# Efficacy of recombinant human fibroblast growth factor-2 (rhfgf-2) impregnated absorbable collagen scaffold in sites with multiple gingival recession defects

**Viswa Chandra Rampalli [1], Rajini Kandikatla[1], Sneha Kidambi[1], Santosh Vallabhdas[1], Amarendhar Reddy Aileni[1]**

**[1]SVS Institute of Dental Sciences, Department of Periodontology, Mahabubnagar, Telangana, India.**

**Abstract**

**Aim:** The aim of this study was to clinically evaluate the regenerative potential of rhFGF-2 impregnated collagen membranes in sites with multiple gingival recession defects.

**Methodology:** One site in each subject was randomly assigned into each of the following experimental groups; Test (FGF-2)(n=20) and control groups(C)(n=20) wherein, gingival recession defects were treated with rhFGF-2 impregnated collagen scaffolds and plain absorbable collagen scaffolds respectively. Outcomes recorded were recession depth (RD), width of keratinized gingiva (wKG) and gingival thickness (GT) at baseline, 3 & 6-months. FGF-2 levels were evaluated in the GCF samples from sites within both the groups at 1,3 & 6-weeks.

**Results:** FGF-2 sites showed significant (3.88±0.33 vs 3.34±0.51; p=0.04) increase in wKG from baseline to 3-months and 6-months respectively over C-group sites. At 6-months, FGF-2 sites showed highly significant (1.38±0.99 vs 2.13±0.62; p≤0.001) decrease in RD as well. No changes in GT were seen between both the groups at all time frames. Significantly higher FGF-2 levels (pg/mL) were seen from FGF-2 sites at 1-week (p≤0.001), 3-weeks (p≤0.001) and 6-weeks (p=0.03) when compared to C-group.

**Conclusion:** rhFGF-2 impregnated collagen scaffolds seem to confer additional benefits over plain collagen membranes in terms of recession coverage and healing following mucogingival procedures.

***Keywords: Biomaterial. Collagen. Regeneration. Periodontal attachment.***

## Introduction

Gingival recession is the exposure of root surface due to apical migration of the gingival margin beyond the cementoenamel junction and can eventually lead to tooth loss if left untreated (Wennstrom, 1996; Goldberg *et al*., 2001; Holmstrup, 1999). The ultimate histological goal of treating such defects is achieving new attachment to the previously denuded root surface (Goldberg *et al*., 2001; Holmstrup, 1999; Stetler *et al*., 1987; Trombelli, 1999; Saito *et al*., 2016). The contour of gingiva is related to the architecture of the underlying tissues (Goldberg *et al*., 2001; Holmstrup, 1999; Trombelli, 1999) and obtaining tissue coverage on exposed and denuded root surfaces involves regeneration of periodontal supporting apparatus including bone, cementum and periodontal ligament with subsequent restoration of mucogingival topography (Trombelli, 1999; Saito *et al*., 2016; Cairo *et al*., 2014).

Various standalone and combination therapies such as soft tissue grafts and advanced flaps in conjunction with guided tissue regeneration (GTR) and growth factors have achieved varying degrees of success in mucogingival surgeries (Wennstrom, 1996; Holmstrup, 1999; Trombelli, 1999; Cairo *et al*., 2014). Techniques such as soft-tissue grafts are successful to some extent, but they have donor site morbidity as a drawback (Wennstrom, 1996; Stetler *et al*., 1987). Tissue engineering can offer scaffolds as an alternative to harvested grafts making it possible to achieve favourable results with less invasive procedures (Saito *et al*., 2016; Cairo *et al*., 2014; Murakami *et al*., 2011).

Correspondence to: Kidambi Sneha
E-mail: kidambi.sneha@gmail.com

Tissue engineering using recombinant human growth factor technology may provide a easier and viable option for the treatment of gingival recession (Saito *et al*., 2016; Murakami *et al*., 2011; Okumura *et al*., 1996; Mayahara *et al*., 1993). Signalling molecules such as fibroblast growth factor-2 (FGF-2), a heparin-binding cytokine with strong angiogenic activity, exhibits tremendous potential for periodontal regeneration (Cairo *et al*., 2014; Murakami *et al*., 2011; Okumura *et al*., 1996). FGF-2 facilitates fibroblastic cell proliferation, angiogenesis, and bone formation (Mayahara *et al*., 1993; Nakamura *et al*., 1995) by potently stimulating the angiogenic and mitogenic activities of mesenchymal cells in the periodontium (Nakamura *et al*., 1995). Previous studies (Okumura *et al*., 1996; Mayahara *et al*., 1993; Nakamura *et al*., 1995; Muramaki *et al*., 1999; Muramaki *et al*., 2003; Takayama *et al*., 2001; David *et al*., 2015) employing animal models with surgically-induced periodontitis revealed that FGF-2 was effective in regenerating periodontal tissues (Mayahara *et al*., 1993; Nakamura *et al*., 1995; Murakami *et al*., 2003). FGF-2 can be conveniently grafted onto scaffold materials (David *et al*., 2015; Akcan *et al*., 2020) and a FGF-2/scaffold combination could possibly enhance periodontal regeneration in sites with gingival recession by promoting angiogenesis and connective tissue formation on the root surface (Takayama *et al*., 2001; David *et al*., 2015; Akcan *et al*., 2020), enhancing the proliferative responses of gingival epithelial cells[20] and by regenerating alveolar bone (Hankemeier *et al*., 2005) effectively contributing to regeneration of soft tissue over a site with denuded root surface (David *et al*., 2015; Hankemeier *et al*., 2005; Delgado-Rivera *et al*., 2009; Yun *et al*., 2010; Murakami *et al*., 2011).

