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**Engineering bioactive glass ionomer cement with tricalcium phosphate and translationally controlled tumor protein for enhanced physicochemical performance and mineral regeneration**

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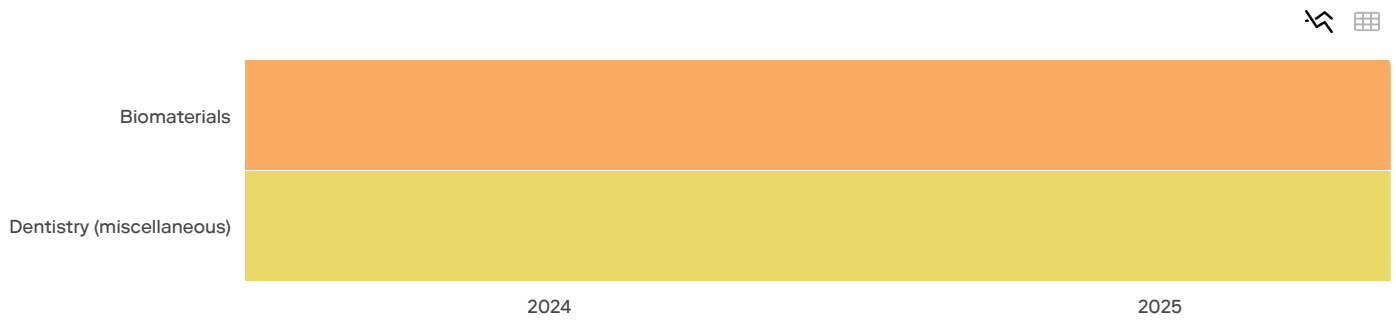
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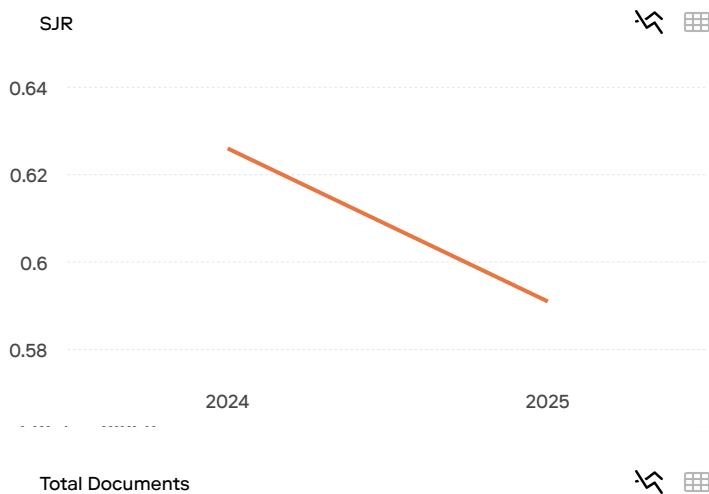
