The use of concentrated growth factor in dental implantology: A systematic review

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INTRODUCTION

Dental implants have come a long way in reinstating the comfort and health of the stomatognathic system. A very good success rate of 94% has been documented for implant-supported prosthesis. However, it is not uncommon to encounter cases with qualitative and quantitative reduction of alveolar bone. The best way to ensure the predictability of implant treatment in such cases is enhancing osseointegration. Various methods in the literature have been proposed to facilitate this process, including alteration of implant topography, surface morphology, roughness, surface energy, strain hardening, chemical composition, the presence of impurities, thickness of titanium oxide layer and the presence of nonmetal and metal composites. Another method of accelerating osseointegration is the modulation of healing after the placement of implant. This is where bioactive molecules called growth factors (GFs) come in picture.

Platelets are a natural source of GFs including platelet-derived GF, transforming GF (TGF)-β1 and β2

Abstract

In the era of evidence based dentistry, a well-documented consolidated data about improvements in dentistry is a necessity. Concentrated growth factor (CGF) is an emerging trend in periodontology and now in implant dentistry. Various studies have been published in the literature evaluating the effect of CGF on implant osseointegration, implant stability, survival rate, sinus augmentation, and peri-implant defects. However, no systematic review has yet been documented. The present systematic review, being first of its kind, aimed to evaluate the potential outcomes of employing CGF in implant treatment. A literature search was carried out in PubMed and Google scholar for articles published between 2001 and 2019, with various keywords such as “CGF,” “dental implant,” “bone regeneration,” “CGF,” and “osseointegration.” The screening of studies was done according to PRISMA guidelines. A total of eleven studies were included in this review. Majority of the included studies pointed toward the beneficial effects of CGF in implant treatment. CGF was seen to promote osseointegration and enhance bone regeneration. Although more clinical studies are required to validate the potential merits of CGF in the long run, the preliminary results seem promising.

Keywords: Bone regeneration, concentrated growth factor and osseointegration, concentrated growth factor, dental implant

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Received: 14th October 2019, Revision: 25th December 2019, Accepted: 27th December 2019, Publication: 27th January, 2020

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How to cite this article: Lokwani BV, Gupta D, Agrawal RS, Mehta S, Nirmal NJ. The use of concentrated growth factor in dental implantology: A systematic review. J Indian Prosthodont Soc 2020;20:3-10.

Access this article online

Quick Response Code: [QR Code Image]
Website: www.j-ips.org
DOI: 10.4103/jips.jips_375_19

How to cite this article: Lokwani BV, Gupta D, Agrawal RS, Mehta S, Nirmal NJ. The use of concentrated growth factor in dental implantology: A systematic review. J Indian Prosthodont Soc 2020;20:3-10.
The literature comprises of several case reports, case series, prospective, and retrospective studies which outline the advantages of using CGF for bone regeneration. However, there is no systematic review analyzing the potential benefits of CGF in dental implantology. Therefore, this systematic review was planned to retrieve a detailed data pool from the published literature to consolidate information on the effects of CGF in implant dentistry.

The focused question was formulated according to the PRISMA Guidelines. The P: Problem/Population, I: Intervention, C: Comparison, O: Outcome, S: Study design question framed was: “Is there any additional benefit of CGF on guided bone regeneration and implant therapy over traditional approaches in terms of clinical, histological, and radiographic outcomes?” The study designs of interest were randomized controlled clinical studies, prospective and retrospective studies [Table 1].

**MATERIALS AND METHODS**

Our study was conducted based on the guidelines of the Cochrane Collaboration.

**Search strategy**

The initial electronic literature search was independently conducted by two investigators (BL and DG) from January 2001 to October 2019, using MEDLINE (PubMed) and Google Scholar for articles in English language published in journals of dentistry using following search terms: “CGF and dental implants,” “CGF and dental implants and bone regeneration,” “CGF and osseointegration,” “CGF in implant dentistry,” “CGF and dental implant NOT plasma rich fibrin.” The search filters were not restricted by design or region. The results were limited to human studies. For Google scholar, the keywords were identified through the “advanced search” option appearing “anywhere in the article.”

The “related articles” option in the search engines was used. An additional hand search was carried out including the bibliographies of the selected papers and other narrative and systematic reviews.

**Inclusion criteria**

1. Studies designed as randomized controlled trials (RCTs), retrospective and prospective clinical studies
2. Studies evaluating placement of dental implant/s in human participants
3. Studies with an observation time of at least 3 months after implant placement
4. Studies evaluating clinical and radiographic changes after use of CGF.

**Exclusion criteria**

1. Implant studies carried out on animal subjects
2. In vitro or bench research studies including finite element analysis
3. Case series, case reports, or review articles
4. Studies which did not have full text retrievable
5. Duplicate studies.