In light of numerous pertinent findings in the current literature, the aim of the present study was to clinically evaluate the regenerative potential of rhFGF-2 impregnated scaffold in sites with multiple gingival recession defects. Outcome measures used to assess results were measures of recession depth (*RD*), width of keratinized gingiva (*w*KG), gingival thickness (*GT*) and evaluation of FGF-2 levels in GCF from sites that have received therapy.

## Materials and Methods

### *Sample Size, Eligibility Criteria and Participants*

Assuming a pooled standard deviation of 1 unit, the study would require a sample size of 17 for each group (a total sample size of 34, assuming equal group sizes) to achieve a power of 80% and a level of significance of 5% (*two sided*), for detecting a true difference of 1 mm of soft tissue gain between the test and reference group. A sample size of 17 per group was calculated (total 34) for an effect size of 2.2, probability of $\alpha$ error of 0.05 and a desired statistical power of 0.8.

Subjects for the study were selected from outpatient section of the Department of Periodontology. Approval from institution ethical committee (SVSIDS/PERIO/3/2019) was obtained and informed consent was taken from all the subjects. This study is also registered in ClinicalTrials.gov (NCT04375618). The inclusion criteria were as follows; 1. Age between 18-55 years. 2. Systematically healthy subjects with ≥2 but ≤3 teeth having Miller's class I or II or a combination of class I & II mandibular anterior recession defects. 3. Probing depth of ≤3mm at all the sites. 4. Easily identifiable cemento-enamel junction (CEJ). Medically compromised patients, subjects who underwent radiotherapy or chemotherapy and are smokers were excluded from the study. From an initial participant pool of 82 subjects, 40 individuals (98 sites; 21 Males; Age: 37.62±11.91 Years) who satisfied the inclusion criteria were selected.

### *Preparation Of FGF-2/bFGF-Collagen Scaffold*

Collagen scaffolds incorporating 10 ng/ml human recombinant basic fibroblast growth factor (FGF-2/bFGF) were prepared as follows. Briefly, standard collagen suspension was produced from type I collagen from bovine Achilles tendon by homogenizing the material in 10 mm Na-butyrate solution (Pro Lab Marketing Pvt. Ltd, New Delhi, India). bFGF was reconstituted in 0.1M phosphate buffer and was added to the suspension. Cross-linking of collagen was promoted by adding 0.16% of glutaraldehyde aqueous solution (Sigma Aldrich Chemicals Pvt Ltd, Bangalore, India) and the resultant solution was placed in individual 1.5×1.5 $cm^2$ and 3×2 $cm^2$ vats which were maintained at 4°C for 12h for gelatin cross-linking. The impregnated and cross-linked membranes were freeze-dried in a commercially available laboratory freeze dryer (Lyophilization Systems Pvt Ltd, Hyderabad, India). Control membranes were made similarly without adding FGF-2. Both test and control membranes were sealed in identical pouches and were numbered. The exact nature of the pouches was known only to the chief investigator (RVC).

### *Randomization, Blinding, Treatment Arms and Outcome Parameters*

The study was designed as a double blind, randomized controlled clinical trial. A coin toss applet (Rossman/Chance Applet®) at 0.5 probability for 40 tosses was used to allot the sites into two groups. Test (*FGF-C; 48 sites- 20 subjects*) and control groups (*C; 50 sites-20 subjects*) wherein, gingival recession defects were treated with rhFGF-2 impregnated collagen scaffolds and plain absorbable collagen scaffolds respectively.

The following were the outcome measures used for assessing the efficacy of the scaffolds at baseline, 3-months and 6-months: Width of keratinized gingiva (wKG) was the site-specific distance between the gingival margin i.e. the most apical point of the margin to mucogingival junction. Recession depths (RD) were measured from cementoenamel junction to the most apical extension of gingival margin across all the 98 sites included in the study. A periodontal probe (UNC-15 probe®; Hu-Friedy, Chicago, IL, USA) was used as a reference for measurement (mm) for the above parameters. Gingival Thickness (GT) –A size 15 endodontic spreader (Kerr© Kavo Dental, Singapore) with a rubber stopper was inserted at a point 8 mm below the tips of papilla interdentally and distal and proximal to sites with gingival recession in a subject (Figure 1; middle panel). The stopper was pushed against the gingiva, removed and this distance was recorded with a periodontal probe. Based on the number of sites with recession, the final readings for GT were obtained by calculating the mean of three or four measurements.

