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Review Article

Self-Assembling Peptide P11-4 For Management Of White Spot Lesions In Subjects Undergoing Orthodontic Treatment. - A Structured Review

Nazleen Valerie Vas[1], Ravindra Kumar Jain[2]

[1]Postgraduate Student, [2]Professor, Department of Orthodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu, India.

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ABSTRACT

White Spot Lesions (WSLs) are early signs of enamel demineralization, often occurring during orthodontic treatment due to hindered oral hygiene maintenance. Traditional treatment methods include resin infiltration or remineralization using fluoride-based agents. However, self-assembling peptides (SAPs), such as Curodont ™ Repair (P11-4), have emerged as potential alternatives for WSL management. This review comprehensively examines the chemistry, mode of action, clinical safety, and efficacy of SAP P11-4 in remineralizing enamel lesions. It synthesizes findings from studies investigating SAP P11-4's remineralizing potential using various assessment methods, including pH cycling models, laser fluorescence, digital subtraction radiography, and confocal microscopy. SAP P11-4, with its ability to mimic the enamel matrix and promote hydroxyapatite nucleation, demonstrates promising outcomes in reducing WSL size and progression. Clinical studies report significant improvements in lesion remineralization with SAP P11-4 treatment, often surpassing the efficacy of fluoride-based interventions. Moreover, SAP P11-4 shows compatibility with bonding procedures and potential for reducing dentin hypersensitivity. They offer a promising alternative or adjunct to traditional fluoride-based treatments for WSL management, providing clinicians with a valuable tool in promoting enamel health and preventing caries progression. Further research is warranted to explore long-term outcomes and optimize treatment protocols for maximum efficacy.

Address for Correspondence:

Dr Ravindra Kumar Jain
Professor,Department of Orthodontics,
Saveetha Dental College and hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS),
Saveetha University,
Chennai-600077, Tamil Nadu, India.
Email id: ravindrakumar@saveetha.com
Phone No: +919884729660

INTRODUCTION

White Spot Lesions (WSL) are defined as the early stage of demineralization on enamel surfaces that are easily discernible to the human eye.[1] Orthodontic appliances hinder the maintenance of oral hygiene resulting in enamel decalcification within 4 weeks of starting orthodontic treatment and with a marked increase in such lesions from the first 6 months of treatment up to 12 months.[2,3] Light reflected differentially from demineralized enamel results in a chalky or milky white appearance, ranging from small lines around the brackets to large decalcification with or without cavitation.[4]

Avenues for treatment of WSLs may either aim to infiltrate the demineralized lesion with low viscosity resin (ICON caries infiltrant) and arrest initial caries or deliver calcium and phosphate minerals lost during demineralization and hence remineralize the lesion. Remineralization is considered the preferred treatment for active, non-cavitated, early-stage caries. Materials developed to remineralize WSLs include casein phosphopeptide-amorphous calcium phosphate, CPP-ACP complex, nano-hydroxyapatite, such as BioRepair and recently, "Curodont ™ Repair" or self-assembling peptides P11-14.[5,6] Incidence of WSLs can be reduced by stringent maintenance of oral hygiene, use of fluoride-based mouthwashes and gels, fluoridated toothpaste, or through in-office procedures, for example, application of fluoride varnish (FV) or 1.1–5% NaF during the regular orthodontic visit.[7] Application of FV has been reported to reduce the incidence of enamel demineralization in orthodontic patients by 44.3%.[8]

SELF ASSEMBLING PEPTIDES

Self-assembling peptides (SAPs) represent biomedical materials characterized by distinctive structures that emerge in response to diverse environmental factors. The divergence in its structures when assembled allows its application as a scaffold for the regeneration of cells and tissue or as a vehicle for drug delivery for target-specific, stable, and controlled drug release.[9]

