, 56.0% and 27.0%, respectively, showed improvement for the three groups. The differences in the distribution of lesion change scores between the negative control group and both the arginine-containing toothpaste and positive control groups were statistically significant ($p < 0.001$), as was the difference between the arginine-containing toothpaste group and the positive control group ($p = 0.006$). The Electrical Caries Monitor end values for the arginine-containing toothpaste, positive and negative controls groups, at the 6-month examination were 7.9 and 1.9 MΩ's, and 387 kΩ's, respectively. The differences between the negative control group and both the arginine-containing toothpaste and positive control groups were statistically significant ($p < 0.005$). The difference between the arginine-containing toothpaste and the positive control groups was also statistically significant ($p = 0.033$).[37]

The superior efficacy of the new toothpaste containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride in preventing caries lesions from progressing to the cavitation level, compared to toothpaste with 1450 ppm fluoride alone, has most recently been demonstrated in a 2-year conventional caries clinical study, further validates this method and illustrates the consistency in outcomes of these shorter term, 6-month studies and the longer term, 2-year study on this toothpaste.[38]

Assessment of the ability to re-mineralize and prevent further de-mineralization of naturally occurring buccal caries lesions using Quantitative Light-induced Fluorescence (QLF)

A number of studies have used the QLF method to assess anti-caries products of known efficacy and have validated the method for the assessment of product efficacy. The first study compared the ability of professional cleaning with and without use of a fluoride varnish to re-mineralize buccal lesions.[39] In the fluoride varnish group, there was a significant improvement between baseline and 6 months for both lesion area and the average change in fluorescence, but there was no significant improvement in the professional cleaning only group. There was also a statistically significant difference in the reduction of loss of fluorescence between the two study groups. It was concluded from this study that ''the QLF method is a sensitive clinical method, suitable for longitudinal quantification of incipient caries lesions on smooth surfaces''.[39]

In the second study, a fluoride-free dentifrice was compared to a dentifrice containing 950 ppm fluoride. At 3, 6 and 12 months, the fluoride dentifrice demonstrated statistically significantly greater improvements in lesion area and loss of fluorescence than the fluoride control. It was concluded that ''since the impact of fluoride dentifrices has been clinically demonstrated on numerous occasions using the conventional caries detection methods, these data indicate the ability of QLF to quantify this effect using a relatively small panel of subjects and a reduced period''.[40]

In a more recent study, two 1450 ppm fluoride toothpastes, one containing NaF, the other containing MFP, were compared to toothpaste without fluoride over a 6-month period. Lesions were longitudinally monitored over time with improvements in lesion parameters seen for the two fluoride groups and the non-fluoride group over the 6 months of the study. Statistically significant differences were seen between both of the fluoride toothpastes and the non-fluoride groups after 6 months. No significant difference was observed between the NaF and MFP products.[41]

Taken together, these studies demonstrate that this clinical trial design, employing QLF to assess re-mineralization of natural buccal caries lesions, is able to distinguish products of known anti-caries efficacy in 6 months in studies involving approximately 150 subjects per group. Further, use of this study design enables the assessment of oral care products that re-mineralize and prevent further de-mineralization of naturally occurring lesions more rapidly and with greater sensitivity than conventional caries clinical trials.

In three more recent studies, the ability of the new toothpaste containing 1.5% arginine and 1450 ppm fluoride, as MFP, in a calcium base to arrest or reverse naturally occurring buccal caries lesions in children was compared to that of control toothpastes.[42–44]

In the first study, the new arginine-containing toothpaste was compared to a matched 1450 ppm fluoride toothpaste (positive control) and a fluoride-free toothpaste (negative control). A total of 446 children, aged 10–12 years, completed the study. Quantitative Light-induced Fluorescence (QLF)

assessments of lesions were made at baseline, and after 3 and 6 months use of the products. For ΔQ, the baseline mean value was 27.30, and at the 3-month examination was 16.76, 19.25 and 25.89 for the arginine-containing toothpaste and the positive and negative control toothpastes, respectively. This represents improvements from baseline of 38.6%, 29.5% and 5.2%. At 6 months, the ΔQ values for the three groups were 13.5, 18.5 and 24.2 representing improvements from baseline of 50.7%, 32.3% and 11.4%. For ΔQ, the differences between the fluoride-free and both the arginine-containing toothpaste and the positive control groups were statistically significant ($p < 0.001$). The difference between the arginine-containing toothpaste and positive control group attained statistical significance after 6 months use of products ($p = 0.003$).[42]