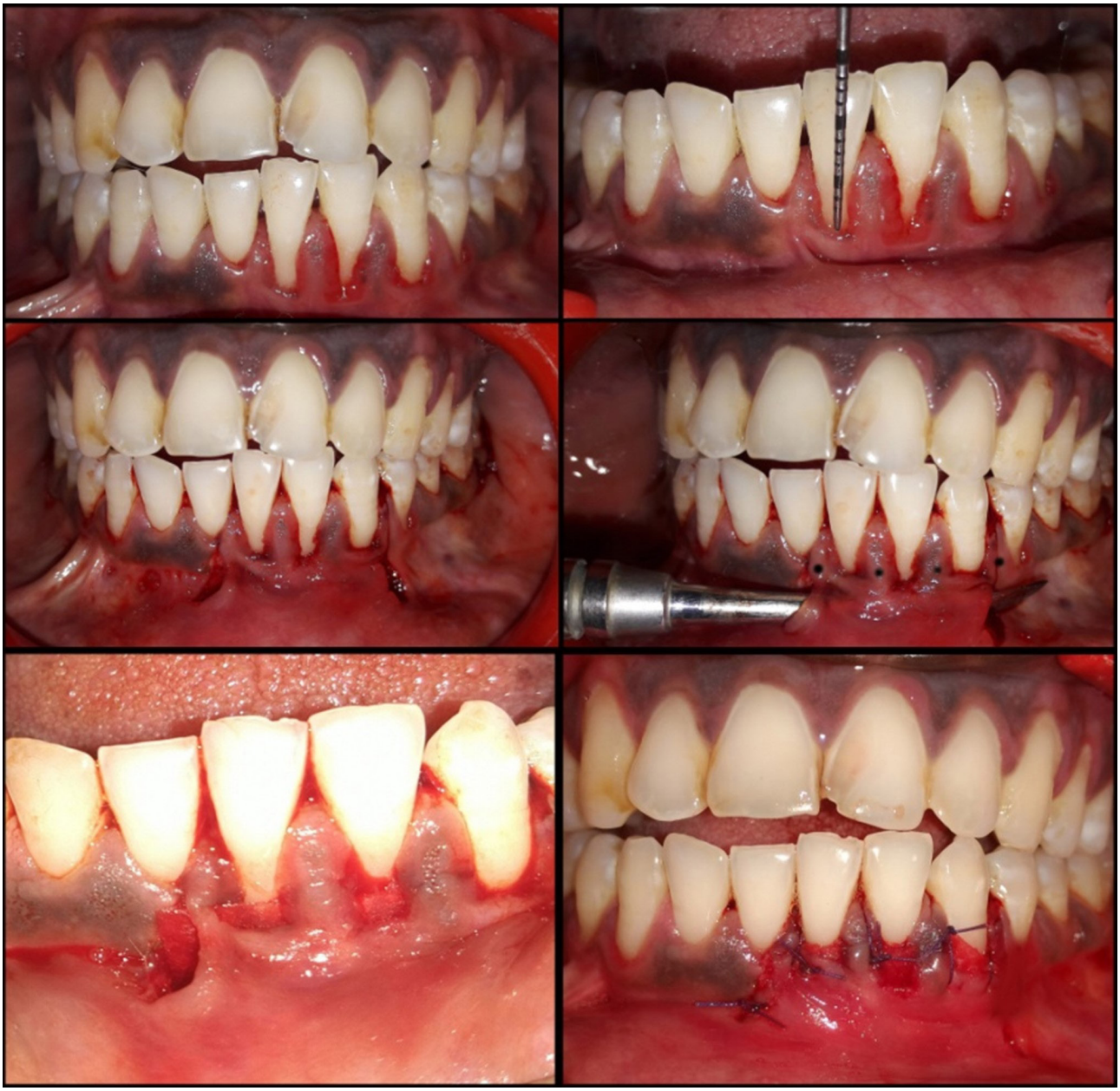

***Figure 1: In sites with GT≥2mm (top-left & right panels), a modified tunnelling technique of Mahn was used to place the scaffold over receded sites. Briefly, two vertical incisions were placed mesial and distal to the sites being treated with the incisions (middle-left panel) beginning below the center of the interdental papillae and continuing into the buccal mucosa. A periosteal elevator was subsequently be inserted through the tunnel created between the vertical incisions (middle-right panel) to eliminate tissue tags to allow easy placement of the graft material. The material was placed (bottom-left panel) and sutures were then introduced through the buccal interpapillary area through the scaffold and subsequently passed interproximally and through the lingual papillae before knot-tying (bottom right panel). Black dots in middle right panel indicate locations of gingival thickness measurement.***

### *Interventions*

Each patient was prepared for surgery with an initial phase-I therapy, which included scaling and root planing (SRP), occlusal adjustment and oral hygiene instructions. To preserve blinding, surgeries were performed by three calibrated operators (KR, AAR & VSG). Based on the GT (Gingival Thickness) values, the scaffold in both the groups was placed in sites with gingival recession through two protocols to ensure proper support and stability for the scaffold. In sites with GT≥2mm, a modified tunnelling technique of Mahn (2001) was used to place the scaffold over receded sites. The technique preserves the papilla due to lack of papilla reflections and increases graft adaptability with increased blood supply. Briefly, two vertical incisions were placed mesial and distal to the sites being treated with the incisions beginning below the center of the interdental papillae and continuing into the buccal mucosa. A periosteal elevator was subsequently be inserted through the tunnel created between the vertical incisions to eliminate tissue tags to allow easy placement of the graft material. The material was placed and sutures were then introduced through the buccal interpapillary area through the scaffold and subsequently passed interproximally and through the lingual papillae before knot-tying (Figure 1). Subjects were then recalled at designated intervals to evaluate healing (Figure 2).