Curodont TM Repair, a "self-assembling" peptide P11-4, is manufactured by Credentis AG in Switzerland and distributed by MS Dental, also based in Switzerland. In Germany, this product is marketed under the brand name Curodont TM Repair by Mectron Deutschland Vertriebs GmbH. It infiltrates a lesion and forms hydroxyapatite crystals. The monomers of SAP P11-4 coalesce to form a 3D network that acts as the enamel matrix scaffold to regenerate enamel. With the help of calcium phosphate from saliva, new hydroxyapatite crystals develop on this matrix, facilitating regeneration.[6]

CHEMISTRY

P11-4 is rationally designed, incorporating an arrangement of 11 amino acids within its chemical composition. It possesses the capability to spontaneously reorganize into more complex structures that emulate the structural characteristics of the enamel matrix in tooth enamel. [10,11]

The surface of P11-4 features four Glu-residues with negative charges, serving as binding sites for calcium. These sites are positioned at a distance of 9.4, mirroring the arrangement of Calcium ions within the crystal lattice of hydroxyapatite. Consequently, this alignment results in a lowered activation energy for hydroxyapatite nucleation,

thereby promoting and facilitating the process of remineralization. [10-12] The amino acid sequence of P11-4 is mentioned below.

Ace-Gln-Gln-Arg-Phe-Glu-Trp-Glu-Phe-Glu-Gln-Gln-NH2

MODE OF ACTION OF SAP P11-4 ON DEMINERALIZED ENAMEL

The hypothesis posited that SAP P11-4 would initially undergo diffusion into the lesion body, where it would self-assemble into more complex fibrils, emulating the natural biomineralization process observed in tooth enamel. Subsequently, it was anticipated that the peptide would endure within the lesion body, serving as a scaffold constructed by the hydroxyapatite generated. The peptides undergo rapid reorganization, transforming into ribbons and tapes within a matter of seconds, with fibers taking shape after 24 hours.[11, 12] P11-4 shifts the balance of reaction towards remineralization, resulting in the uptake of minerals from saliva and a net increase in the mineral content within the lesion which can be observed by increased microhardness in the lesion.[12-15]

METHOD OF APPLICATION OF SAP P11-4

First, the superficial pellicle is removed by applying 2% sodium hypochlorite, followed by 35 % phosphoric acid for 20 seconds. The surface of the tooth is rinsed and dried and assessed for the appearance of pores which will allow the peptide to infiltrate the lesion. SAP P11-4 is then applied using an applicator and allowed to diffuse into the lesion for 5 minutes. [16] Time is an important factor in the process of remineralization. Thus, multiple applications of the peptide over 3 to 6 months to achieve remineralization, however single application of the peptide was reported to produce significant enamel regeneration.[17] The application of fluoride can aid in this process, but it is not advisable to use fluoridation agents with concentrations exceeding 5000 ppm.

CLINICAL SAFETY OF SELF-ASSEMBLING PEPTIDES

In the preliminary safety evaluation of SAP P11-4, arrested carious lesions on the buccal surfaces involving 15 adults were studied by Brunton et al. Given the absence of documented adverse effects during the use of the product and the blinded assessment revealing a significant reduction in lesion size and perceived progression, the feasibility of conducting further clinical studies was established. Notably, the study employed a laboratory formulation, conclusion that the formulation was safe and promoted remineralization of WSL - subsequent clinical investigations utilized the formulation present in Curodont Repair. [17]

ASSESSMENT OF REMINERALIZING POTENTIAL OF SAP P11-4

Over recent years, the efficacy of SAP P11-4 to remineralize enamel has been studied by various authors. Various methods have been used to evaluate the remineralizing potential of SAP P-114, as enlisted in Table 1. pH cycling is used to simulate the environment of developing caries as marked by the alternating phases of demineralization and remineralization. [18] Laser fluorescence systems and systems that employ cameras to note the depth of the lesion in-depth like DIAGNODENT (DD) and VistaProof (VP) present non-invasive methods to evaluate WSLs. Digital Subtraction Radiography and MicroCTs are radiographic assessment tools used to assess the remineralization potential

of SAP P11-4.[19] Confocal Microscopy and Atomic Field Microscopy are high-resolution imaging tools, used to assess the depth of penetration of resin into the lesion on the tooth.[20]

