Volume 9, Issue 9, September– 2024 International Journal of Innovative Science and Research Technology
ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP1161

Concentrated Growth Factor (CGF): A Potential New Player in Periodontal Regeneration

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Abstract:- Regenerative procedures have become a key focus in contemporary rehabilitation therapies. In dentistry, research on growth factors for bone regeneration has identified autologous growth factors as the most effective stimuli for tissue regeneration and healing. These bioactive proteins play a crucial role in wound healing. Concentrated growth factor (CGF) is a recent advancement in 2nd generation platelet concentrates. The use of different centrifugation speeds helps to obtain a significantly dense fibrin. Also, it contains more amount of growth factors than the other platelet concentrates available.

Keywords:- *Growth Factors, Regeneration, Platelet-Rich Fibrin, Healing.*

I. INTRODUCTION

Periodontal disease is an inflammatory disorder that consequently and ultimately results in loss of attachment and tooth loss. After managing the inflammation associated with the disease, the main aim of treating periodontal disease is to regenerate the damaged tissues. The regeneration of periodontium involves the rebuilding or reconstruction of damaged tissues to bring back their original form and work.1This has to be differentiated from the term ‘‘new attachment’’ which describes the formation of new cementum with embedding collagen fibres on a root surface deprived of its periodontal ligament, but doesn’t inescapably describe regeneration of the entire periodontium. Indeed, periodontal regeneration can only be demonstrated histologically.2

Growth factors are a broad category of naturally occurring proteins that play a prime role in promoting cell multiplication (mitogenesis), directed movement, and metabolic activity within the body. In tissue repair, the three essential cellular processes are proliferation, migration, synthesis and remodelling of the extracellular matrix. For a growth factor to be effective in periodontal regeneration, it must encourage the formation of mineralized tissues (such as bone and root cementum) and non-mineralized tissues (like the periodontal ligament and gingival connective tissue). Using a combination of growth factors might be more effective, with one factor promoting the formation of mineralized tissues and another enhancing the development of non-mineralized tissues.3

The regeneration of Periodontal tissues is best demonstrated histologically, where the different constituents of the periodontium can be observed. The new focus in regenerative dental science is on finding biocompatible materials. This is particularly relevant in cases such as large bone defects following enucleation. In dentistry, platelet concentrates have emerged as promising second option to chemical or bovine membranes for Guided Bone Regeneration therapies. These platelet concentrates, being derived from the same individual, circumvent potential biocompatibility problems associated with non-autologous materials.4

Various cells are involved in wound healing, and this process is controlled by growth factors. Platelets are known as natural healers of injuries; when activated, they release autologous growth factors. These platelets produce a significant amount of growth factors, including Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor-β1 (TGF-β1), TGF-β2, Fibroblast Growth Factor (FGF), Vascular Endothelial Growth Factor (VEGF), and Insulin-like Growth Factor (IGF). These factors promote cellular multiplication, matrix remodeling, and angiogenesis (Dohan E et al., 2010; Farina et al., 2013). Intini. G after his

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP1161

investigations done in 2009 stated that platelets have potential growth factors such as FGF, IGF, TGF are required for osteogenesis. They basically are proteins that signal cells for growth, proliferation, and differentiation, playing a key role in mediating inflammation. Additionally, they guide the directed migration and metabolic activity of cells.5

Recently, there has been growing interest in using growth factors for treating oral and maxillofacial conditions, particularly after invention of platelet concentrates.6These autologous blood preparations are enriched with platelets and are non-toxic and non-immunogenic, which makes them effective in accelerating osteogenesis. Successful osteogenesis requires the presence of-

- Scaffolds
- Mesenchymal Stem cells
- Growth Factors

All of the above factors are contained in platelets and hence they are proven to be ideal in regenerative dental science. As Badran et al. in 2017 has stated that an ideal platelet concentrate should have increased amount of growth promoting factors, with an ideal increase being 5-fold. Autologous Platelet Concentrates (APCs), which are rich in growth factors and derived from the patient's own blood, have shown promising improvement in the outcomes of periodontal treatments.7

Concentrated Growth Factor is the new, second-generation platelet concentrate introduced by Sacco in 2006.8

II. HISTORICAL BACKGROUND

Ross in 1974 first described Platelet-Derived Growth Factor (PDGF). According to Bornfeldt et al., (1995) it is produced by giant cells and plays a pivotal role in stimulating formation of new blood vessels, new bone formation, differentiation, and mesenchymal stem cell division. PDGF also promotes fibroblast and collagen formation.8,9

PDGF and TGF-β are particularly recognized for enhancing tensile strength and callus formation, which positively impacts the healing of both bone and soft tissue as stated by Cromack et al., Bolander et al, Pierce et al., Tsay et al., in the year 1990, 1992, 1994 and 2005 respectively.8,10,11,12,13

Tsay has suggested that growth factors such as PDGF and TGF-β cause signaling, attraction and direction of precursor cells of osteoblast to sites where bone formation is needed, followed by proliferation and differentiation of Bone forming cells.13

