The efficacy of slow-release fluoride devices in combating dental caries

- A literature review

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Masters of Science

Adam Segal

Supervisors:

Dr. Jacques Veronneau DDS

Dr. Simon Tran DMD, PhD, FRCD(C)

School of Graduate and Postdoctoral studies
Faculty of Dentistry
McGill University
Montreal, Quebec
Canada

March, 2012

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Abstract

The aim of this project was to conduct a thorough literature review on past and current slow- release fluoride randomized-control trials to determine whether the devices are effective in treating high caries-risk patients who traditionally do not comply with oral hygiene standards. Such high risk individuals are often characterized by rampant prior caries experience, low socioeconomic status, high *streptococcus mutans* counts in the saliva and inadequate levels of fluoride in their drinking water supply. I believe that third world countries could see a dramatic positive shift in overall systemic health by instituting public access to these simple devices as studies have shown conclusively that there is a positive correlation between oral health care and lowered heart disease and stroke risks. Based upon the current literature the consensus is that the slow-release concept presents an intriguing option for caries susceptible individuals as evidenced by significantly lower DMFT/DMFS scores in the treatment group upon completion of Toumba and Courzon's landmark 2005 trial using British school children as test subjects. This study showed that the slow-release device could successfully raise intra-oral salivary fluoride concentrations over an eighteen month span. Its only major drawbacks were the participant drop-out rate and the integrity of the device itself as retention numbers were not encouraging. Further studies should also be carried

out on broader, more general populations rather than solely high-risk subsets. A recent 2010 study by Al Ibrahim, Tahmassebi and Toumba improved upon the original slow-release device by encasing the fluoride glass pellets within removable plastic brackets which drastically improved retention, simplified the replacement procedure and increased patient satisfaction. Due to the manageable production costs and long-term viability of the device the slow-release concept has seen its popularity surge in recent years and has recently cemented itself as a widely accepted treatment option for clinicians who wish to target caries prone individuals with poor office attendance habits.

Resumé

Le but de ce projet était de procéder à un examen approfondi de la littérature sur les passées et actuelles à libération lente de fluorure randomisé de contrôle des essais afin de déterminer si les dispositifs sont efficaces dans le traitement de la carie élevé des patients à risque qui, traditionnellement, ne sont pas conformes aux normes d'hygiène buccale. Ces personnes à risque élevé sont souvent caractérisées par la prévalence des caries avant rampante, le faible statut socio-économique, haute Streptococcus mutans compte dans la salive et des niveaux insuffisants de fluorure dans leur eau potable. Je crois que les pays du tiers monde pourrait voir un changement radical positif dans la santé systémique globale en mettant en place l'accès du public à ces dispositifs aussi simples que des études ont démontré de façon concluante qu'il existe une corrélation positive entre les soins de santé bucco-dentaire et réduit les maladies cardiaques et accidents vasculaires cérébraux risques. Sur la base de la littérature actuelle, le consensus est que le concept à libération lente présente une option intéressante pour les personnes caries sensibles comme en témoigne CAOD significativement plus faible / scores DSFM dans le groupe de traitement à la fin de Toumba et Courzon point de repère de 2005 d'essai en utilisant des écoliers britanniques en tant que test sujets. Cette étude a montré que le dispositif à libération lente pourrait réussir à élever intra-orales des concentrations de fluorure salivaires sur une durée de dix-huit mois. Ses seuls inconvénients majeurs sont le participant le taux d'abandon et de l'intégrité de

l'appareil lui-même que les numéros de rétention ne sont pas encourageants. De nouvelles études devraient également être effectuées sur les populations plus larges, plus générales et non pas uniquement à haut risque sous-ensembles. Une récente étude de 2010 par Al Ibrahim, Tahmassebi et Toumba amélioré l'original à libération lente dispositif en enfermant les pastilles de verre de fluorure dans les supports amovibles en plastique qui a radicalement amélioré la rétention, a simplifié la procédure de remplacement et satisfaction accrue des patients. En raison des coûts de production et gérables à long terme la viabilité du dispositif, la notion à libération lente a vu son élan de popularité ces dernières années et s'est récemment cimenté comme une option de traitement largement accepté pour les cliniciens qui souhaitent cibler des individus caries exposées avec le bureau des pauvres habitudes de fréquentation.

Acknowledgements

I would like to thank the following people for their help and dedication:

1. Dr. Simon Tran for his continued support and supervision during this project.
2. Dr. Jacques Veronneau for taking me on as his MSc trainee and seeing me through to the completion of my projects.
3. The McGill University Faculty of Dentistry's resources, professors and encouragement.
4. The New York University College of Dentistry for their invaluable resources and support of this thesis.
5. Angella Lambrou for her help conducting the literary search and her private EndNote X5 tutorial session.

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List of Abbreviations

F – Fluoride

DMFT – Decayed, missing, filled teeth

SFG – Slow-release glass device

RCT – Randomized control trial

IFRD – Intra-oral fluoride releasing device

Introduction

While it is common knowledge that fluoride plays a major role in the defense against dental caries it is not as clear cut when attempting to answer such questions as how much to administer (commonly measured in parts per million), when and where to use it and which vehicle is ultimately most adept at minimizing its risks and maximizing its rewards. In order for fluoride to aid in the process of remineralization it must be present in an aqueous, soluble form most commonly found when it is a component of saliva in its ionic state. [1] This protective effect of fluoride in its free, soluble form counterbalances the demineralization in the biofilm area brought on by cariogenic bacteria and forms the basis of its well reputed anti-caries potential. (Fig. 1)

The precise scientific mechanism of action of how fluoride is incorporated into the biofilm need not be elucidated completely; rather it is imperative to understand that fluoride does not function by strengthening teeth nor does it increase their resistance to cariogenic intra-oral acid producing microbes such as *s. mutans* or *lactobacillus*. The inherent protective powers of fluoride, specifically how it counterbalances the demineralization of the enamel is explained by the presence of a less soluble mineral phase called *fluorapatite.* The purpose of this substance is to chemically reduce the mineral loss brought upon by the

aforementioned production of acids, often caused by exposure to sugars ingested through the diet. [2]

Figure 1

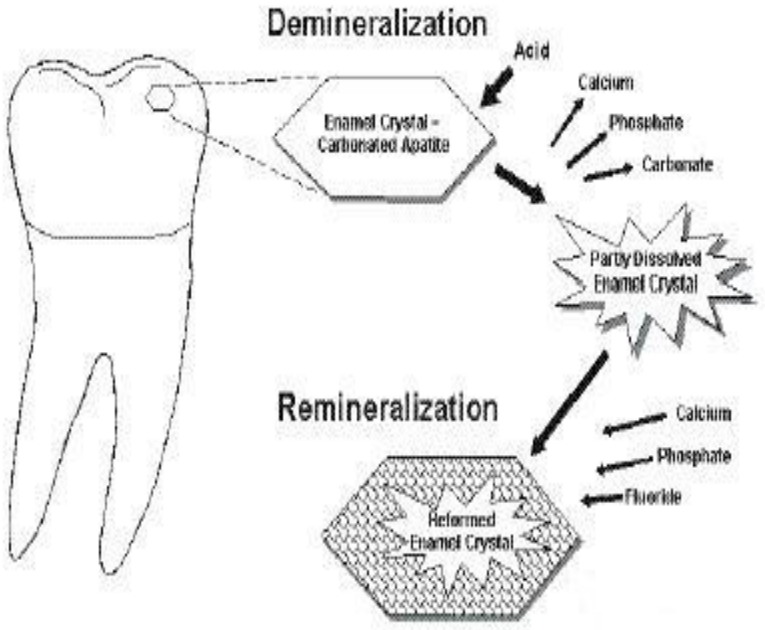

Figure 1 – Graphical representation of the ongoing process of remineral and demineralization which have a vital impact on the strength and hardness of dental enamel

In the evaluation of various fluoride vehicles it is necessary to point out where the carious lesions are located. Specifically, is the mineral loss occurring in enamel, dentine or possibly in exposed sub-cervical roots. It also helps to consider whether one is dealing with deciduous teeth as opposed to permanent teeth. The crystal structure of dentine is far more complex and organized than that of dense, calcified enamel and as such is more soluble, leading to an increased susceptibility to the formation of carious lesions. [3] The method of delivery is also dependent upon where the lesions occur; in the case of root caries it is possible that the roots may become exposed to the surface of the oral cavity through periodontal disease or other pathological gateways. During instances of gingival recession the cementum becomes exposed leading to further susceptibility to attack due to the fact that cementum, like dentine, has a higher critical pH value than enamel meaning that demineralization of dentine and cementum is more likely to occur. [4] Roots however possess a greater reuptake ability of fluoride than enamel which accounts for their resiliency in arresting caries, a feature that enamel does not share.

In the case of young children it must be established that deciduous teeth have higher pH thresholds than adult teeth and not surprisingly are more prone to developing lesions that would otherwise have not occurred in the sound enamel of healthy permanent teeth. Fluorosis is also a factor when dealing with small children as the critical period for exposure to fluoride is between 1 and 4 years of age. [4] Excessive fluoride can manifest itself as white spots in mild cases and as dark, brown mottling of enamel in more severe cases. Once the teeth have erupted into the oral cavity concern about producing fluorosis diminishes, as the biological process affecting developing enamel ceases. [5]

The salivary concentration of fluoride in its ionic form necessary to begin reversing the demineralization process is 0.02 parts per million (ppm). [5] This value attests to the tremendous impact fluoride has on controlling dental caries. At this minute concentration the saliva becomes supersaturated with mineralized fluorapatite and is able to carry out its main protective function by inducing the precipitation of minerals on the teeth. Once the teeth have incorporated the fluoride into their structure by replacing the original hydroxyapatite, forming new fluorapatite, there is a marked increase in the resistance to cariogenic bacteria (Table 1). The significance of these numbers correlates with the solubility product constants of the various salts. Fluorapatite, being less acid soluble than hydroxyapatite allows enamel to demineralize slower when subjected to

cariogenic, stagnated or mature acid producing biofilms thereby delaying mineral loss and allowing the teeth to resist a prolonged time period in which incipient lesions can be clinically observed. [6]

Table 1

Salt	Ionic Composition	Solubility Product
Brushite	$Ca(HPO_4).2H_2O$	$2.32x10^{-7}$
Tricalcium phosphate	$Ca_3(PO_4)_2$	$2.83x10^{-30}$
Octacalcium phosphate	$Ca_4H(PO_4)_3$	$2x10^{-49}$
Hydroxyapatite	$Ca_5(PO_4)_3OH$	$2.34x10^{-59}$
Fluorapatite	$Ca_5(PO_4)_3F$	$3.16x10^{-60}$

Table 1 – Solubility product constants of various salts. Note the lowest solubility which is found in Fluorapatite, a crystalline mineral formed from hydroxyapatite in the presence of fluoride that has a hardening effect on bones and teeth.