As tunnelling in thin biotype is likely to cause perforations or tearing of the gingiva, in sites with GT<2mm, a protocol involving coronally advanced flap (CAF) without vertical releasing incisions was utilized to place the scaffold (Zucchelli *et al*., 2009). Briefly, horizontal incisions were given at mesial and distal aspects of involved tooth splitting the papillae and a full thickness envelope-type flap was reflected followed by thorough debridement of the site. De-epithelization of the papillae was done. The scaffold was placed upon the recession site and stabilized with 4-0 absorbable suture material (TRUGLYDETM, Healthium Medtech Pvt. Ltd, Bangalore, India.). Then the flap was coronally advanced and 4-0 non-absorbable sutures (TRULENETM, Healthium Medtech Pvt Ltd, Bangalore, India) (Figure 3). Subjects were then recalled at designated intervals to evaluate healing (Figure 4).

### *Estimation of FGF-2 Levels*

5mm Whatman absorbent paper discs (Whatman, Mumbai, India), sterilized in a dry oven, were placed in all sites that received therapy at 1,3 and 6-weeks. If the filter paper was observed to be contaminated with blood, it was discarded, and the procedure was repeated after 30 minutes. The filter papers with GCF were immediately immersed in 100 µL of distilled water and were stored at −30°C. A commercially available ELISA kit (FGF2 Human ELISA Kit©, Thermo Fisher Scientific, Hyderabad, India) was utilized and a standardized curve was used to determine the concentration of the samples in pg/mL. The laboratory steps for ELISA test procedure were carried out carefully according to company instructions on 50 µL aliquots.

### *Statistical Analysis*

Data was analyzed by using Prism8® (GraphPad Software, La Jolla, USA). Intragroup comparison was performed by using ANOVA followed by multiple comparisons using Bonferroni correction. One-way ANOVA followed by the post hoc test was used for intragroup and intergroup comparisons. A p≤0.001 was considered as highly significant, p≤0.05 as significant and p>0.05 as non-significant.

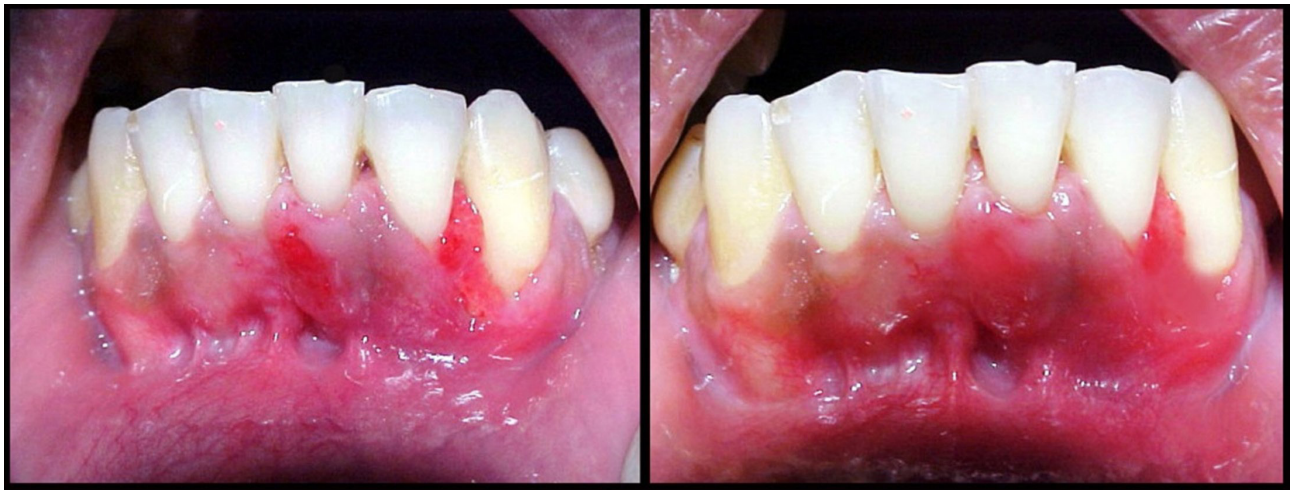

***Figure 2: Post-operative clinical picture of site treated with tunneling at 3-months (left panel) and 6-months (right panel).***