Ai-Aql et al. in 2008 stated TGF-β is released by burst open platelets during the initial stages of injury. It promotes the extracellular matrix proteins expression and influences osteoblasts in their early developmental stages. Additionally, it initiates collagen production by fibroblasts, aiding in the regeneration of bone and cartilage.14

According to Linkhart et al., (1996), IGF supports cell differentiation and promotes osteogenesis. Specifically, Insulin Growth Factor-I and II enhance osteoblast proliferation and their specialized actions, such as the production of collagen type I, serving as key paracrine and autocrine regulators.15

Similar to PRP and PRF, CGF exhibits a repeated concentric layer structure. However, according to Rodella's research, CGF contains higher concentrations of growth factors. Most studies have concentrated on its clinical uses, such as in sinus uplifting procedures and ridge augmentation (Tayapongsak et al., 1994; Sohn et al., 2009; Sohn, 2009a; Sohn, 2009b; Sohn et al., 2010; Sohn et al., 2011).16,17,18,19,20

CGF was introduced by Sacco in 2006, and its morphological characteristics are not as thoroughly documented as those of Platelet-Rich Plasma and Platelet-Rich Fibrin. There is limited information available regarding its biological and morphological properties.8

According to Rodella et al. the varying centrifugation cycles used for production of CGF enables the separation of a larger, thicker fibrin matrix that is more enriched with growth factors compared to other types The fibrin clot's high cohesive nature results from the aggregation of fibrinogen, thrombin and factor XIII.21 According to Tayapongsak et al., when thrombin activates factor XIIIa, it causes the fibrin to clot, which helps protect the fibrin from degradation by plasmin, leading to increased tensile strength and stability of the fibrin.8

Rodella et al. in his histological analysis revealed that the main feature of CGF is its fibrin network, which includes platelets, WBCs, and growth factors. This serves as a scaffold for cellular migration of fibroblasts and endothelial cells, which are essential for angiogenesis and tissue remodelling. The platelets in CGF are particularly significant due to their release of high levels of biologically active proteins that aid in cell recruitment, growth, and morphogenesis.21

Sacco's membrane exhibits a complex 3D structure, presenting it as a biomaterial that is rich in fibrin, platelets, leukocytes, and growth factors. This composition makes it highly beneficial for both patients and clinicians (Dohan et al., 2006a; Dohan et al., 2006b; Dohan Ehrenfest et al., 2009).22,23,24,25

➢ *Classification of Growth Factors(Table1)*

Growth Factors are typically classified into families according to factors like functional characteristics, or the cell types and cellular processes they regulate.

➢ *Method of Preparation of CGF*

Sacco in 2006 has introduced a protocol of centrifugation for the preparation of CGF. Blood is collected from a patient in a Vacuette tube. The tube contains silicon coating for clot activation. Tubes containing blood is then

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP1161

placed in a special centrifugation machine. (Figure1)(Medifuge MF200, Silfradentsrl, Forlì, Italy).21

Fig 1 Medifuge MF200

The machine is set with the following sequence: an initial 30 secs of acceleration, 2 minutes of centrifugation at 2,700 rpm, 4 minutes at 2,400 rpm, another 4 minutes at 2,700 rpm, and 3 minutes at 3,000 rpm, applying forces of 692 gm, 547 gm, 592 gm, and 855 gm respectively. The process concludes with 36 seconds of deceleration before stopping.8 This will lead to the formation of four distinct blood layers.(Figure2).

Fig 2 Phases of Blood after Centrifugation and CGF

- *Superior Phase:*

Also known as platelet-poor plasma (PPP), this clear, straw-colored liquid is the lightest and most fluid part of the blood. It comprises 92% water and 7% solutes, including lipids and proteins, various enzymes, hormones, and inorganic electrolytes. PPP is utilized to arrest bleeding, disinfect the surgical site, and isolate and protect regenerated areas.

- *Interim Phase:*

Referred to as the fibrin phase, this contains a gel-like network of fibrinogen molecules arranged in a three-dimensional polymer structure. When seen under an electron microscope, this layer displays fibrin components, forming a robust fibrin network. The fibrin blocks in CGF are enriched with fibrinogen, factor XIII, and thrombin, with thrombin-activated Factor XIII to stabilize the fibrin clot. This stabilized clot offers enhanced tensile strength and stability, promoting the faster proliferation and differentiation of osteogenic cells. CGF(Figure3) is utilized to create membranes for guided tissue regeneration and can be used alone or combined with bone graft for regeneration of bony defects. K Isobe (2017) stated that, CGF's tensile strength is equivalent to PRF and superior to PPTF (platelet-poor plasma-derived fibrin). PPTF degrades faster than CGF which is equivalent to A-PRF.26