After considerable demineralization has occurred fluoride is incapable of producing any marked effects in the reversal process of remineralizing the now porous surface, a major weakness of its protective power. This is often the case when clinicians are able to detect a distinct white spot via optical methods that can visualize possible early erosion or decay. If there appears to be early

decalcification without any underlying bacteria then it's probably best to avoid using an explorer as further probing could lead to increased or forced cavitation. In this scenario the fluoride will still allow remineralization to occur leading to a change in lustre from soft and chalk-like to hard and shiny. [6] Fluoride also has no effect on the initial causes of caries, namely the consumption of fermentable sugars through diet, nor does it possess any innate ability to control bacteria metabolism at low concentrations. At higher concentrations however (over 10 ppm) there is evidence that fluoride can interfere with the acid production of *s.mutans* which may or may not have a significant effect on its cariogenicity. [3] Other limitations include difficulties optimizing the fluoride concentration of drinking water supplies. In communities with naturally high fluoride levels enamel fluorosis is prevalent despite carefully monitored drinking water concentrations. [7] Fluorosis is also a major concern when swallowing toothpaste in young children. The spike in blood concentration seems to be directly responsible for white chalky areas in the still mineralizing teeth (Fig. 2).

Figure 2

Figure 2 – Case of mild fluorosis as evidenced by white spots on the maxillary central incisors.

Attempts to alter fluoride concentrations in the water supply have been met with success and a decrease in caries incidence in urban areas where water eufluoridation is legislated. Fluoride is also ingested through a multitude of sources (food, beverages, and various dentifrices) making it rather difficult to ascertain any conclusive evidence pertaining to the true efficacy of water fluoridation. A study in Hong Kong showed that lowering the level of fluoride from 1.0 to 0.7 ppm lead to decreased fluorosis. [7] In Wigtownshire, Scotland communal water fluoridation ceased completely, resulting in a noticeable increase (over 100%) in caries

prevalence. [8] Tinkering with water supplies must be done with extreme caution, and if fluoridation is to be discontinued there must be suitable preventive measures in place to offset the loss of a consistent source of fluoride. Topical fluorides in the form of mouth rinses, varnishes or supplements could be used as replacements. Non-professional methods of delivery also have the inherent problem of being used ineffectively, severely jeopardizing their intended protective benefits. The problem with the professional method of delivery is that their use is restricted to the dental office, thus limiting their exposure and availability.

Background and History

The slow-release concept has piqued the interest of investigators due to its low associated costs and long-term viability. The glass pellets used to house the fluoride are easily attainable and follow-up costs are also low as they do not require constant supervision by the investigators or any extensive expertise in measuring the change in DMFT/DMFS scores. Once the beads are affixed to the teeth there only exists a need to conduct follow-ups at baseline, mid-study and termination, usually over a two year period in a randomized control trial. Any more than this would be unnecessary as a certain amount of time must be allotted in order to properly gauge it's efficacy on a potentially chronic problem like caries incidence.

To attack a problem at its source is the best way to eradicate it. The main slow-release randomized control trials have been carried out on children. KJ Toumba and Larry Courzon, the principal investigators behind the slow-release concept, realized the value in arresting the spread of caries before it has a chance to spread and wreak further havoc on teeth. High risk children from low socioeconomic backgrounds are the perfect test subjects due to their naiveté and poor attendance records at the dental office.

Table 2

Safe to administer
Cheap and cost-effective
Easily manufactured
Easy and quick to apply
Robust
Long-term fluoride release of at least 1 year
Provide a continuous low concentration of intra-oral fluoride
Act topically at the tooth surface
Do not rely on patient compliance or motivation
Prevent dental caries clinically

Table 2 – List of the implied advantages of the slow-release device within the clinical setting.

One of the above points, specifically not having to rely on patient compliance or motivation, is a major advantage of the slow-release approach. Unmotivated, apathetic or ignorant patients are often seen when dealing with high levels of caries activity. The perpetual concept of fluoride being continuously released without the patients having to do anything or make the trip to the dentist's office is a major coup. Previous attempts to provide fluoride to high-risk individuals have centered on dental materials such as cements or resins which tend to exhibit a 'burst effect' with the fluoride only capable of delivering a short term benefit. [9] The SFG devices are designed to exhibit a long-term effect, thus

distinguishing from previous studies tailored to increase intra-oral salivary fluoride.

The genesis of the slow-release concept was borne in the realization that newer options were needed which could better harness the power of fluoride ions and release them over a given time period at a fixed rate. Frequent applications of topical fluoride would be most beneficial in maximizing its caries-protective effects however this would be impractical to the patient. The SFG device makes this a feasible endeavor by remaining affixed to the patient's tooth at all times without the need for constant reapplication. A device capable of releasing pre-determined amounts of fluoride directly into the oral cavity quickly became the subject of various randomized control trials in the late 1990's. According to a 1999 paper by Featherstone and Cate, "the consensus of current scientific opinion is that a constant supply of low levels of intra-oral fluoride, particularly at the plaque/enamel/saliva interface, is of most benefit in preventing dental caries". [1] Fejerskov et al (1981) determined with virtual certainty that "it is the activity of the fluoride ion in the oral fluid that is of most importance in reducing solubility of the enamel rather than a high content of fluoride in enamel". [10]

Toumba and Courzon postulated that if a device was capable of providing long-term intra-oral supplies of fluoride ions without explicitly depending on patient cooperation then such a device could be extremely valuable to high risk

patients. [11] To date the co-polymer membrane has shown the greatest potential of being the de-facto choice for the slow-release vehicle due to its ability to release fluoride over a much longer period of time than the previous materials (cements, acrylics, resins etc). [12] It was originally developed in the USA by Cowsar et al. in 1976. Initial duration of release was shown to be between 30 and 180 days with salivary fluoride levels remaining elevated throughout a 100 day test period. [12] Animal studies by Mirth et al (1983) showed that copolymer device could lower caries prevalence by 63% in rats over a one month trial using 0.15mg of fluoride per day while a similar study also on rats by Shern et al (1991) found that the devices significantly restricted the development of carious lesions on the sulcal-morsal surface. [13] Glass was the other main type of slow-release device capable of raising salivary fluoride levels on a long-term basis. They originated in the UK and were first used in animal husbandry to combat feed deficiencies of trace elements such as copper, selenium and cobalt. [14] When placed in the mouth it dissolves slowly in saliva and releases fluoride without any detrimental effects to the device's original integrity.

Slow-release devices are in theory an excellent solution to those who do not regularly see a dentist, brush their teeth effectively and/or fail to make proper use of dentifrices (toothpaste, rinses, gels, varnishes). Such patients would be characterized as high-caries risk due to their apathy towards proper oral hygiene. A

high risk individual often comes from a lower socioeconomic class and typically neglects to schedule regular dental check-ups. They are also characterized by increased levels of *s. mutans* bacteria in their saliva and prior history of caries activity. Previous attempts at raising fluoride concentrations inside the oral cavity such as ingesting fluoride tablets or topical methods like gels and rinses have been met with limited success. [14] The reason for that is simple in that they relied too heavily on active participation from the subjects or were too expensive to keep up due to the logistics of having to emply high cost dental practitioners. Their benefits were also short-lived.

Slow-release devices are specifically designed to release low levels of fluoride into the saliva at a constant flow rate to ensure remineralization. [15] The devices are fitted intra-orally, usually on the buccal surface of the right maxillary first permanent molar and typically last anywhere from two to three years (Fig. 3). It is basically a cost effective way of keeping an elevated concentration of fluoride ions in the saliva of high risk individuals who do not have the resources or the knowledge to benefit from regular dental care. This sustained elevated salivary fluoride concentration has been statistically shown to decrease the incidence of DMFS (decayed, missing and filled surfaces) in both primary and permanent dentitions. [15]

Figure 3

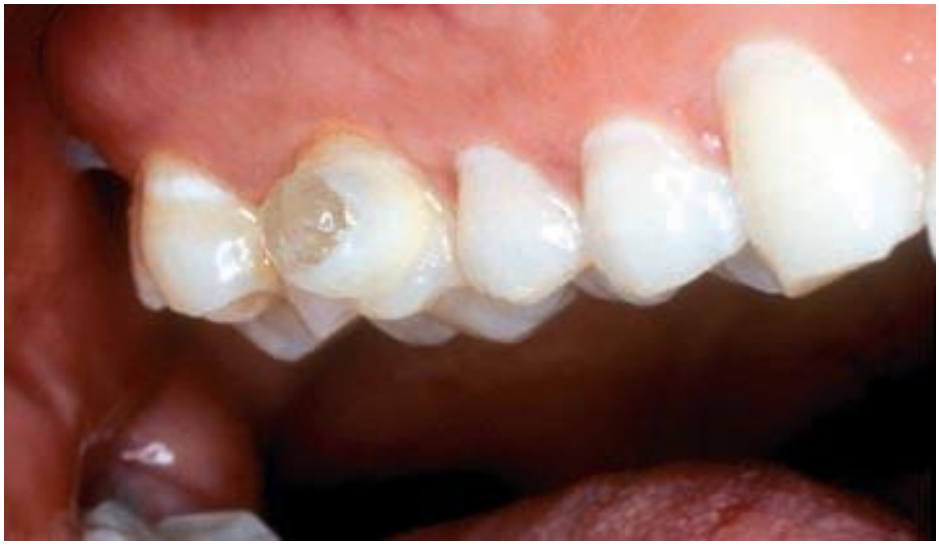

Figure 3 – Slow-release glass bead device attached to buccal surface of the first permanent right maxillary molar

The first randomized control trial carried out on slow-release devices focused on British school children as test subjects, all 8 years of age who came from low socioeconomic backgrounds from a small working class town in Northern England. The young subjects all had prior history of caries as well as inadequate access to water sources with sufficient levels of fluoridation. Past studies have also shown that most other preventive methods aimed at high-risk groups failed because they relied too heavily on patient compliance. [14] This realization ushered in the need for a novel system of sustained, constant F delivery that did not explicitly rely on patient cooperation as there was conclusive evidence

that higher intra-oral salivary F concentrations correlated with a lower prevalence of carious lesions as was the case in areas in well fluoridated water supplies (Fig. 4). This correlation was seen in a 1998 study by Shields et al. which showed that a F concentration of 0.04 ppm in the saliva of children resulted in much lower caries activity than children with levels of 0.02 ppm or less. [16] 0.02 ppm is generally considered an acceptable level of F concentration for low to moderate-risk individuals however it remains inadequate at providing protection in high-risk groups. [16] The slow-release device, if viable, would be an extremely cost-effective method in preventing dental caries in high risk individuals. All that was required now was a long-term clinical trial in order to assess its effectiveness and reliability.