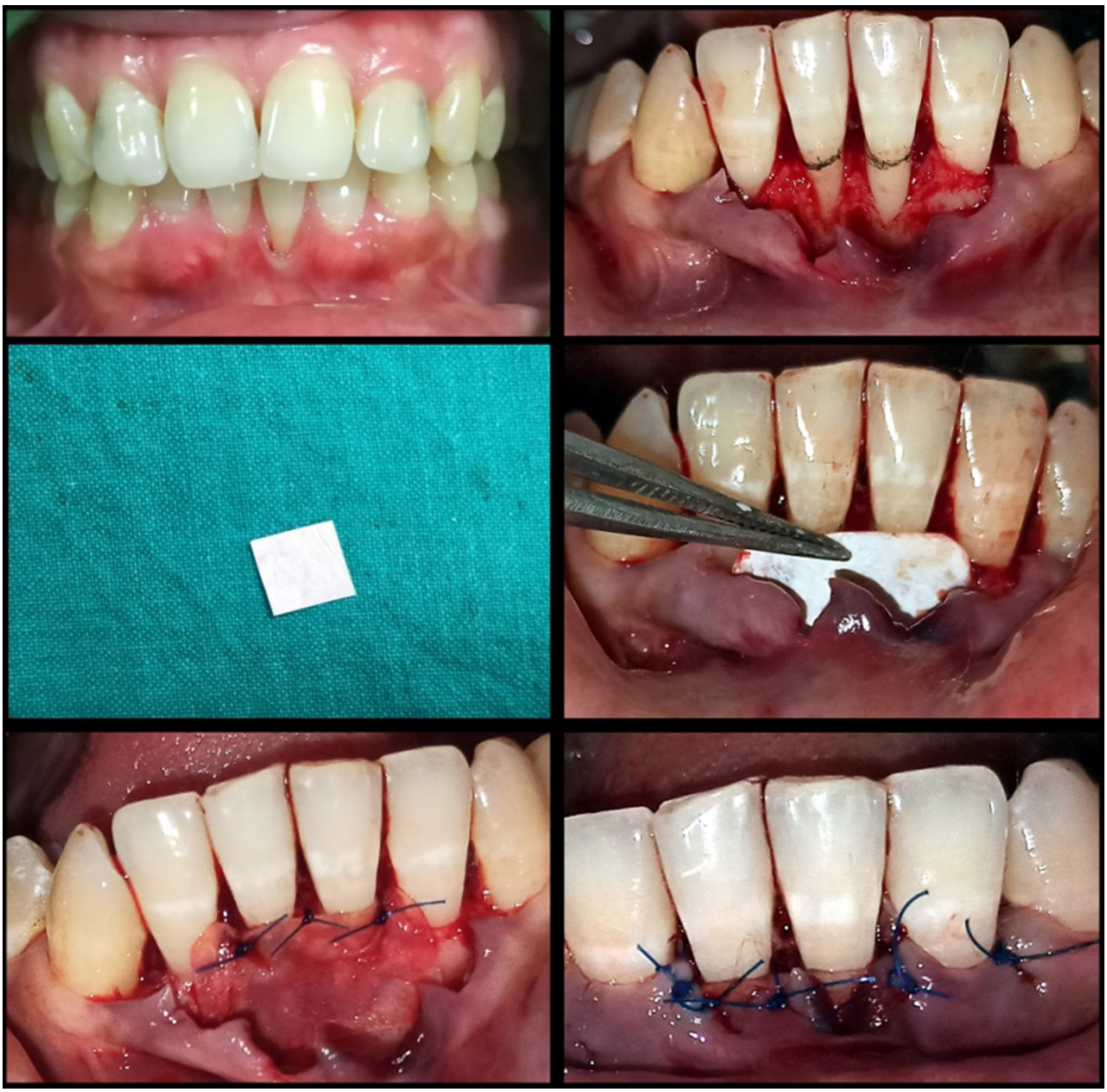

***Figure 3: In sites with GT<2mm, a protocol involving coronally advanced flap (CAF) without vertical releasing incisions was utilized to place the scaffold (top-left panel). Briefly, horizontal incisions were given at mesial and distal aspects of involved tooth splitting the papillae and a full thickness envelope-type flap was reflected (top right panel) followed by thorough debridement of the site. De-epithelization of the papillae was done. The scaffold (middle-left panel) was placed (middle-right panel) upon the recession site and stabilized with 4-0 absorbable suture material (bottom-left panel). Then the flap was coronally advanced and 4-0 non-absorbable sutures (bottom right panel).***