In the second study, the new arginine-containing toothpaste was compared to a toothpaste containing 1450 ppm fluoride as sodium fluoride in a silica base (positive control) and a matched fluoride-free toothpaste (negative control). A total of 438 children, aged 9–13 years, completed the study. Quantitative Light-induced Fluorescence (QLF) assessments of lesions were made at baseline, and after 3 and 6 months use of the products. For ΔQ, the baseline mean value was 27.26, and at the 3-month examination was 18.00, 20.71 and 24.50 for the arginine-containing toothpaste, the positive control and negative control groups, respectively. This represents improvements from baseline of 34.0%, 24.0% and 10.1%. At 6 months, the ΔQ values for the three groups were 13.46, 17.99 and 23.70 representing improvements from baseline of 50.6%, 34.0% and 13.1%. Once again, for ΔQ, the differences between the fluoride-free and both the arginine-containing toothpaste and the positive control groups were statistically significant ($p < 0.001$). The differences between the arginine-containing toothpaste and positive control groups attained statistical significance after 6 months use of products ($p = 0.008$).[43]

In the third study, the new arginine-containing toothpaste was compared to a matched 1450 ppm fluoride toothpaste (positive control). A total of 331 children, aged 7–14 years, completed the study. As with the other two studies, Quantitative Light-induced Fluorescence (QLF) assessments of lesions were made at baseline, and after 3 and 6 months use of the products. For ΔQ, the baseline mean value was 28.62, and at the 3-month examination was 20.53 and 23.38 for the arginine-containing toothpaste and the positive control toothpaste, respectively. This represents improvements from baseline of 28.3% and 18.3%, respectively. At 6 months, the ΔQ values for the three groups were 15.86 and 20.34 representing improvements from baseline of 44.6% and 28.9%, respectively. For ΔQ, the difference between the arginine-containing and positive control toothpastes attained statistical significance after 6 months use of products ($p < 0.001$).[44]

In fact, in all three studies, the reductions in lesion size (ΔQ) achieved after just 3 months use of the arginine-containing toothpaste were similar to those achieved after 6 months use of conventional fluoride toothpastes indicating that lesions were re-mineralizing twice as quickly with the arginine-containing toothpaste as with the fluoride toothpastes.[42–44]

As discussed above, the superior efficacy of the new toothpaste containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride in preventing caries lesions from progressing to the cavitation level, demonstrated in a 2-year conventional caries clinical study, further validates this method and illustrates consistency in outcomes of these shorter term, 6-month studies and the longer term, 2-year study on this toothpaste.[38]

3. Conclusion

It is clear that consideration of early enamel and dentin lesions is vital to the assessment of the efficacy of oral care products in the context of our new understanding of the caries process. Significant advances in caries detection and monitoring methods have been made which now provide the opportunity to assess technologies and products which act on early lesions to arrest and reverse dental caries. Biesbrock et al.[45] concluded that

> ''if alternative detection methods or designs are to be used as tools to differentiate between and among products based on cariostatic activity, they should be required to demonstrate external validity similar to that demonstrated by conventional two- to three-year caries clinical studies. In this context, a minimum expectation for acceptance as a replacement for conventional testing should be that the method or design can differentiate products of known efficacy from one another, and that the efficacy relationship observed in a two- to three-year conventional study can be observed with the new method or design. It is desirable that the results be replicated in at least two studies to demonstrate the robustness of the methodology.''[45]

The results of the studies reviewed in this document satisfy these criteria. It can be concluded that quantification of the remineralization provided by oral care products assessed using buccal caries and root caries designs is an important and valid approach to developing understanding of the mechanism of action of a new technology and to establishing its clinical efficacy in respect of arresting and reversing early caries lesions, and it complements, enhances and may, ultimately, supplant the information from a conventional two- and three-year clinical trial.

Conflict of interest statement

Dr. Ellwood is an employee of the Colgate-Palmolive Company. Dr. Pretty has no conflict of interest.

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