Figure 4

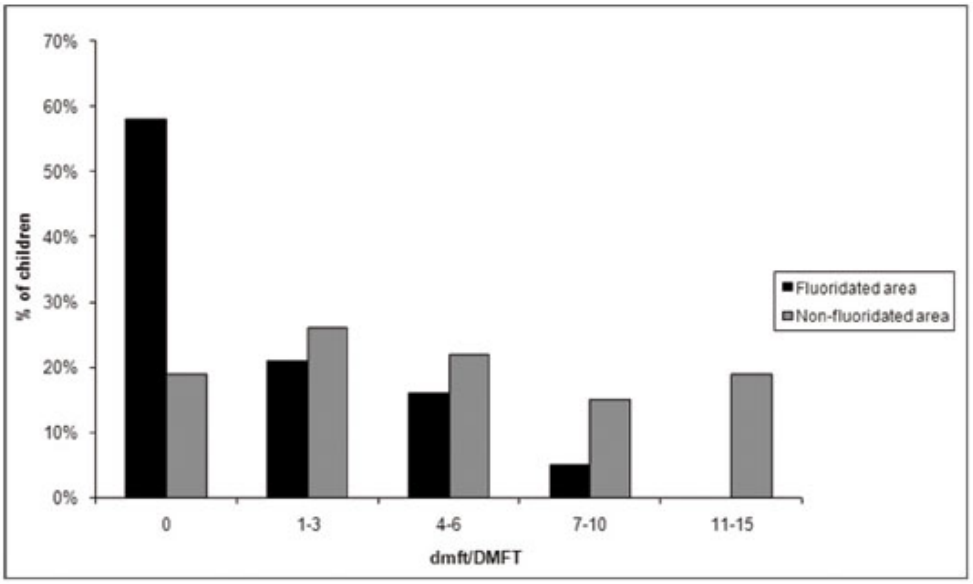

Figure 4 – Distribution of the dmft/DMFT index for children from fluoridated and non-fluoridated areas. It represents a lower incidence of decayed, missing or filled teeth in children who reside in areas with adequate water eufluoridation.

Search Methodology and Inclusion Criteria

An extensive literature review was carried out on April 23rd, 2012 regarding the strengths and weaknesses of randomised controlled trials of certain types of slow-release devices to answer the question of whether they are capable of reducing dental caries in high-risk individuals at the clinical level. There has been evidence to suggest that these devices are effective in arresting and even reversing the progression of caries on both deciduous and permanent teeth most notably in an RCT carried out by Toumba and Courzon in 2005 on British school children. This study in particular was the primary focus as the main benefactor of such devices would be children at high risk of developing caries later in life, the preferred target demographic, although trials involving adults were not excluded. Toumba and Courzon's study represented one of the few blinded randomized control trials that successfully compared the slow-release device with some form of alternative treatment or placebo.

Searches were conducted for potential randomised control trials in the following databases: PubMed, Web of Science, OVID Online and Medline based on the search criteria outlined in Appendix 1. To ensure thoroughness Google Scholar was referenced to check who else was citing the 2005 RCT by Toumba and Courzon as well as to verify whether any recent advancements have been made

that failed to show up during the literary search. Since KJ Toumba is the foremost expert on the slow-release concept an author search was conducted to see all of his other articles which were then gauged for relevance to the project. Lastly references cited in all relevant articles garnered through the literature search were scanned for any possible additional material that may have been missed. An attempt was also made to hand search the 2005 Caries Research journal where Toumba and Courzon published most of their work however the Life Sciences library did not currently carry it and the inter-loan option was not available for that specific volume.

Four emails were also sent to Toumba and Courzon themselves which outlined the goal of this thesis and sought to inquire on current, unpublished studies which may or not be relevant to the conclusion. Regrettably the email to Courzon bounced back and Toumba failed to respond. Despite the failure to communicate directly with the authors it can be reasonably assumed based on the search criteria that there exists only two other randomized control trials that tested the SFG device within the clinical setting. A 2006 study by Andreadis et al. which focused on an improved ergonomic design strategy for the glass bead as well as a 2010 study by Al Ibahim et al. which implemented novel plastic brackets to secure the SFG devices were carried out and led to noticeable improvements in retention compared with the original 2005 Toumba and Courzon RCT.

In addition various sources of information including Cariology textbooks by Lebrun and Fejerskov, review articles from The Cochrane Library and assorted grey literature including conference/lecture materials from the New York University College of Dentistry were referenced. These were mostly used to formulate the basis of the introduction and help build a foundation on the history of early caries detection methods.

The search criteria implemented in Appendix 1 yielded thirty-six results. Only nine of those were found to be relevant. Three of these nine entries were reviews leaving six journal articles to analyze.

In chronological order the first entry was a 1999 study by Marini et al. This study introduced an intra-oral fluoride releasing device (IFRD) to achieve a constant rate of continuous fluoride release in patients receiving orthodontic treatment of 0.02 to 1.0 mg per day for up to six months' time. The problem with this study, besides the obvious shortcoming in that it only focused on patients fixed with orthodontic appliances, was that they did not construct a 'dummy' device for their control group. The lack of a placebo factor in conjunction with no real evidence of blinding rendered this study inadequate on the basis of an elevated risk of bias.

The next potentially relevant entry was a 2001 research report by Toumba himself on the history of slow-release devices and the various materials that they were comprised of in past studies. It was not a trial but rather an introduction to the novel concept of a slow-release device that would raise the intra-oral concentration of fluoride in the human mouth over a predetermined stretch of time. It outlined toxicity and safety reports and clearly is not representative of a full randomized control trial. Toumba would go on to publish those findings in the landmark 2005 paper along with his counter-part Courzon which is the third entry.

Toumba and Courzon's 2005 RCT study formed the crux of the results criteria in which the question of whether slow-release devices show a marked improvement in decreasing caries incidence, the alternative hypothesis, or whether they fail to do so thus proving the null hypothesis of no difference. The Toumba and Courzon collaboration was also the only study deemed relevant to the main results section in a systematic review carried out by Bonner, Clarkson, Dobbyn and Khana. [17] This review was located in the 2006 Cochran Database of Systematic Reviews and concluded that evidence to support the on-going efforts to administer slow-release glass bead devices in caries susceptible persons was unreliable due to the small scope of the Toumba and Courzon study and the apparent lack of more generalized random control trials.

Toumba and Courzon attempted to support the alternative hypothesis that children fitted with slow-release devices showed significant decreases in new carious lesions (in either dentine or enamel) compared to the control group which received the slow-release glass pellets devoid of fluoride. Only one investigator was used to install the devices in the children's mouths who all hailed from various elementary schools in the town of Beeston located in Leeds, England. The investigator also remained blinded to the study up until final data was obtained. Regarding bias I would assess the risk as high given that only 63 of the initial 174 participants were included due to retention problems and deliberate dislodging of the devices. Those who did not retain the devices were not included in any way in the final results, representing an unacceptable follow-up loss of 64% which left 31 participants from the intervention group and 32 from the control. Aside from the bias issue it was unfortunate how Toumba and Courzon only completed one trial on a very limited number of participants from a high-risk population in a small town in Northern England. Clearly, based on the positive results they saw in decreased DMFS (decayed, missing and filled surfaces) there was a need to expand the trial to a broader population comprised of varying degrees of risk. More work also needed to be carried out on the retentive capability of the device either through new technology or improving the contour of the glass bead-like structure to assure a more secure fit to the buccal surface.

The fourth entry was a randomized control trial on fifteen children by Andreadis et al. They in essence took Toumba and Courzon's dome-shaped design and fashioned it into a more compact, lighter kidney-shape device with smaller dimensions. The main changes were flattening out the side that attaches to the buccal surface of the tooth and making the opposite side convex, thus exposing a larger surface area to the oral environment. After a period of 4-7 days all children reported being virtually unaware that they were carrying the attached device. No local or systemic side-effects were reported and retention rates climbed to 86%. 93% if you discount one of the female subjects who accidentally swallowed her device after the first day. The new kidney shape combined with a circumferential retentive groove etched into the surface of the maxillary right first permanent molar made it almost impossible for the children to dislodge if they were so inclined. This represented a major boost in retention in comparison to the 48% seen in Toumba and Courzon's 2005 RCT. Seemingly the only issue that remained now was figuring out a way to avoid having to repeat the entire bonding and replacement procedure once every two years. In patients from low-socioeconomic backgrounds where attendance is usually poor this is a major problem as the intended effects are meant to be long-term, lasting well above and beyond a two year span.

The fifth article found was highly relevant to this project as it sought to test new plastic brackets initially designed to house the disc-shaped fluoride glass pellet and substantially improve attachment and replacement procedures. [18] Al Ibrahim, Toumba, and Tahmassebi engineered a two phase study in which they placed the new SFG in distilled water and saliva to assess activity *in vitro* and then proceeded to test it out *in vivo* in adults. Ultimately it was found that the brackets did not cause any discomfort in the subjects and did not interfere with the release of F. During recall visits the SFG no longer needed to be de-bonded and retention numbers shot up to 86%, a marked improvement over any previous slow-release trials given that it replacement of the device was now a simple matter of recharging with a new F filled glass pellet. A new standard was set in construction of the SFG that no longer relied on flimsy dome-shaped pellets or kidney-shaped glass beads that could only be changed via time consuming de-bonding procedures within a dental office.