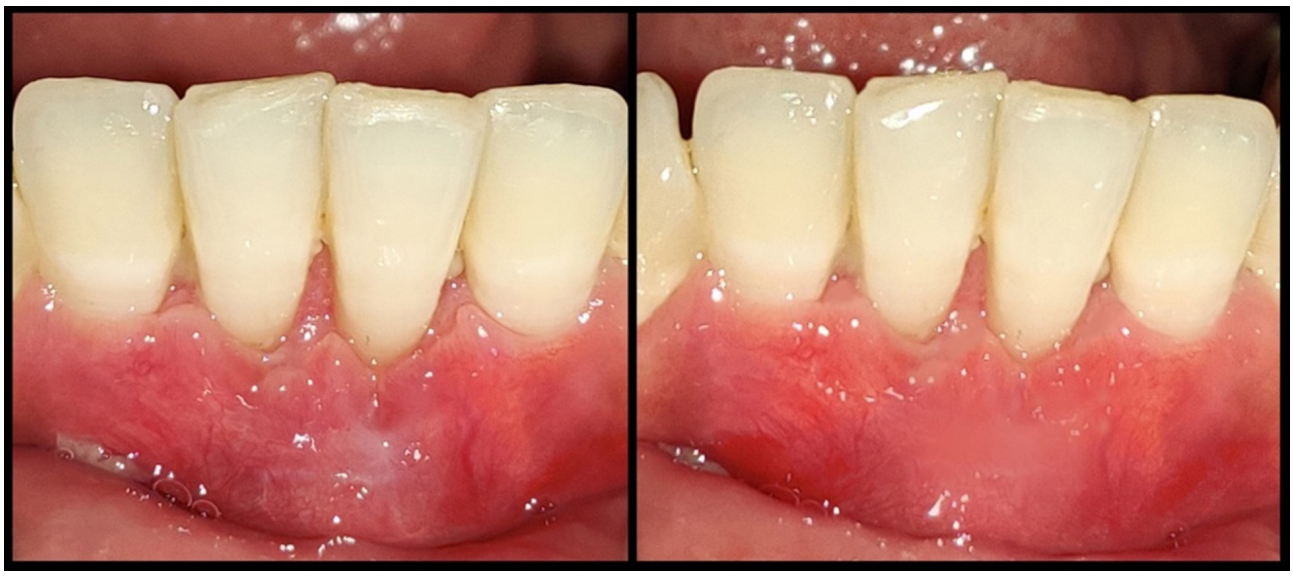

***Figure 4: Post-operative clinical picture of site treated with coronally advanced flap at 3-months (left panel) and 6-months (right panel).***

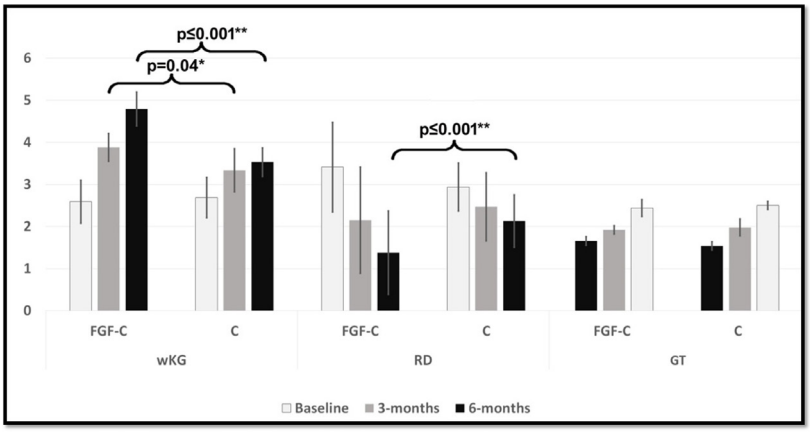


***Figure 5: FGF-C sites showed significant (p=0.04) to highly significant (p≤0.001) increase in wKG from baseline to 3-months and baseline to 6-months respectively over sites from the C-group. At 6-months, FGF-C sites showed highly significant (p≤0.001) decrease in RD as well. No changes in GT were seen between both the groups at all time frames. *Significant, **Highly significant.***

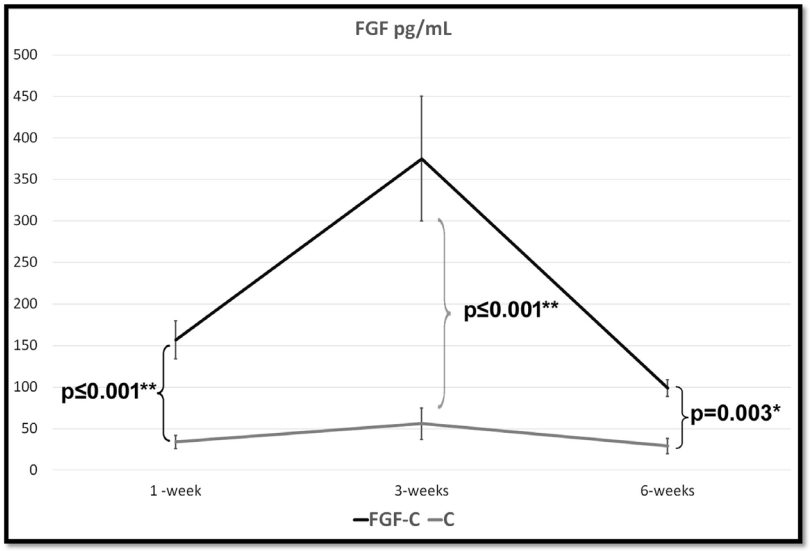


***Figure 6: Significantly higher FGF-2 levels were seen from FGF-C sites at 1-week (p≤0.001), 3-weeks (p≤0.001) and 6-weeks (p=0.03) when compared to sites from C-group. *Significant, **Highly significant.***

## Results

In FGF-C and C-groups, scaffolds were placed in 22 and 26 sites respectively by using the coronally advanced flap (CAF) technique without vertical releasing incisions. Regardless of the technique used, all treated sites exhibited favourable clinical healing; the most common complications were inflamed gingivae beyond one-week (*n=12*), development of residual periodontal pockets (*n=4*) and no reduction in recession depths (*n=5*). 5 subjects from the study pool were lost during follow-up and the final statistical analysis was limited to 17 (*43 sites*) and 18 subjects (*45 sites*) from the FGF-C and C-groups respectively.