**Screening and selection of studies**

Publication records and titles identified by the electronic search and hand search were independently screened by two reviewers (BL and DG) based on the inclusion criteria. Discrepancies were solved by discussion including a third reviewer (Rheumatoid arthritis [RA]). Cohen’s Kappa coefficient was used as a measure of agreement between the readers. Thereafter, full texts of the selected abstracts were obtained. The two reviewers independently performed the
screening process, and then, articles that met the inclusion criteria were processed for data extraction.

Data extraction and quality assessment
The data extraction was done based on the inclusion criteria. The studies were classified according to study design and outcome variables. Then, outcomes were compiled in tables. All extracted data were double-checked, and any questions that came up during the screening and the data extraction were discussed within the authors to aim for consensus. Two reviewers (BL and DG) independently evaluated the methodological quality of all included studies. Any disagreement was discussed with the third reviewer (RA) until consensus was achieved.

The Newcastle–Ottawa scale was used to assess the methodological quality of the included prospective and retrospective cohort and case–control studies [Table 2].[18]
The Jadad scale was used for assessing RCTs [Table 3].[27]

RESULTS

After the independent screening process by two reviewers, the inter-rater agreement was calculated by Cohen's Kappa coefficient as 0.82 indicative of almost perfect agreement.

Selection of studies
A total of 2029 studies were identified from the initial search through the databases. After removal of the duplicate records (n = 944), 388 articles were screened. Twenty-two full-text articles were then assessed for eligibility separately by two different authors (BL and DG), of which 11 were selected to be included in the final review [Figure 1 and Table 4].

For all the included studies, the data were tabulated with information about the type of study, year of publication, duration of study, number of patients and implants, site of operation, the test and control group of each study, and the result obtained. Because of high heterogeneity present in the included studies with regard to outcome measures and study designs, a meta-analysis was not feasible. The included studies were divided into different categories depending on the outcome variables they measured [Tables 5–8].

Alveolar bone gain:
Six included studies depicted alveolar bone regeneration which could easily be identified through subsequent radiographs.[19–23,28] The bone gain was seen in various forms such as decrease in the vertical defect depth after 12 months as analyzed through computer software,[28] or simply as vertical bone gain by increase in bone height around the implants measured from specific points.[19–23]
or even as increase in bone width measured from implant shoulder to the apical point [Table 5].\cite{22}

**Implant stability quotient:**

Two of the included studies measured implant stability quotient (ISQ).\cite{24,25} Measurements were taken through resonance frequency analysis using the Osstell® device at the time of implant placement and at the 1st, 2nd, and 4th weeks\cite{24} and at the 1st and 4th weeks after implant placement [Table 6].\cite{25}

**Bone density around implant threads:**

The quality of bone formed around implant threads was assessed through radiographic analysis in two studies.\cite{20,21} Another study employed the texture analysis of panoramic radiographs comparing the results obtained immediately after implant placement and after 8 months postoperatively as area under curve.\cite{28} All the three studies concluded that CGF had a positive impact on the quality of bone formed around implants [Table 7].

**Implant survival rate:**

The survival rate of implants was measured in six of the included studies.\cite{19,21,23,26,30} It was determined on the basis of number of complications during the follow-up period of the study. All the studies showed a high survival rate of almost 100% for implants placed along with CGF [Table 8].

**DISCUSSION**

The literature has a dearth of studies determining the effects of CGF and their potential role in implant dentistry. The present systematic review, being first of its kind, was conducted to contribute to the literature of evidence-based dentistry. The aim was to evaluate the clinical indications of CGF in all fields of dental implantology such as alveolar bone gain, improved bone quality around implants, enhancement of osseointegration, maxillary sinus augmentation, achievement of implant stability and implant survival rate.

CGF is now emerging as a viable treatment option due to various reasons. First, it has the capability for...
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The Journal of Indian Prosthodontic Society | Volume 20 | Issue 1 | January-March 2020

extended release of GFs, presenting a stronger effect on enhancement of wound healing around implants. Second, it can be used alone or in combination with synthetic graft materials and facilitate osseointegration. Third, it is easy to prepare and manipulate, and it is inexpensive. The various outcomes discussed in the included studies show a positive trend toward the use of CGF in implant dentistry, although statistically significant conclusion cannot be drawn.

Alveolar bone regeneration

The primary aim to employ CGF for bone augmentation is to facilitate implant placement in a prosthetically driven position. Two studies evaluated the vertical bone gain after sinus augmentation and reported positive outcomes. In both the studies, the technique used for sinus augmentation was different, but the graft material utilized was CGF. Sohn et al. reported that CGF induced fast new bone formation in sinus augmentation. Furthermore,
Sohn et al. proved in a clinical and histological evaluation that CGF, as a sole material, when inserted alone in sinus augmentation, induced rapid new bone formation in the new compartment under the elevated sinus membrane through the transcrestal and the lateral approaches.\(^{26,42}\) As the result, bone regeneration along the implant body was evident radiographically and statistically significant.