A sixth and final 2011 study by Toumba and a new team of collaborators investigated the effect of an SFG on unstimulated saliva and undisturbed plaque biofilms over a one week span. While the experiment was a randomised control double blind cross-over study it ultimately failed to be a key source of results due to the fact that the trial only lasted seven days. The short duration of this trial was a primary reason why the final data showed no effect in raising F concentration in

dental plaque and unstimulated whole saliva. They concluded that longer periods of time were probably needed in order to achieve their desired outcome.

Materials and Methods

There are two main types of slow-release devices, one developed in the UK and the other in the United States. The American version featured a polycarbonate based block copolymer membrane and consisted of a small pellet that was meant to be attached to the tooth surface while the UK device is made of glass.[19]

The membrane portion of the copolymer American device is what controls the rate of release. It is comprised of an inner-core of hydroxyethyl methacrylate and methyl methacrylate mixture, usually in a 50/50 ratio. The inner-core is further surrounded by a 30:70 hydroxyethyl methacrylate to methyl methacrylate copolymer membrane which controls the precise rate of release of the sodium fluoride (NaF). [19] Hydration within the oral cavity triggers the device to release controlled amounts of NaF. The membrane features precise water absorption rates that ensure reliability and accuracy of NaF release. Once triggered the fluoride moves spontaneously from the matrix through the membrane and into the saliva.

The device itself (Fig. 5) is 3 mm in length and 2 mm in width. Its thickness is approximately 1.5 mm and is almost always attached to the buccal surface of the first permanent molar. The method of attachment varies and is still up for debate. Some researchers have spot welded stainless steel retainers to standard orthodontic bands while others used resins. [19] No matter which method was used retention of

the devices consistently has proven to be the biggest problem in overall effectiveness. Young subjects have tended to revolt against a foreign object in their mouths by deliberately dislodging the device as was evidenced in Toumba and Courzon's 2005 RCT. [20]

Figure 5

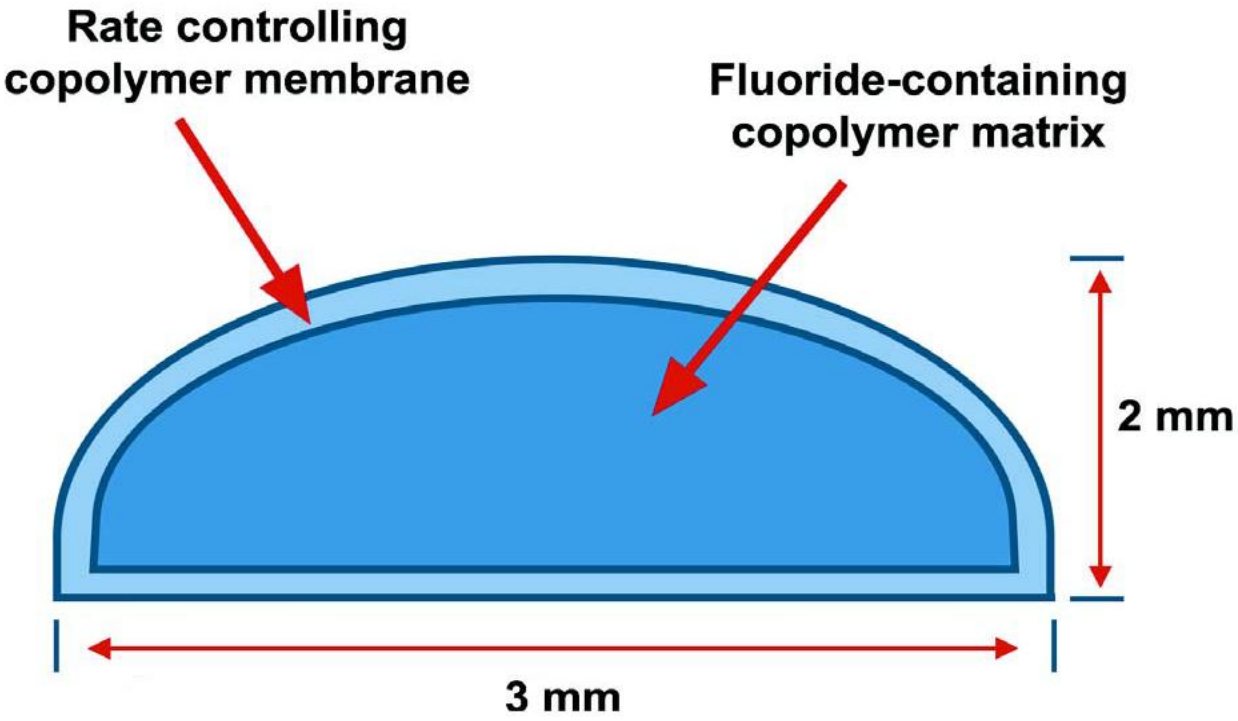

Figure 5 – Cross-sectional view of the copolymer device

Fluoride release rates in the American design are traditionally between 0.02 and 1.0mg per day for up to six months. At about the four month mark it was

demonstrated that salivary fluoride levels were elevated before they began to drop off somewhat. [19] Longer experimentation times could have been achieved through a higher concentration of fluoride placed in the inner core.

The UK device is different than the copolymer US design in that once it's exposed to saliva it begins to slowly dissolve. It is approximately 6mm long, 2.5mm wide and 2.3mm deep so it is somewhat smaller. [19] Its original shape was dome-like and then later evolved to a kidney-shaped pellet as seen in Andreadis' 2006 RCT. [21] (Fig.6) An example of the UK device was this improved upon kidney-shaped SFG designed by Andreadis in concert with Toumba and Courzon, one year after their 2005 RCT. This version of the device also attached to the flat buccal surface of the tooth with the convex outside surface bulging into the oral cavity. A group of children aged 6-16 from The Leeds Pediatric Dental Clinic were recruited for the study by Andreadis et al. To see how large a sample size was required Andreadis set his retention rate goal at 90% for the anticipated outcome and performed a power calculation based on the formula:

$$N = \frac{\text{success} \times \text{failure in study A} + \text{success} \times \text{failure in study B}}{(\text{success on study A} - \text{success on study B})^2} \times \text{magic number}$$

Study A was recorded at 0.90 while Study B was 0.48, representative of the low retention rate from Toumba and Courzon's study. The magic number chosen

by Andreadis was 7.8 for a significance level of 5% and a power of 80%. This computed to a sample size of 15. [21]

Figure 6

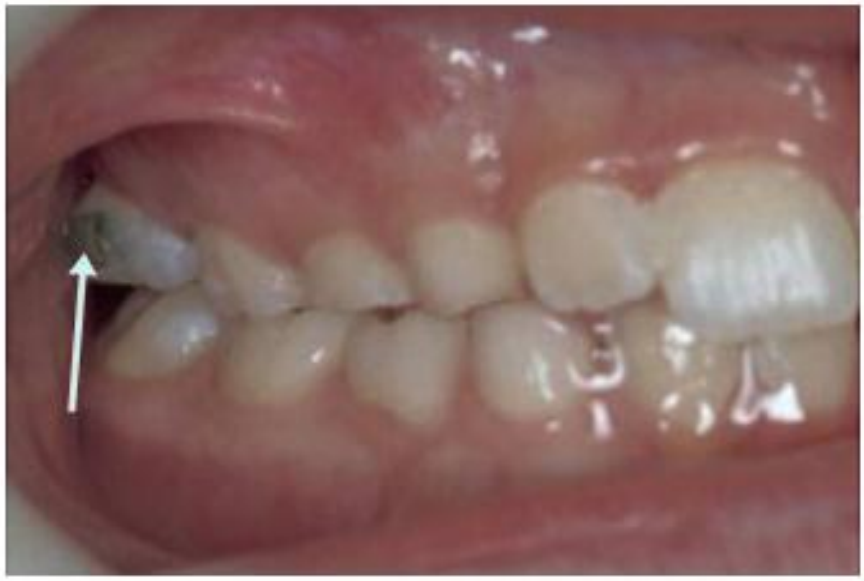

Fig. 6 – Representation of the kidney-shaped SFG attached to the maxillary right first permanent molar. This was also carefully positioned so as not to interfere with occlusion. A substantial amount of composite resin was required for attachment of this particular type of SFG which caused excess plaque accumulation on top of the device.

The new kidney-shaped devices were affixed to the children's molars using the acid etch composite resin technique, similar to Toumba and Courzon's method of attachment. Saliva samples were collected at baseline and then analyzed 30 and 180 days later to determine the amount of F present. The samples were analyzed immediately or after a simple freezing process where they were stored at -12℃

using an ion-specific electrode. The authors also looked for evidence of gingivitis and any potential damage to soft tissues on day 1, day 90 and day 180. In addition the soft tissues were inspected for ulcers, erythema or irritations. Upon conclusion of the trial Andreadis prepared a questionnaire for the parents of the children in which they had an opportunity to gauge their child's complaints or any difficulties encountered with the device. Student's t tests and non-parametric Wilcoxon paired tests measured the intra-oral F levels at baseline and at the end of the study.

The most recent trial by Al Ibrahim, Tahmassebi and Toumba involved newly constructed plastic brackets designed to house smaller glass pellets and drastically improved the ease of replacement and overall retention (Fig. 7). As with most slow-release devices, retention was an ongoing problem, hence a new modification in the form of a disc was introduced in order to facilitate attachment (Fig. 8). This disk-like structure was able to be inserted inside a plastic bracket so that a new device could be easily implemented without the need for de-bonding and removal of leftover resin. The brackets were divided and placed into three separate falcon tubes containing distilled water in which their daily release of F was measured and recorded. [18] The first group contained five glass beads. The second contained five SFG devices with the brackets facing downwards while the third group also contained five SFG's facing upwards. The F levels were evaluated daily for one week, weekly for a month and then monthly for 18 months. The

researchers kept them frozen at -12℃ until it came time to conduct the analysis where F ion concentration was determined using an ion chromatograph.