*Width of keratinized gingiva (wKG)*

The mean wKG (in *mm*) in FGF-C and C-groups were 2.59±0.51, 3.88±0.33 & 4.79±0.40 and 2.69±0.48, 3.34±0.51 & 3.53±0.34 respectively at baseline and at the end of 3 and 6 months. The intra group increase in wKG, when compared from baseline to 3 and 6 months was highly significant in both the treatment groups (p≤0.001).

*Recession depth (RD)*

The mean RD (in *mm*) in FGF-C and C-groups were 3.412±1.06, 2.15±1.25 & 1.38±0.99 and 2.94±0.57, 2.47±0.81 & 2.12±0.62 respectively at baseline and at the end of 3 and 6 months. The intra group decrease in RD, when compared from baseline to 3 and 6 months was highly significant in both the treatment groups (p≤0.001).

*Gingival Thickness (GT)*

The mean GT (in *mm*) in FGF-C and C-groups were 1.72±0.45, 1.92±0.78 & 2.48±0.78 and 1.66±0.66, 1.97±0.60 & 2.52±0.99 respectively at baseline and at the end of 3 and 6 months. The intra group increase in GT, when compared from baseline to 3 and 6 months was highly significant in both the treatment groups (p≤0.001).

*FGF-2 Levels*

The mean FGF-2 levels (in *pg/mL*) in FGF-C and C-groups were 157±23, 375±75 & 99±10 and 34±8; 56±19 & 29±9 respectively at 1,3 & 6-weeks. The intra group increase in FGF-2 levels from 1-week to 6-weeks was highly significant (p≤0.001) and statistically insignificant (p=0.07) in FGF-C and C-groups respectively.

***Intergroup Comparisons***

FGF-C sites showed significant (p=0.04) to highly significant (p≤0.001) increase in wKG from baseline to 3-months and baseline to 6-months respectively over sites from the C-group. At 6-months, FGF-C sites showed highly significant (p≤0.001) decrease in RD as well. No changes in GT were seen between both the groups at all time frames (Figure 5). Significantly higher FGF-2 levels were seen from FGF-C sites at 1-week (p≤0.001), 3-weeks (p≤0.001) and 6-weeks (p=0.03) when compared to sites from C-group (Figure 6).

## Discussion

Growth factors are the natural biologic mediators which are capable of mediating important cellular events in wound healing process (Mayahara *et al*., 1993; Nakamura *et al*., 1995). Therapies using biologically active, soluble factors such as growth factors or cytokines have been investigated for potential clinical use in regenerating lost periodontal tissue due to periodontitis. Growth factors are a potential agent to target specific tissue reactions because of their regulatory roles in cellular functions, including adhesion, proliferation, migration, and differentiation in the epithelium, bone, and soft connective tissues and nerves (Nakamura *et al*., 1995). Fibroblast growth factor (FGF) is a representative growth factor which has shown the potential effects on the repair and regeneration of tissues (Cairo *et al*., 2008; Cheung *et al*., 2004; Addin *et al*., 2017; Camargo *et al*., 2001; Cortellini *et al*., 2012). It was originally identified as a protein capable of promoting fibroblast proliferation. FGFs exert multiple functions through the binding into and activation of fibroblast growth factor receptors (FGFRs) and the main signalling through the stimulation of FGFRs is the RAS/MAP kinase pathway (Kim *et al*., 2018).

The present study clinically evaluated the regenerative potential of rhFGF-2 impregnated collagen membranes in sites with multiple gingival recession defects. FGF-C scaffolds showed significant increase in keratinized gingiva and decrease in recession depths over plain collagen scaffolds at the end of study period. This can be attributed to a myriad of reasons; during the early stages of periodontal regeneration, FGF-2 increases the number of PDL cells while suppressing differentiation into osteoblasts and cementoblasts. During the subsequent healing processes, periodontal ligament cells begin to differentiate, inducing marked periodontal soft-tissue regeneration (Murakami *et al*., 2003; Hankemeier *et al*., 2005; Yun *et al*., 2010). Particularly, on the root surface, the early formation of connective tissue extending from the existing PDL also seems to contribute to inhibiting down-growth of gingival epithelial tissue and in maintaining the height of gingival tissue. It was shown that FGF-2 acts differently on PDL cells and gingival epithelial cells in vivo in terms of proliferative response (Mayahara *et al*., 1993; Nakamura *et al*., 1995). FGF-2 synergistically enhances the proliferation of gingival epithelial cells when PDL cells are in abundance (Murakami *et al*., 2003; Hankemeier *et al*., 2005; Yun *et al*., 2010; Cairo *et al*., 2008). All these mechanisms can logically contribute to new gingival

corium generation and reduction in gingival recession.