Two other studies\(^{21,28}\) revealed new alveolar bone formation for CGF group at the follow-up period of 12 months when compared to baseline values. Although the control group exhibited greater bone formation than the test group, the results were not statistically significant.

The study by Yang et al.\(^{21}\) showed improved buccal bone width after 1 year of immediate implant placement. This has been attributed to the GFs in CGF which regulate wound healing, cell proliferation, and cell migration. Furthermore, another study revealed vertical bone gain on all four aspects (buccal, lingual, mesial, and distal) after immediate implant placement.\(^{23}\) The jumping distance was filled with CGF because it provides for higher fibrin tensile strength and stability due to agglutination of fibrinogen, factor XIII and thrombin.\(^{43}\) Furthermore, CGF acted as barrier membrane to accelerate soft tissue healing, and when mixed with bone graft, it could accelerate new bone formation.\(^{20}\)

**Implant stability quotient**

Investigators have recommended that implants with ISQ <49 measured when placed should not be loaded during the 3-month healing period; implants with ISQ ≥54 may be loaded.\(^{23}\) In some studies, there is a meaningful reduction in ISQ values measured sometime after the placement of implants.\(^{44-46}\) Subsequently, there can be an increase in the value indicating greater stability. This increase or decrease is due to continuous alveolar bone remodeling during healing. In one of the included studies, an increase in the ISQ values was seen in the test group.\(^{25}\) This suggested that CGF administration improved the implant primary stability by accelerating the osseointegration process. However, another study did not report any significant benefits of CGF on improving implant stability.\(^{24}\) Similarly, Ergun et al.\(^{47}\) evaluated the effect of local application of PRP on the outcome of early loaded implants and found no statistically significant differences between ISQ values of PRP and non-PRP implants in the follow-up periods. However, Dohan Ehrenfest DM.\(^{48}\) reported in a different experimental study that L-PRF usage during implant placement may enhance and increase the wound healing and early implant stability. Hence, while studies may indicate the use of CGF for implant stability, conclusive results can still not be drawn. Therefore, the use of CGF remains questionable with regard to implant stability.

**Bone density around implants**

The quality of bone formed around implants is indicative of implant osseointegration activity. In two studies,\(^{25,26}\) bone density of the newly formed bone around implants was measured using CBCT in Hounsfield units. Both the studies revealed a significant increase in bone volume. The test group showed better statistically significant bone quality as compared to the control group which was attributed to the faster bone formation with CGF as observed by Kim et al.\(^{49}\) Another study\(^{29}\) employed textural analysis (an intensity based registration method that utilized the mean square error metric) to compensate any minor geometrical distortions between the two panoramic radiographs (preoperative and postoperative) of each patient. The results revealed that the CGF group exhibited higher values indicating increased osseointegration activity in the bone-to-implant region. Thus, the positive outcome obtained from the three studies could be attributed to the fact that CGF induced increased osteoblastic differentiation promoting early osseointegration.

**Implant survival**

The success of implant restorations is determined on the implant stability and absence of complications during the follow-up period. Six studies measured the implant survival rate.\(^{19,21,25,26,30}\) Two studies\(^{20,21}\) reported a 100% survival rate at 6 months. One retrospective study\(^{23}\) concluded that all implants were stable and pain free with 100% survival rate over a period of around 20 weeks. However, in a RCT,\(^{54}\) two implants were lost in both, the test group and the control group, indicating a survival rate of 96.4% in test group and 96.1% in control. After maxillary sinus augmentation, a survival rate of 98.2% has been reported after 10 months in a study\(^{19}\) because of membrane perforation occurring in a few cases. Very similar outcomes were also obtained in an investigation, in which autologous fibrin-rich blocks with CGFs without grafting materials were used in the sinus augmentation by lateral window approach.\(^{49}\) Another study has demonstrated that both PRF and CGF preparations contain significant amounts of GFs capable of stimulating periosteal cell proliferation,\(^{50}\) suggesting that PRF and CGF preparations act not only as a scaffolding material but also as a reservoir to deliver certain GFs at the site of application.\(^{26}\)

Although statistically significant conclusions cannot be drawn, a higher recovery limit of CGF (due to its
osseinductive platelet factors and osseocoeductive fibrin grid) can still be considered as a potential benefit for use in dental implantology. [51]

CONCLUSION

Based on limited studies with a limited statistical power, the present systematic review suggests that:

1. CGF might aid in obtaining vertical bone gain around implants, when used alone or in combination with allogenous and xenogenous grafts
2. The quality of new bone formed around implants is significantly improved with the use of CGF
3. There is lack of adequate studies evaluating the effect of CGF on implant stability, sinus floor augmentation, soft tissue healing and implant survival per se, although the preliminary data seems promising.

Future directions

The studies included in this review are limited, and thus, the clinical relevance of the measured outcomes remains questionable. Some may suggest the use of CGF in all fields of implant dentistry, but the potential benefits cannot yet be established. Well-designed RCTs with long-term follow-ups are required to substantiate the findings due to the present study limitations.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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