Figure 7

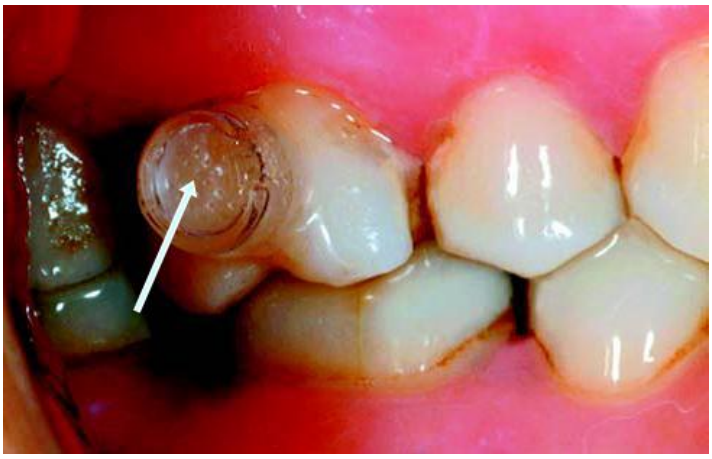

Figure 7 – Latest glass device and bracket attached to upper first permanent molar. This made replacement a much simpler process as it eliminated the need for advanced de-bonding and new acid etching in order to install a new device.

Figure 8

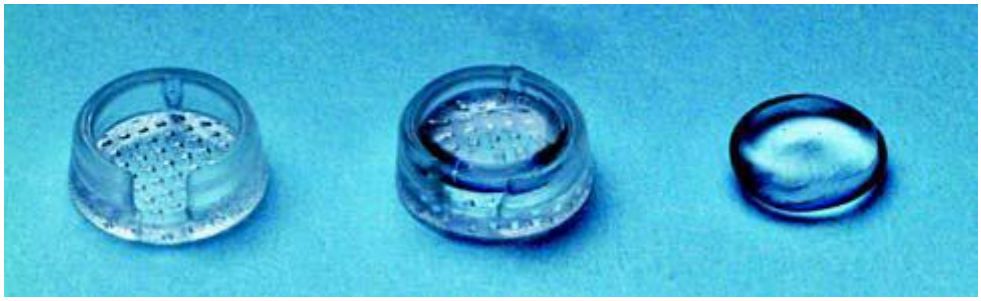

Figure 8 – Plastic retention brackets containing the glass bead fluoride device which represent the latest version of the slow-release delivery method.

Release rates in the glass pellets depended on the initial amount of fluoride present within the device as well as the solubility of the glass used. A concentration of 13.3% showed higher rates of release than large percentages. This was explained by the presence of aluminum in higher concentrated glass devices which would bind to fluoride and slow down its release. [19] Since the UK glass design was shown to have much longer lifetimes than the copolymer design it is now entrenched as the de facto form of slow-release device. Copolymer membranes cease to release significant amount of fluoride after six months while the glass bead structures could function up to two years, a fact which rendered te copolymer design obsolete.[22]

KJ Toumba and Larry Courzon of The University of Leeds conducted a hallmark 2005 slow-release fluoride study on 174 eight year old children from a low socioeconomic area of Leeds, UK. The location was chosen due to strong epidemiological evidence that showed a much higher DMFS score than the UK average of 2.3.[20] The trial took place in the inner city of Beeston which had an average DMFS score of 4.0 as well as poor records of dental care and attendance. They used two slow-release devices, the test device containing fluoride and one without which acted as the control. Initial saliva samples were taken followed by another sample every six months thereafter for a period of two years. They looked specifically at DMFS based on caries at the dentin threshold. White, potentially

reversible lesion spots were overlooked. They utilized the glass slow-release model and attached it to the buccal surface of the right permanent maxillary molar via a novel acid etch composite resin material. In addition they cleaned each tooth with a fluoride free paste and then proceeded to etch for 30 s with 40% phosphoric acid gel to increase the bond strength between the composite resin and the enamel. A Scotchbond light-cured bonding agent was then applied to the etched surfaces of both the tooth and the fitting area of the glass device. After light-curing for 30 s another thicker layer of Herculite resin was applied to each surface then cured for a full minute. Soflex discs were then used to smooth away and polish any resin cuffs.

DMFS assessments were then made using the gold standard method of Palmer et al [1984]. [23] *S. mutans* counts were also determined using the method of Kohler and Brathall [1979]. [24] Also in order to ensure reproducibility of the primary investigator's original epidemiological data, 25 children were re-assessed two hours after initial diagnosis. It was determined that the initial caries measurements were accurate after examining each of the children in random order to avoid any bias. Salivary concentrations were also taken at the time of examination and analyzed for fluoride via the method of Taves that used an F-ion specific electrode after acid diffusion [1968]. [25]

To attempt to ensure clinical significance and remove as much initial bias as possible Toumba and Courzon designed identical glass pellet devices, regardless of

whether they were part of the control or not. An independent investigator coded each device and then placed them in individual plastic bags and randomly numbered them 1 to 200 so that there were 200 controls and 200 non-controls containing the fluoride. The code detailing which numbers were test devices or controls was also kept in a sealed envelope and hidden away in a safe in the Department of Child Dental Health until completion of the trial. Replacements were also on hand should the original fail to properly attach. Statistical analysis in the form of a paired student's t test was used to analyze differences between the control and test groups. [20]

Before evaluating the clinical outcome of such a device Toumba and Courzon conducted a pilot study to know conclusively whether it was even feasible that a glass-like device could be retained in the mouth long enough to release fluoride at precisely designated flow rates. [15] If so, what concentrations would be necessary to stimulate a long lasting intra-oral presence of fluoride and what would be the inherent risks with such a foreign device being attached to teeth? In 2003, about six months before their clinical trials on Leeds school children Courzon and Toumba designed a study capable of answering these questions in order to see whether or not they should advance to the clinical phase of the trial. To do so they looked at glass that contained various inorganic radicals used in animal husbandry to help raise and feed livestock. [22] They postulated that if these glass

devices were able to contain trace elements designed to supplement feeding deficiencies in cattle then they could also be combined with F to combat caries in humans, F being the most commonly recognized anti-caries trace element.

They initially looked at baseline non-F salivary levels by giving fluoride-free toothpaste to one volunteer over a two week period. The volunteer was then fitted with a slow-release F dome-shaped glass device containing 13.3% F where saliva measurements were then taken at fixed time periods over an 18 month span at which point the device was removed. Gingival and buccal mucosa were then checked for damage. Early signs of caries were also checked at 3 month intervals using an explorer while bitewing radiographs were taken at 6 month intervals. [11]

To analyze which F percentages within the glass devices were most effective Courzon and Toumba tried three separate amounts; 13.3%, 18.3% and 21.9%. Each device weighed the same but contained varying amounts of fluoride, measured in milligrams. Again they studied adult volunteers who had been instructed to use F-free toothpaste for three weeks prior to the commencement of the study. The glass devices were then attached to buccal surfaces of the right first permanent maxillary molar using common resin techniques. Saliva samples were taken for two minutes, four times a day at 7:00, 12:00, 18:00 and 23:00 hours for the first five days, then down to once a week for a month. Analysis was carried out using the Taves acid diffusion method. [25]

To analyze the potential risks of toxicity in a pilot study such as this they needed to assess the effect on blood plasma F should the glass device become dislodged and swallowed. Once more, five adult volunteers used F-free toothpaste for two weeks prior to testing to minimize any background F exposure. On two separate occasions each of the volunteers swallowed either a glass device pellet or a NaF pellet which acted as the control. Blood samples of 10ml were collected at baseline and then at 2.5, 5, 10, 20, 30, 45, 60, 90 and 120 minutes after ingestion of the devices. Plasma F levels were measured according to the Taves acid diffusion method. Blood samples were then centrifuged at 2,000 rpm while standards of F at baseline and at 0.01, 0.025, 0.05, 0.10, 0.25, 0.50, 1.00 and 5.00 mg were also measured after acid diffusion to produce standard curves which allowed them to ascertain the levels of plasma F in the various samples. [11]

Results

Results from the pilot study were exceedingly positive and convinced Toumba and Courzon that their hypothesis of a slow-release F device significantly reducing dental caries prevalence in high risk humans was on the verge of coming to fruition.

The first test on F release and saliva concentration conducted in the pilot study on a single adult volunteer showed an early erratic fluctuation yet seemed to settle down soon after the initial burst (Fig.9).

Figure 9

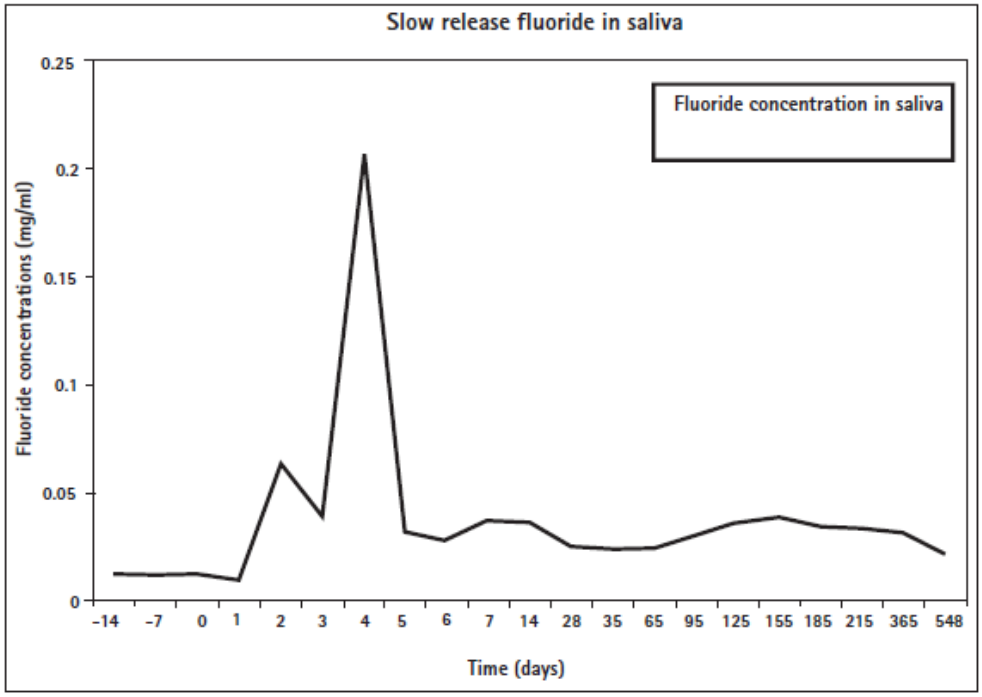

Figure 9 – Graph that shows fluoride concentration over an 18 month span in an initial volunteer in a pilot study by Toumba and Courzon. The early spike can probably be attributed to an overly reactive rough initial surface. The release rate then settles down to a more uniform pace.