EFFICACY OF SELF-ASSEMBLING PEPTIDES IN REMINERALIZING ENAMEL

The mineralizing capability of SAP P11-4 has allowed versatile application. It has however been most commonly applied to remineralization of white spot lesions. The administration of SAP P11-4 for initial carious lesions resulted in enhanced remineralization, particularly in subsurface lesions within the SAP P11-4 treated group in comparison to the control teeth.[36] Table 1 summarizes the various studies assessing the efficacy of SAP in remineralizing enamel.

Table 1 gives a detailed description of the different in vitro methods of assessing remineralizing with Self Assembling Peptide.

Sr No	Author/Year	Methodology	Results
1	Kirkham et al/2007[11]	pH Cycling model, Transmission electron microscopy	SAP was able to induce hydroxyapatite nucleation and inhibit demineralization and significantly increase remineralization of the lesions within 5 days.
2	Jablonski et al/ 2014[6]	DD, VP (Fluorescence systems.)	Fluorescence detected a perceptible change in between intervention and control groups 8 weeks to 12 weeks, confirmed further by scanning electron microscopy images that showed 93% of the samples had large areas of remineralized enamel.
3	Schlee et al/ 2014 [21,22]	Digital Subtraction Radiography (DSR)	At 6 months of Assessment: 31% of the treated carious lesions showed strong remineralization, according to the International Caries Detection and Assessment System (ICDAS) Index while 65 % of the lesions had no progress in caries and one lesion showed further demineralization. At 1-year assessment: 72% displayed an overall regression, 14% displayed no change, and 14% of the lesions progressed further. [21,22]
4	Kind et al/ 2017[12]	Confocal Microscopy, µCT imaging	31% of SAP P11-4 was retained within the enamel of the specimen for 2 weeks of detection, suggesting that retained fibers of SAP P11-4 formed the scaffold within the lesion. P11-4 treated samples displayed an increase in mineralization of 68% within 14 days. The placebo treated samples had an increase in mineralization of 20%.
5	Silvertown et al / 2017[23]	Photothermal radiometry and luminescence using the Canary System and The Canary Lab	After 50 days of being stored in artificial saliva, the baseline Canary Number reduced in the group treated with SAP P11-4 indicating remineralization of lesions.
6	de Souza et al/ 2018[24]	Atomic field microscopy, Surface plasmon resonance analysis	SAP P11-4 interacts with Type I collagen to increase their width and binds to immobilized collagen I in a dose-dependent and saturable manner thus leading to a hybrid layer that is more stable for bonding with restorative composite.

IN-VIVO STUDIES ON THE EFFICACY OF REMINERALIZATION OF SAP P11-4 AND FLUORIDES

Despite the widespread utilization of fluoride in the preventative management of WSL (white spot lesions) and dental caries, its efficacy falls short of complete caries elimination, and it lacks the capacity to achieve full remineralization of the lesion in toto.[25] In a meta-analysis conducted by Rathore et al, it was observed that the utilization of SAP P11-4, either on its own or in conjunction with FA, exhibited superior effectiveness in the remineralization process compared to the sole application of FA. This assessment was gauged through laser fluorescence, Nyvad caries activity, and ICDAS score evaluations.[26]

Four studied concluded that SAP had higher remineralizing potential than FV. [14, 15, 31-33] Two studies conceded that SAP in conjunction with FV yielded better remineralization than with FV alone.[27, 29] SAP demonstrated a higher efficacy in treatment of WSL than Casein Phosphopeptide Amorphous Calcium Phosphate Fluoride (CPP-ACPF) and Tricalcium Phosphate Fluoride (TCPF), but lesser than resin infiltration.[25,28,30] One study among 11 studies reported that the difference in change in lesion size between SAP and FV was not statistically significant.[35]

pH cycling model was used to simulate the pattern of caries development in the oral environment in most studies. Classifications applied to grade efficacy of remineralizing potential of SAP included Nyvad diagnosis criteria and ICDAS index as well as the visual analog scale (VAS) and Global Impression of Change Questionnaire (GICQ) for clinical assessment.