Several preclinical studies revealed that FGF-2 induced significant periodontal regeneration comprised of new cementum with Sharpey's fibres, new functionally oriented periodontal ligament fibres and new alveolar bone. Two multicentred human trials (Khoshkam *et al*., 2015; Aoki *et al*., 2021), where rhFGF2 was used in intrabony defects observed attachment gain, radiographic bone gain and pocket depth attributing to the fact that cellular attachment, proliferation and synthesis of selected extracellular matrix proteins such as laminin and osteopontin are enhanced by FGF-2 in periodontal ligament fibroblasts, osteoblasts and cementoblasts. These clinical studies showed that the use of recombinant human FGF-2 (rhFGF-2) in human surgical periodontal treatment is safe and clinically effective (Khoshkam *et al*., 2015; Aoki *et al*., 2021). However, the present study is the first human trial to the best of our knowledge where rhFGF2 was used for treatment of gingival recession defects.

FGF-C scaffolds showed an increase in gingival thickness than plain collagen scaffolds; however, this increase was statistically not significant. The increase in the thickness can be attributed to the action of FGF-2 in promoting endothelial recruitment, fibroblastic proliferation, enhanced connective tissue formation and better vascularisation (Mayahara *et al*., 1993; Nakamura *et al*., 1995). The role of surgical technique and the scaffold itself cannot be discounted. Healing occurs mainly through formation of long junctional epithelium, the manipulation of flap through coronal advancement (Cheung *et al*., 2004) in itself can affect the gingival biotype and can lead to reduction in recession depth and enhanced root coverage (Cheung *et al*., 2004; Addin *et al*., 2017). Most commonly used delivery vehicles for regenerative materials are collagen based biomaterials, because they can form a polyanionic complex with FGF-2 (Camargo *et al*., 2001; Cortellini *et al*., 2012; Kim *et al*., 2018). If stabilized properly through atraumatic techniques such as placing the scaffolds by tunnelling procedures, biomaterials containing FGF2 show favourable results in terms of bone & cementum regeneration (Cardaropoli *et al*., 2014; Murakami *et al*., 2011). FGF-2 impregnated collagen scaffolds can survive post-implantation for 8-weeks ensuring availability of FGF-2 at least for 3-weeks (Hong *et al*., 2010; Hoshi *et al*., 2016; Kao *et al*., 2009; Cha *et al*., 2017; Rakmanee *et al*., 2019). Animal studies (Hong *et al*., 2010; Hoshi *et al*., 2016; Kao *et al*., 2009) which utilize a higher dose of FGF-2 (~50 μg/ml or 0.3% rhFGF-2 ) report a complete replacement of the membrane within three weeks by osteoid tissue. When utilized for root coverage, FGF-2 showed higher amount of root coverage at 4 weeks and over 80% of mean root coverage was achieved in 16 weeks (Rakmanee *et al*., 2019). These observations commensurate with the release profile seen in the current study. Though the FGF-2 levels in the scaffold was vastly lower in our study (10 ng/ml), maximum FGF-2 levels were found at around 3-weeks with a precipitous drop to a level almost corresponding to those seen in tissues undergoing regeneration. It also appears that the use of biomaterials such as GTR membranes also result in an increase in growth mediators; one study reported FGF-2 (Kuru *et al*., 2004) levels of almost 350 pg/mL at 7-days in sites receiving regenerative therapy; the maximum level of FGF-2 in this study was 450 pg/mL at 3-weeks.

The results of the present study confirmed that using rhFGF2 impregnated membrane showed gain in width of keratinized gingiva, recession coverage, but it has no effect on probing depth reduction but significant improvement in gingival biotype as observed when compared to CAF group. Both test group and control group showed increase in width of keratinized gingiva. Gingival recession defect treated with CAF healed by long junctional epithelium with minimal amount of new attachment (Trombelli, 1999; Zucchelli *et al*., 2009; Mayahara *et al*., 1993). On the other hand, the defect treated with GTR-based root coverage procedures resulted in new attachment formation comparable to these traditional approaches (Kao *et al*., 2009). The test group show statistically greater increase in width of keratinized gingiva compared to the control group because FGF-2 on root surface histology shows early formation of connective tissue extending from the existing PDL seems to contribute to inhibiting down-growth of gingival epithelial tissue (Cha *et al*., 2017).

This study has some limitations worth noting. To facilitate scaffold stability and survivability, two surgical techniques were utilized based on the gingival biotype (Kuru *et al*., 2004). which differ in parameters such as operator skill, trauma to the soft tissues and flap design and may affect outcomes within both the groups (Stetler *et al*., 1987; Trombelli, 1999; Saito *et al*., 2016; Cairo *et al*., 2014). However, similar proportions of sites (22/43 sites and 26/45 sites) were treated with identical procedure in both the groups and we feel that this limitation is not disconcerting. The release profile of FGF-2 could have been clearer with the inclusion of values at baseline. While we did collect GCF samples at baseline, FGF-2 could be estimated only in very few samples and hence a statistical analysis could not be carried out; this observation was seen in another study as well (Kuru *et al*., 2004).

## Conclusions

The current study showed promising results for rhFGF-2 impregnated collagen scaffolds on outcomes of gingival recession. Further validation in larger study cohorts and at longer study intervals is needed to establish the effectiveness of the material.

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