An early spike in fluoride release of about 0.04 mg is seen on the above graph, possibly due to the reactive nature of the surface of the molar. As the surface became smoother F release became more uniform and eventually settled to a level of 0.035 mg after one week. Mean F concentrations were 0.030 mg after the first month, 0.033 mg after six months, 0.031 mg after a year and 0.038 mg upon termination of the study at one and a half years. There were also no signs of enamel demineralization or adverse effects of any kind on the buccal surface of the volunteers' maxillary molars where the device had been attached. [11]

Analyzing which percentage of F proved to be the most effective, Figure 10 clearly illustrates that 13.3% was the ideal amount to be placed within the glass device. It was the clear choice as it provided the most consistent level of release. The reason for this was the presence of aluminum in the higher percentage pellets but not in the 13.3% version.

Figure 10

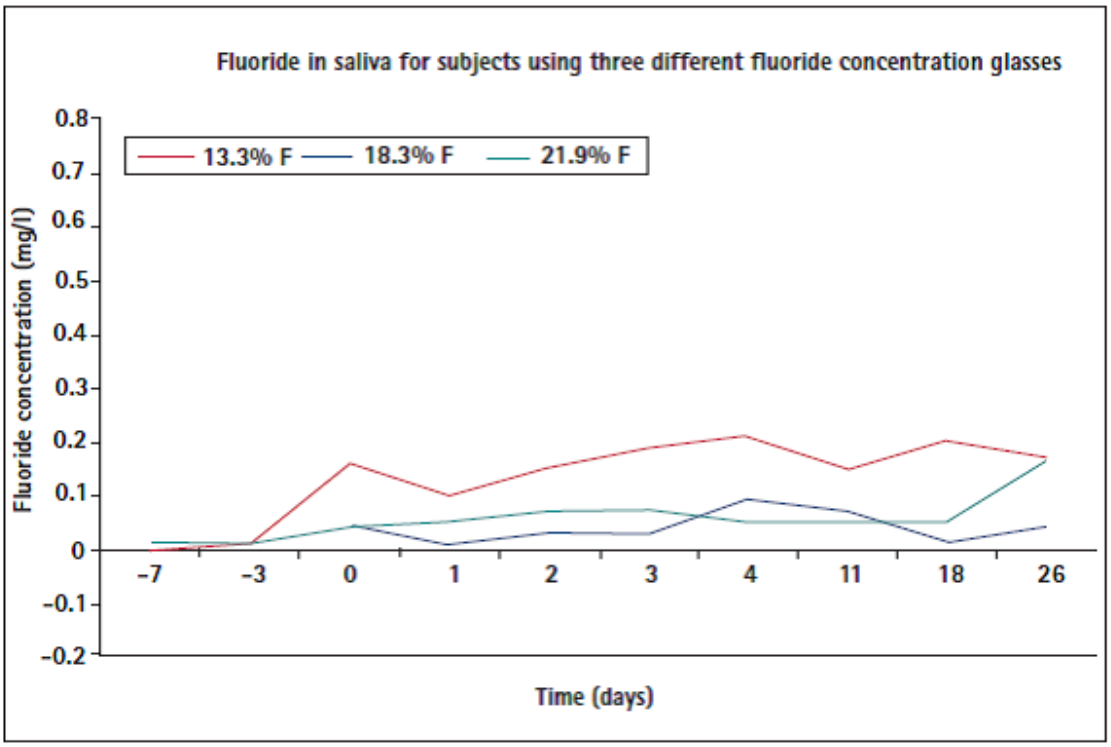

Figure 10 – Mean fluoride concentrations from three volunteers which showed that 13.3 was the most suitable percentage for the slow-release glass device as it gave the most consistent level of fluoride release.

To see whether ingestion of the glass pellet, accidental or deliberate, could lead to toxicity problems the researchers looked at blood plasma F levels three hours after forced swallowing of the experimental glass pellets and the control pellets containing NaF. Ingestion of the slow-release glass pellets produced no marked increase in plasma F levels while the NaF tables did show a small increase

that peaked at 30 minutes but then proceeded to level off after the three hour time frame (Fig. 11).

Figure 11

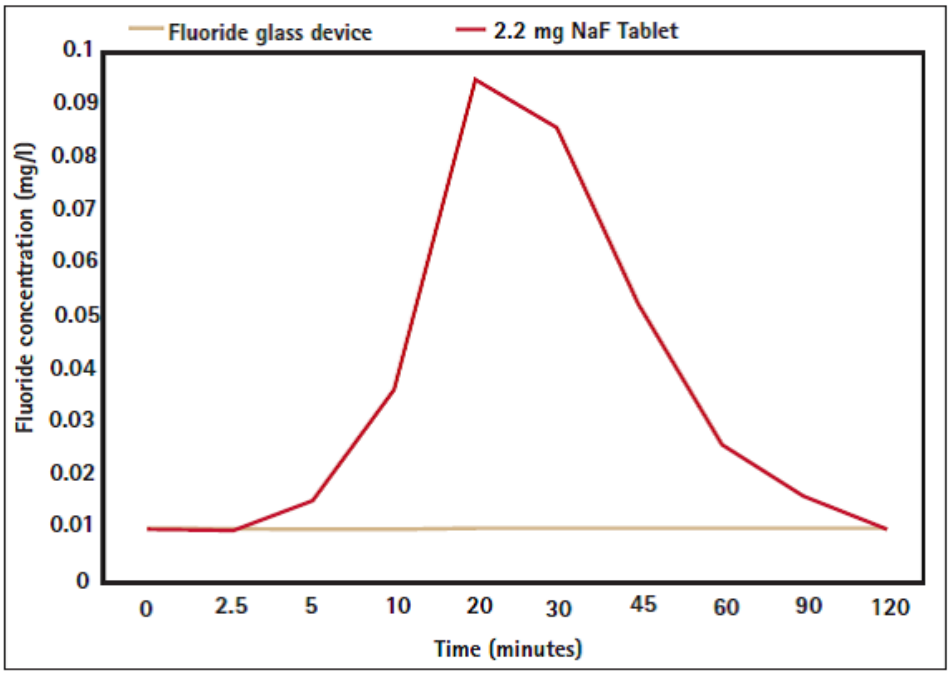

Figure 11 – Graph which illustrates the safety of the slow-release glass device. Upon swallowing of the device there was no change in blood plasma F concentration within a three hour window of ingesting the device. The NaF tablet showed a temporary elevation but soon returned to baseline levels.

Turning our attention to the 2005 clinical study on British school children conducted by Toumba and Courzon, remarkably encouraging results were seen after final analysis of the children fitted with the fluoride containing glass devices.

The two year trial saw 132 or 75.9% of the original 174 that were deemed eligible to undergo the study complete the protocol. Of these 132 only 63 had their devices remain intact throughout the period of the trial as the others were lost to follow-up after the devices became dislodged, either accidentally or on purpose. By the end of the trial there were 31subjects left from the control group and 32 from the treatment. Some of the children had apparently made concerted efforts to pry off the glass device thereby terminating their involvement in the study. Those that did not lose their slow-release pellet reported no irritation, showing the device was not cumbersome as others had predicted. [26]

Baseline characteristics of both the control and test groups were virtually identical at the start of the study thus eliminating any initial bias. Chi-square statistical analysis was used to make this determination at the beginning and at the end of the trial. Neither showed significant differences between the two groups. Table 3 provides a quick overview of the inclusion and exclusion criteria for selection of which children were eligible test candidates.

Table 3

Inclusion criteria
Children residing in the Beeston area of Leeds, UK, within postcode LS11
Children attending one of seven primary schools in Beeston
Children with dates of birth between 1.1.1983 and 31.12.1983
Signed informed consent from a parent/guardian
Completed medical history questionnaire
Children with dental caries of dmft or DMFT >1.0
Mutans streptococci counts of >1.00 $\times$ 10^6 cfu/ml in saliva
Exclusion criteria
Caries-free children
Mutans streptococci counts of <1.00 $\times$ 10^6 cfu/ml in saliva
Medical contraindications such as haemophilia, epilepsy, heart disease, etc.
Children not living within the postal code district of LS11

Table 3 – Inclusions and exclusion criteria implemented by Toumba and Courzon in the selection of children to participate in their slow-release clinical trial.

Table 4 allowed for an in depth comparison between the groups which showed the mean values for age, salivary F, *S. mutans* counts and caries levels determined at baseline, one year later and at the time of completion. The striking finding was that the salivary F concentrations in the T group were substantially higher at the end of the trial indicating that the device was successful in fulfilling its role. A student's paired t test analysis confirmed that the DMFS and DMFT ($p > 0.01$ and $p > 0.001$ respectively) scores were significantly lower for the T group versus the C group representing a decrease in incidence of dental caries. (Table 4)

Table 4

Parameter	Group T	Group C	Significance Student's t test
Baseline			
Number	31	32	
Mean age, years	8.84	8.85	NS
Salivary F, mg/l	0.05	0.05	NS
S. mutans, cfu/ml × 10^4	252.00	302.00	NS
dmft	4.03	4.31	NS
dmfs	10.90	11.41	NS
DMFT	0.48	0.38	NS
DMFS	0.55	0.53	NS
dmft + DMFT	4.51	4.69	NS
dmfs + DMFS	11.45	11.94	NS
Intermediate (1 year)			
Number	31	32	
Mean age, years	9.87	9.89	NS
Salivary F, mg/l	0.15	0.05	<0.001
S. mutans, cfu/ml × 10^4	174.53	197.74	NS
dmft	4.38	4.59	NS
dmfs	11.51	13.09	NS
DMFT	0.60	0.63	NS
DMFS	0.71	1.12	NS
dmft + DMFT	4.98	5.22	NS
dmfs + DMFS	12.22	14.21	NS
Completion (2 years)			
Number	31	32	
Mean age, years	10.92	10.94	NS
Salivary F, mg/l	0.11	0.03	<0.001
S. mutans, cfu/ml × 10^4	185.80	202.60	NS
dmft	1.19	3.03	<0.01
dmfs	0.68	1.28	NS
DMFS	0.84	2.34	<0.05
dmft + DMFT	1.87	4.31	<0.001
dmfs + DMFS	3.10	10.75	<0.001

Table 4 – This table represents measurements of age, salivary F, S. mutans counts and caries levels taken at baseline, intermediate and completion times between the test and the control group. Of note are the significantly lower dmft/dmfs scores in the test group upon completion of the trial. This was statistically proven by conducting a paired t test analysis at $p \leq 0.001$.