Methods of assessing the remineralization of lesions were varied including macroscopic assessment using fluorescence systems like Diagnodent, VistaProof and QLF-D Biluminator, and microscopic assessment techniques like surface plasmon resonance analysis, atomic field microscopy, Transmission electron microscopy, and Scanning electron microscopy.

Table 2: Studies comparing the efficacy of Self Assembling Peptide P11-4 and Fluorides.

S.No	Author/Year	Interventions	Assessment Method	Inference
1.	Soares et al/ 2017 [25] Goa, India	Casein Phosphopeptide Amorphous Calcium Phosphate Fluoride (CPP-ACPF), Bioactive Glass (BAG), Fluoride enhanced Hydroxyapatite (HA) gel SAP P11-4	pH cycling model Surface microhardness analysis SEM	A significant difference ($p<0.05$) was evident in the remineralization between the SAP P11-4 group and the BAG and fluoride-enhanced HA gel group. Despite there being no statistical difference between the SAP P11-4 and the CPP-ACPF group, the SAP P11-4 exhibited a superior capability to effectively remineralize enamel lesions.
2.	Alkilzy M, 2018 Germany [27]	SAP P11-4 and FV	Laser fluorescence, Nyvad Caries Activity, ICDAS,VAS	More lesions treated with both, SAP P11-4 and FV exhibited improvement in ICDAS scores compared to control lesions. The study reported no allergic reactions, no adverse effects, nor medical complications associated with the treatment involving SAP P11-4.
3.	Gozetici B, 2019 Turkey [28]	SAP P11-4, FV	ICDAS-II, Diagnodent	The greatest lesion regression was observed with resin infiltration, which differed statistically significantly from SAP P11-4, Duraphat and control, followed by DG which differed statistically significantly from CG.
4.	Bröseler F, 2020 Germany[14,15]	SAP P11-4, FV	VAS, GICQ, morphometric measurement	The early carious lesions treated with SAP P11-4 exhibited a significant reduction in size as compared to those treated with FV.
5.	Doberdoli D, 2020 Croatia[29]	Monomeric SAP P11-4 in combination with FV Polymeric SAP P11-4 Matrix	Laser fluorescence, ICDAS-II, VAS, Nyvad Caries Activity	This trial demonstrated that the application of SAP P11-4, either along with FV or with twice-weekly SAPM, proved to be more effective in treating WSL as compared to FV alone.

6.	Kobeissi R, 2020 Lebanon[30]	SAP P11-4 Tricalcium Phosphate Fluoride (TCPF)	Laser fluorescence, ICDAS-II	Remineralization of WSL was significantly better on treatment with SAP P11-4 as compared to TCPF.
7.	Kondelova SP, 2020 Geneva [31]	SAP P11-4, FV	Laser fluorescence, Nyvad Caries Activity, GICQ, VAS morphometric measurement	The treatment with SAP P11-4 led to a superior regression of caries compared to both the control and FV.
8.	Riad MF, 2020 Cairo[32]	SAP P11-4, FV	VAS and color change by Vita Easy shade	The better color change results using Curodont Repair in treatment of white spot lesion
9.	Sezici et al, 2021 Turkey[33]	FV Enamel matrix protein(EMP) SAP P11-4 derivatives with varying chemical compositions	QLF-D Biluminator ™ (Inspektor-Pro, Amsterdam, The Netherlands)	SAP P11-4 and Clinpro XT (FV) demonstrated greater effectiveness in reducing fluorescence loss and lesion area than EMP at various time points. SAP showed higher lesion area changes between the 1st - 2nd week whereas FV achieved the highest reduction from the 2nd week of the observation period.
10.	Gohar et al, 2022 Cairo[34]	SAP P11-4. FV	DIAGNOdent fluorescence system	SAP P11-4 achieved a higher degree of subsurface remineralization as compared to FV.
11.	Atteya et al, 2023 Alexandria	SAP P11-4 Nano silver Fluoride (NSF) Sodium fluoride (NaF)	ICDAS score, Nyvad scores Diagnodent	The change in ICDAS scores by SAP P11-4 and NSF was not significantly different from NaF.