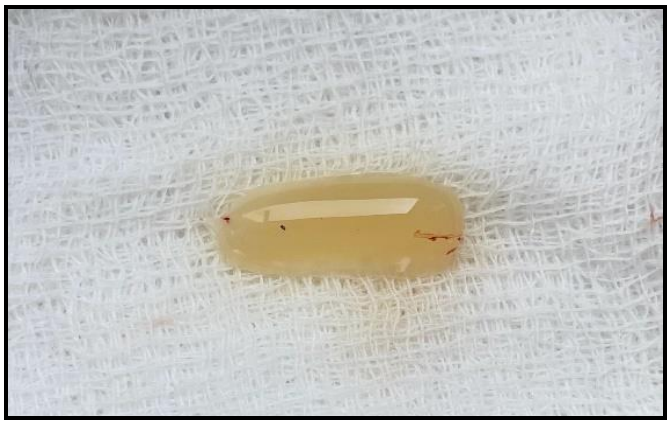

Fig 3 CGF

- *Liquid Phase:*

This phase contains growth promoters, leucocytes, and mesenchymal stem cells capable of differentiating into specialized cell types. The liquid phase can be mixed with autologous bone grafts to enhance performance. It includes CD34-positive cells and a 3-4 mm layer of red blood cells below it. For osteogenesis, CGF and a portion of the RBCs are used in regenerative therapy. CD34+ cells, as noted by Majka et al. (2001), contribute to vascular maintenance, neovascularization, and angiogenesis, thereby accelerating bone regeneration.

- *Lower Phase:*

This dark reddish, dense gel contains a high concentration of red blood cells, along with some white cells, platelets, and clotting factors. It can be used in its pure form or mixed with bone grafts to fill large cavities.

➢ *Applications of CGF in Periodontal Regeneration.*

- CGF in soft tissue augmentation procedures.
- CGF is used as a bandage in gingival depigmentation procedures.
- CGF in bone regeneration.
- The use of CGF in dental implantology.
- Alveolar ridge and extraction socket preservation.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP1161

III. DISCUSSION

Regenerating periodontal tissues involves a complex interplay between cells and the extracellular matrix, with growth factors orchestrating these interactions to promote healing and tissue regeneration. Current research indicates that the optimal combination of growth factors in appropriate concentrations is ideal for periodontal regeneration. Concentrated Growth Factor (CGF) represents a significant advancement in tissue engineering for dentistry, offering a natural and cost-effective autologous solution that enhances the regeneration of both hard and soft tissues.

Being a fully natural, physiological, and economical autologous product, CGF mitigates concerns related to immunogenic reactions and disease transmission. Despite these advantages, research on CGF is still in its early stages. To better understand its effectiveness in regenerative procedures, larger sample studies and randomized controlled trials are needed to explore its clinical applications.

CGF is an advanced form of Platelet-Rich Fibrin (PRF) with promising applications in various dental procedures, including sinus floor elevation and alveolar ridge augmentation, pre-implant procedures, regeneration of deep bone defects (such as those following periapical cyst removal), and initiating the proliferation of periodontal ligament mesenchymal stem cells. CGF offers greater tensile strength, higher growth factor level, increased viscosity, better adhesive properties compared to earlier platelet concentrates like PRF. Its autologous fibrin serves both as a scaffold and a reservoir for growth factors at the treatment site, potentially reducing postoperative complications such as pain, inflammation, and morbidity.

However, there isn't enough scientific research on the effects of CGF on periodontal ligament cells, bone defects, peri-implant bone defects, and dental implant osseointegration. Studies by Qiao et al.27 found that CGF significantly improved the clinical outcomes of bone graft materials for treating intrabony defects. Gokmenoglu et al.28 observed positive results from combining CGF with bone grafts for bone defect treatment, while Mirkovic et al.29 suggested that CGF could be effective for reconstructing bone defects following large jaw cyst removal. Durmuslar et al.30 evaluated CGF's impact on peri-implant bone defect healing in rabbits, and Pirpir et al.31 noted its benefits for implant stabilization and osseointegration.

IV. CONCLUSION

Despite its advantages, researchers highlight the need for longer duration randomized controlled trials with greater sample sizes to fully assess the clinical efficacy of CGF.

- *Conflicts of Interest: Nil*

Table 1 Classification of Growth Factors

Superfamily	Family	Examples
TGF-β (Transforming growth factor- β)	TGF- β	TGF- β1, β2, β3
	INHIBIN	INHIBIN A, B, C
	BMP (Bone morphogenetic proteins)	hBMP-2, hBMP-3
PDGF (Platelet derived growth factor)	PDGF	PDGF-AA, BB, AB
	VPF (Vascular proliferating factor)	VPF, VEGF (Vascular endothelial growth factor),
	CTGF (Connective tissue growth factor)	CTGF, CEF-10
EGF (Epidermal growth factor)	EGF	EGF, TGF-alpha, AR
NO SUPERFAMILY	FGF (Fibroblast growth factor)	aFGF, bFGF, INT-2
NO SUPERFAMILY	IGF (Insulin-like growth factor)	Insulin, IGF-1,IGF-2

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