Table 5 shows data for occlusal surfaces only where the mean new caries increment values were significantly lower for the test group than for the control group, particularly in the permanent dentition ($p \leq 0.01$). Given that occlusal lesions are often hard to detect due to their 3D structure, numerous fossae and grooves this was a particularly encouraging finding.

Table 5

Dentition	Group T (n = 31)	Group G (n = 32)	Difference	95% CI of difference	Student's t test p value
Primary	0.32 ± 0.13	0.59 ± 0.16	0.27	–0.69, 0.14	0.18
Permanent	0.19 ± 0.10	0.81 ± 0.18	0.62	–1.03, –0.21	0.01*
Both	0.52 ± 0.15	1.41 ± 0.26	0.89	0.29, 1.49	0.01*

CI = Confidence interval.
* Statistically significant difference.

Table 5 – This represents caries found only on the occlusal surfaces in both test and control groups. The important finding was that mean new caries was significantly lower at the $p \leq 0.01$ level for the test group upon completion of the trial.

- Note that Group G should read Group C. This is an authors' typo

The 2006 Andreadis trial assessed the saliva samples of fifteen young subjects to see whether their new kidney-shaped device could improve on the retention problems associated with the 2005 Toumba and Courzon RCT. The mean baseline salivary concentration was 0.025 ± 0.005 ppm and at day 180 they were

$0.17^{\pm}0.10$ ppm. A paired t test confirmed this to be a statistically significant difference. Of the fifteen participants only one girl lost her SFG device which had dislodged accidentally three weeks into the trial as a result of biting into hard candy. The young girl swallowed the device but there were no repercussions as SFG's are safe to ingest. Retention rate after three months was an astounding 86% compared to the 48% result by Toumba and Courzon's prior study however after six months three devices became damaged. The damage was minor as only small perforations were found in the glass that had most likely dissolved. Some of the improved retention could be explained by the large amount of composite resin used to attach each device which did make it rather difficult to de-bond and complicated the replacement procedure. No side effects whatsoever were reported and all soft tissues were found to be healthy and unperturbed. The only sign that there had been an SFG device present was the minor gingival bleeding near the buccal surface of the tooth where it had been attached. Conversing with the children the authors concluded that after 2-3 days, 12 of the children reported they had gotten used to the presence of the intra-oral device. The other 3 children reported reaching a level of comfort and acceptance after 4-7 days.

In the most recent study by Il Ibrahim et al. involving the plastic brackets the SFG devices were attached to the right and/or left maxillary first permanent molars of each of the twenty adults who participated in the trial. [18] Of the twenty

subjects half received unilateral devices with the other half receiving two-sided bilateral devices. Saliva samples were taken at baseline and then collected immediately after attachment of the SFG. They were then taken at the end of the first week, first month, three months and finally at six months' time. F concentration was measured using an ion-specific electrode on fresh samples or samples that had been frozen at -12℃.

Results showed higher salivary F levels for both groups compared with the baseline measurement. Based on an independent sample test there appeared to be no significant difference between the total F released by the unilateral and bilateral devices over a six month span. The brackets themselves proved resistant and vastly simplified the attachment and replacement of the SFG device. No longer did replacement require de-bonding followed by new acid etching. Retention topped out at 86% with a couple of the brackets damaged by biting into hard food. [18] No local side effects were reported and the plastic brackets did not interfere on any level with the continuous delivery of F ions thus rendering the new device a success.

Discussion

The initial pilot study by Courzon and Toumba conducted on four adult volunteers confirmed their hypothesis that a glass pellet could be retained within the mouth and raise saliva F concentration over a given time frame. After a few days the subjects reported that the awareness of having the glass pellet attached to their molars diminished greatly, showing that such a method could be feasible on a much larger scale. One of the primary concerns before undertaking the study was that patients would spurn the idea of having a foreign device become part of their intra-oral environment however this fear proved unjustified as none of the subjects reported any ill feelings or dissatisfaction with the presence of the glass pellet.

The pilot study allowed Toumba and Courzon to fine-tune their novel idea by modifying the solubility of the glass device after preliminary readings showed only modest increases in salivary F concentration. The 13.3% version functioned best due to its unique glass composition when compared with the higher percentage options. The other more highly concentrated devices contained Aluminum which reacted with F to form a less soluble compound. [11] In a double blind crossover study it was determined that a similar slow-release glass device could raise F levels in plaque ten-fold after only one month of placement. [16] This

led to the acceptance that raising the salivary F levels is theoretically possible using this type of a device.

Toxicity concerns were also somewhat laid to rest when it was shown that swallowing the F containing pellets produced no change in blood plasma F concentration in the five volunteers who ingested them. Baring in mind that this study only used five subjects meant that further testing on a larger scale would be necessary to attain conclusive proof that the bloodstream would not be affected by an accidental swallowin.

Looking at a past study by Mirth et al. showed that a fluoride containing co-polymer membrane device could release F and inhibit dental caries over a six month span. [13] Toumba and Courzon sought to prolong fluoride release from the device after it was fixed intra-orally *in vivo*. They succeeded in doing so by extending the functionality of the device from six months to eighteen months. Even after the eighteen months it was still shown that there was a significant amount of F left in the glass pellet. [26] The slow-release F device designed by Toumba and Courzon had the inherent ability of recharging itself, most likely by absorbing fluoride from food due to its porous, reactive nature. Recall that fluoride-free toothpaste was used for the duration of the study so the source of new fluoride could not have come from that dentifrice. Based on the results it was determined that their new device could have potential as a long-term preventative agent of

caries, particularly in high-risk individuals who had previously demonstrated a proclivity to neglect their oral health.

Toumba and Courzon saw their investigation proceed to a phase IV *in vivo* trial by testing the device it on 174 Leeds school children. [14] Throughout the study the children were closely monitored to ensure that oral hygiene practices remained on par with pre-trial conditions. Upon completion it was discovered that quantities of *S.mutans* bacteria remained unchanged. Clearly the slow-release devices did not have an effect on the bacterial count. What they did do however was significantly raise the salivary F levels by the end of the trial. When analysis showed that these new numbers correlated with lower indices of caries it was determined that a higher concentration of intra-oral fluoride directly coincided with inhibition of enamel demineralization and a subsequent decrease of carious lesions. [27]

The Leeds study produced a 76% decrease in carious surfaces, an impressive statistic given that previous trials using water fluoridation and topical fluoride varnishes had shown only 50% and 30% reductions, respectively. One possible conundrum was that the Toumba and Courzon study focused on a very distinct sector of the population, 8 year old Leeds children from low socioeconomic backgrounds at high risk of developing dental caries. The fact that this study was not based on a general population running the gamut of high, moderate and low-

risk individuals could have been an early indication that the 76% result obtained was overstated due to poor generalizability. However one could argue that since the slow-release device was originally intended to service high-risk populations this was not considered a major shortcoming.

Another glaring weakness of the study was the low retention rate of the device as 52% of the 132 that completed the study lost their glass pellet at some point during the trial phase. The major reason behind this was deliberate dislodging of the device by the children, leaving final analysis to include only 36% of the original 174 sample population. Much of the low retention issues in this study can be attributed to the fact that the subject pool was comprised of school children. Success rates would certainly have been higher recruiting adult subjects who would have been less inclined to deliberately dislodge the device.

The dome-shaped glass bead device designed by Toumba and Courzon needed to be improved upon in order to increase retention numbers. A prior 2003 study by Wilson et al. suggested implementing a retention groove around the periphery of the glass bead to improve retention. [28] A 1999 study by Marini et al. investigating white spot lesions associated with orthodontic appliances used a new holder called CIPI, made with a biocompatible elastic alloy, a four wire cage system with a cannula and a clasp for fastening.[29] After one year retention rates were 98% however this device, aptly referred to as an IFRD (inta-oral fluoride

releasing device) was only of use to patients with orthodontic appliances. In comparison, Toumba and Courzon used the standard dome-shaped device on the Leeds school children who did not have any orthodontic appliances installed.

Andreadis et al. improved on the somewhat flimsy dome shape by constructing a kidney shaped glass device with circumferential retentive grooves that was shorter in height (2.5 mm vs. 4mm) than the original dome shaped pellet. (Fig. 12) Combined with a more efficient resin, the new kidney shaped device lead to retention rates of 93% and 86% for adults and children, respectively. [21] This was a drastic improvement over the 48% final retention rate seen in Toumba and Courzon's study. The new kidney-shaped design in conjunction with an improved bonding technique seemed to boost the efficiency of the SFG device. Though the device was reported as slightly cumbersome by its fifteen young subjects it was still a highly successful improvement upon the original dome-shaped device as seen in strong patient satisfaction numbers. This was reinforced by the authors' questionnaire filled out by the parents of the child participants regarding opinions on any complaints or difficulties encountered during the three months. Its overall effectiveness was also remarkably powerful given the final 0.17 ppm F count, a number more than capable of inducing remineralization.