SAP IN MANAGEMENT OF WSLS IN SUBJECTS UNDERGOING ORTHODONTIC TREATMENT.

Fixed orthodontic treatment subjects patients to an elevated risk of developing WSLs, with a reported incidence of 45.8% according to a meta-analysis by Sundararaj et al.[37] Application of fluoride is one of the oldest and most commonly applied caries- prevention aid, by application of fluoridated toothpastes, APF or FV.

A study by Jablonski-Momeni et al reported that use of highly concentrated P11-4 peptide prior to topical fluoride application resulted in a greater degree of remineralization than that of single application of FV, and thus would benefit patients undergoing orthodontic treatment and other patients at high risk of caries.[38] Prior to bonding of brackets on

enamel, prophylaxis with brushes is carried out, which increases the surface energy of the enamel, favoring adhesion. However, topical application of fluoride solutions is reported to decrease the surface energy and reduce the spread of the adhesive.

Dina Mohamed Ali Ismail et al., studied the remineralizing potential of Self-assembling peptide P11-4 group (Curodont ™ Repair /Regenamel®), and Amorphous Calcium Phosphate varnish (Enamel Pro® Varnish 5% Sodium Fluoride Premier Dental) on post orthodontic enamel white spot lesions using a spectrophotometer (Vita Easy® Shade spectrophotometer from Vita Zahnfabrik, Germany) and laser fluorescence (Diagnodent® from KaVo Dental Corporation, USA) over a period of 6 months. The authors reported superior WSL recovery and the highest remineralization in the groups treated with both SAP and the Amorphous Calcium Phosphate Varnish, followed by the group treated with SAP. [39]

EFFECTS ON BONDING

A study by Meng et al noted an adverse effect on the bond strength of enamel, possibly due to the formation of globular CaF on the surface of etched enamel.[40] Leódido et al as well studied the effect of fluoride solutions on the shear bond strength of orthodontic brackets and reported that APF application roughened and made the enamel coarser, but degraded the enamel due to its acidity and adversely impacted the bond strength.[41] In contrast, a study by Knaup et al in 2021 concluded that the shear bond strength was not affected by application of P-114 SAP before bonding of brackets.[42]

The prevalence of dentin hypersensitivity among patients undergoing orthodontic treatment, considering both self-reported symptoms and clinical tests like tactile, bellows, triple syringe, and thermal assessments, shows a wide range between 39% and 91%.[43]

A study compared the efficacy of P-114 SAP and a varnish like polymer containing nano-fluorapatite, amine fluoride olaflur, and nano-calcium fluoride in treating Dentinal Hypersensitivity, reporting that both were effective in reducing DH. The latter by virtue of occlusion of the dentinal tubules, required a single application to alleviate DH. P-114 SAP however, required 4 applications for eliminating DH, since the process of hydroxyapatite formation needs more time.[44, 45]

CONCLUSION

In conclusion, SAP P11-4 have excellent biocompatibility when tested in bovine and human enamel. Its clinical use seems safe and showed promising results in remineralizing early enamel caries lesions. *In-vivo* and *in-vitro* tests have revealed that this innovative material has better bioactivity, remineralizing ability and biocompatibility than its counterparts.

CONFLICT OF INTEREST

No conflict of interest among the authors of this study.

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Nil

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