Figure 12

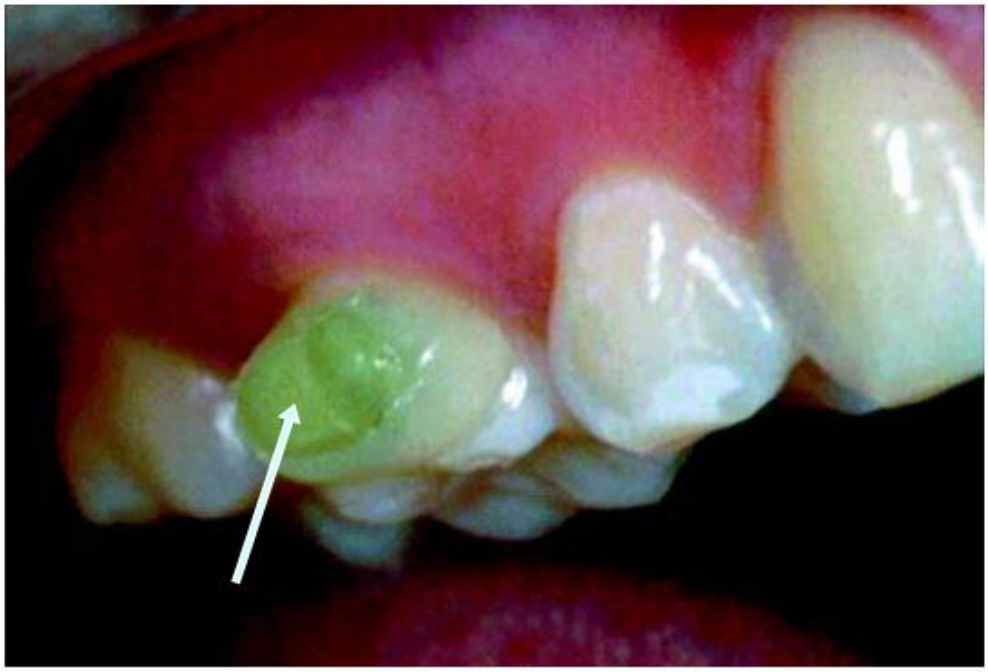

Figure 12 - This represented an intermediate between Toumba and Courzon's original and more cumbersome dome shaped device and the latest improvement involving newly shaped plastic brackets to house the slow-release glass pellet. Notice the kidney shaped device indicated by the arrow. It is noticeably smaller and narrower than the original dome-like device.

Despite the 93% retention rate in the Andreadis study the authors correctly surmised that a more efficient method of replacement would be of tremendous help to clinicians who employed the SFG device. After the devices were attached to the molars using the acid etch composite resin technique they would need to be completely redone after a period of two years. In high-risk patients whose

attendance records are poor it would be imperative to have the device last well beyond a two year time frame and to modify the manner in which the glass pellet was eventually replaced. In order to deal with this problem the authors suggested the development of a bracket capable of holding the device in place which would allow for easy replacement. Forced with the arduous task of removing the bulk of the remaining composite resin at the end of the trial they fully realized the value in simplifying this stage of the process. With the implementation of easily reloadable brackets this time-consuming step would no longer be necessary.

The loss of participants in Toumba and Courzon's study was alarming. Final analysis was done on only 63 children of the original 174. Had the authors used the intention-to-treat approach to analyze their data they could have strengthened their evidence by maintaining randomization and avoiding the effects of drop outs. Rather the final participants were selected based on a per protocol basis with the deciding factor being whether the glass pellet was successfully retained or not which lead to some bias. There was also no report of caries incidence in the 52% of the participants left out of the final analysis. Clearly there was a need for a larger, more general trial as well as an improved bonding technique.

Al Ibrahim et al. addressed these retention concerns and consequently found the solution to the attachment and de-bonding conundrum presented by the

Andreadis study. The aim of the 2010 Al Ibrahim RCT was to investigate the effects of plastic brackets on the level of F released by the new SFG devices *in vitro* and to look at how they function *in vivo* in adult participants. In regards to the concerns raised by the Andreadis study, they successfully eliminated the need for costly de-bonding and reattachment of SFG devices by utilizing plastic brackets to encase the F pellets that could be easily handled and replaced when the F supply ran dry. Due to this advancement the investigators no longer needed to engage in time consuming acid etch de-bonding during the end of the two year period upon which the glass pellets would need to be recharged with new F.[18] Similar to Andreadis, retention hovered around the 90% mark and patients reported no dissatisfaction in the comfort level of the intra-oral device. No local side effects were observed and the introduction of the plastic brackets did not interfere with the release of the F ions.

The toxicity concerns addressed in the pilot study by Courzon and Toumba were found to be unsubstantiated as it was conclusively proven that swallowing of the slow-release device lead to no changes in blood plasma F concentration three hours after ingestion. The only concern with this was that it was an extremely small scale investigation consisting of five adult volunteers. Since the main trial used children as the guinea pigs it would have made more sense to conduct similar tests on younger subjects and on a larger pool of participants. Fluorosis is also a

major concern with children 8 years of age or under, particularly in a trial involving the cumulative intake of fluoride during enamel development. At no point in the study did the authors state the mean daily dose of fluoride emitted by the pellet making it difficult to ascertain exactly how much they were exposed to on a regular basis. Seeing as how it is well understood that subjecting children to more fluoride than is necessary is not desirable it would be prudent to obtain more information on the daily release rates.

One fascinating and somewhat unexpected result from Toumba and Courzon's two year double blind trial was the 55% decrease in caries incidence on the occlusal surfaces. Fluoride was generally perceived to maintain its effect on the smooth surfaces of the teeth as most water fluoridation studies mention greater reductions in smooth surface caries and neglect the occlusal numbers. The effect on occlusal surfaces could probably be attributed to the nature of the slow-release study in that constant delivery of F on a 24 hour a day basis provides an environment sufficient in protecting these surfaces that typically possess complicated three-dimensional shapes.

A study by Mirth et al in 1983 showed that rats in a test group fixed with slow-release F devices had 63% less caries development than the control group. [13] There were also 40% fewer carious lesions on the occlusal surfaces which marked the first time that investigators realized that an abundance of fluoride,

administered carefully over a given amount of time could offer protection to the occlusal fissures and cavities as well as approximal and free surfaces.

The Toumba and Courzon study's primary focus was to prove that a slow-releasing F device could enhance remineralization *in vivo* by increasing microhardness of the enamel on both sides of the mouth. Most past studies used *in situ* models of the slow-release F delivery concept to reduce white spots brought on by orthodontic appliances, combat root caries and to treat dentine sensitivity. [4, 30, 31] The 1999 study by Marini used a copolymer device to release F over a six month span which resulted in a major decrease in white spot lesions commonly associated with small areas of enhance plaque adherence caused by the presence of braces or a similar orthodontic appliance.[32] A similar copolymer device was used on patients who reported increased dentine sensitivity after undergoing periodontal surgeries. After a four month period the symptoms dissipated to the point and sensitivity was no longer an issue.[30] An *in situ* study investigating root caries showed that the roots below the cervical margin could take up F more efficiently in the presence of a slow-release device than using simple mouth rinses or varnish. [33]

Conclusion

The 2005 study by Toumba and Courzon yielded encouraging results but ultimately fell short of acting as a definitive source of evidence to support the slow-release device by losing far too many of their SFG's during the course of the trial. They also failed to treat their data on an intention-to-treat basis and opted to conduct a per protocol analysis by only focusing on the participants who successfully retained the glass beads. Evidence therefore was unreliable and the risk of bias was moderate to high. On the positive side the subjects that were able to retain the device throughout the entire duration of the trial experienced a significant long-lasting increase in intra-oral F concentration followed by an overall 66% reduction in carious teeth and a 76% reduction in carious surfaces. These were encouraging numbers for high risk groups, the target demographic of slow-release devices. Fortunately the retention problems of Toumba and Courzon's dome-shaped device were improved upon in later studies by Andreadis and Al Ibrahim. Andreadis implemented a kidney-shaped pellet that increased overall retention to 86% while Al Ibrahim's research team introduced plastic brackets to secure the glass bead and drastically improved the ease of attachment and replacement all while maintaining excellent retention numbers and improved patient satisfaction. These latest studies showed that continuous, safe and controlled delivery of F is not only a reality but that their reliability, efficacy and

cost-friendly production make them a viable means of combating decay. The devices have seen their popularity surge as a result of the new plastic bracket modification effectively cutting down costs, time and simplifying the replacement procedure. Looking towards the future we would need to see unequivocal financial support from third world countries' respective governments to ensure complete public access. In first world countries the devices might be able to be covered under various insurance or government Medicaid plans to allow access to the needy. Instituting adequate oral care amongst underprivileged populations would lead to subsequent improvements in overall health as has been proven by numerous studies showing the positive correlation between a healthy oral environment and a decline in systemic disease. The genius of the SFG device is that its proficiency in providing consistent elevated concentration of intra-oral salivary F has rendered systematic efforts to control decay a virtual non-necessity in caries prone individuals whom are characterized by poor oral health habits and sparse attendance records at the dental office.

Appendix 1 – Search Strategy

(April 23rd, 2012)

1 exp Tooth Demineralization

2 Dental Caries Activity Tests

3 Dental Caries Susceptibility

4 (caries or carious or decay* or cavit*).mp.

5 (slow releas* and (dental or caries or fluoride)).mp.

6 ((demineral* or remineral*) and (tooth or teeth or enamel or dentin or root)).mp.

7 1 or 2 or 3 or 4 or 6

8 Fluorides

9 fluoride*.mp.

10 (slow near releas* or slow dissolv* or copolymer membrane* or control near releas* or delay* action).mp.

11 8 or 9

12 10 and 11

13 5 or 12

15 limit 14 to (english language and randomized controlled trial)

16 14

17 limit 16 to English

18 (random* or placebo* or blind*).mp.

19 17 and 18

20 15 or 19

21 exp Fluorides/ and exp Delayed-Action Preparations

22 (slow and releas* and fluoride*).mp.

23 21 or 22

24 limit 23 to English

25 limit 24 to humans

26 limit 25 to randomized controlled trial

27 20 or 26

28 27 not osteo*.mp.

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Figure 1:

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Figure 3:

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Figure 4:

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Figure 6:

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Figure 7:

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Figure 9 + 10 +11:

Curzon M.E.J,Toumba, K.J., *In vitro and in vivo assessment of a glass slow fluoride releasing device: a pilot study.* Br Dent J. 2004 May 8;196(9):543-6

Figure 12:

Andreadis G.A.,Toumba, K.J., *Slow-release fluoride glass devices: in vivo fluoride release and retention of the devices in children.* Eur Arch Paediatr Dent. 2006 Dec;7(4):258-61

Table 1:

http://www.oralenvironment.co.uk/assets/images/casaltssols.gif

Table 2:

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Table 3 + 4 + 5:

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