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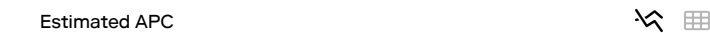
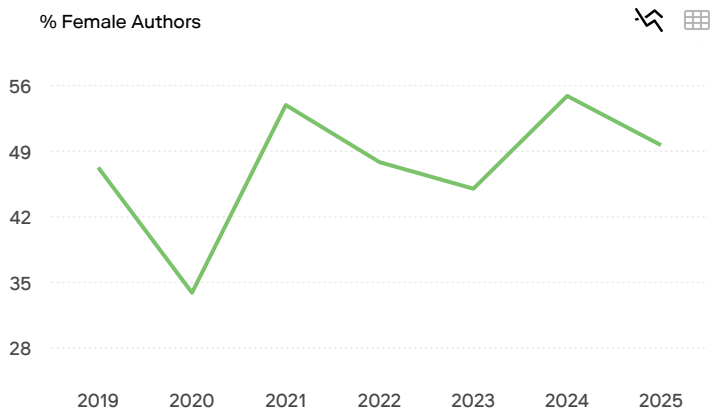
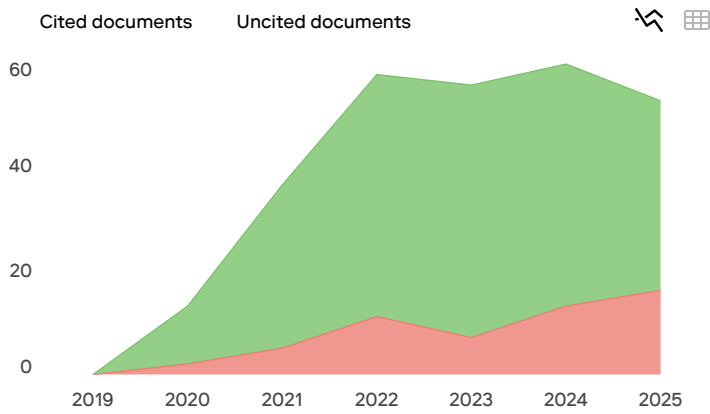
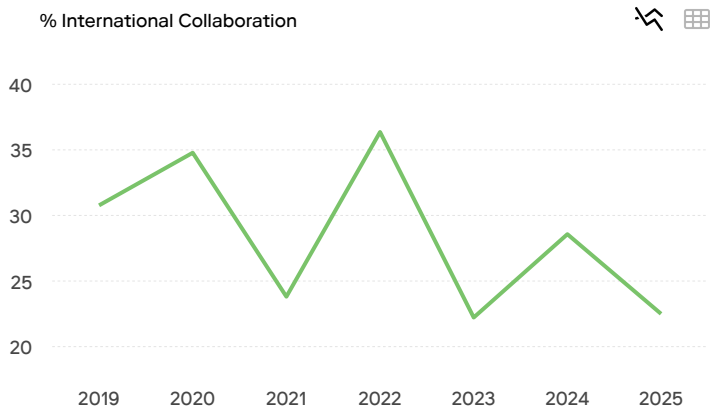
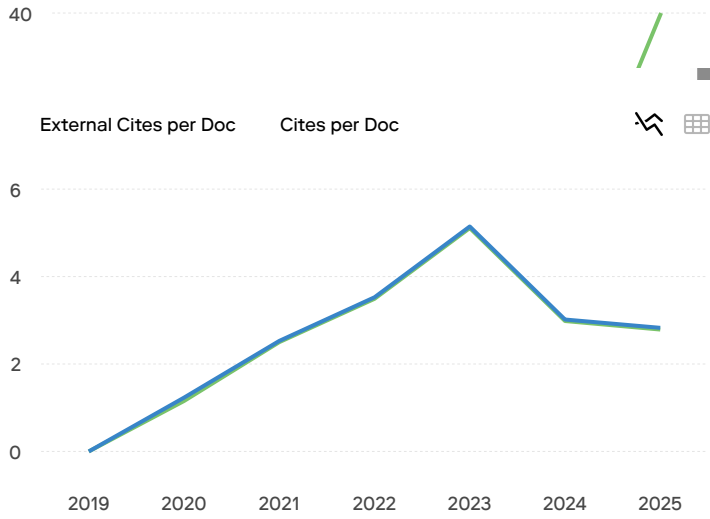
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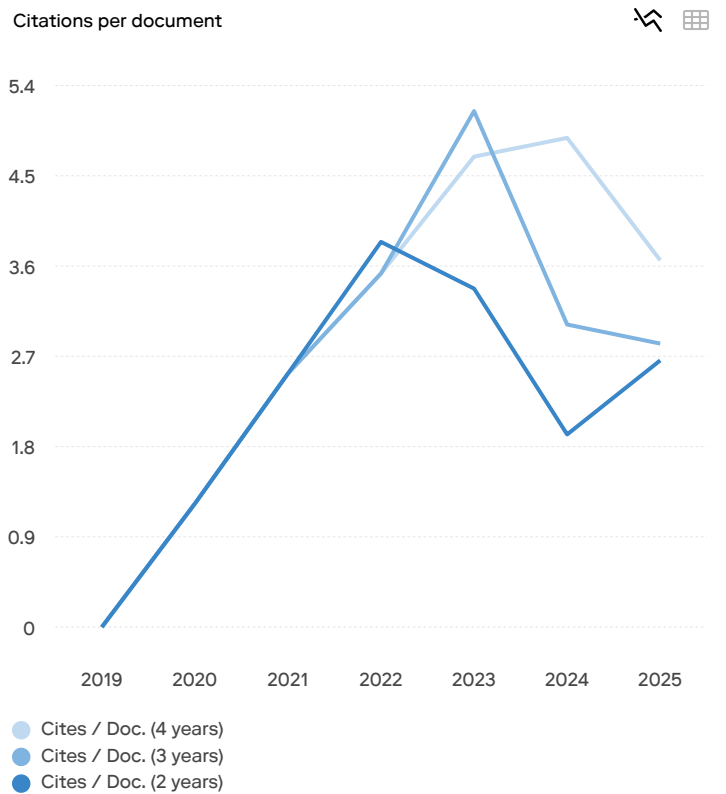
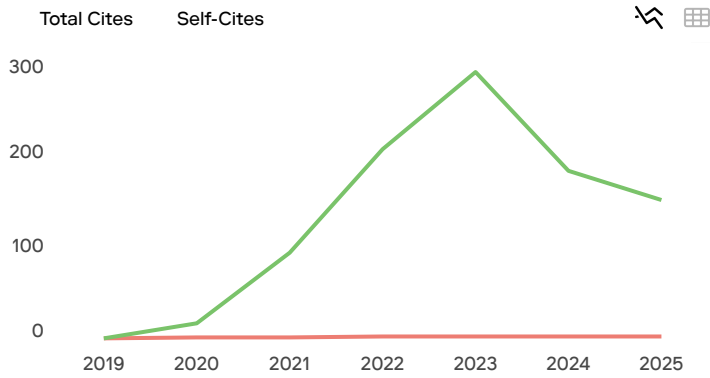
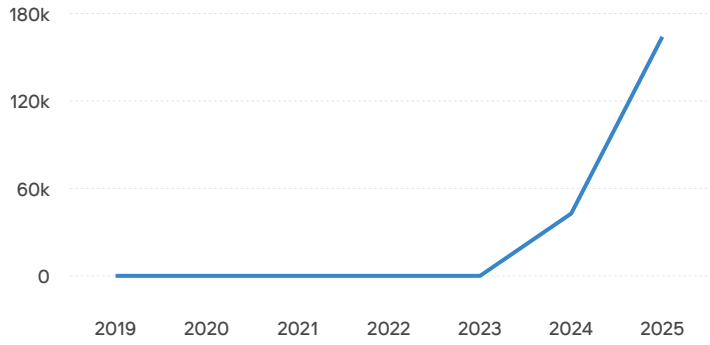


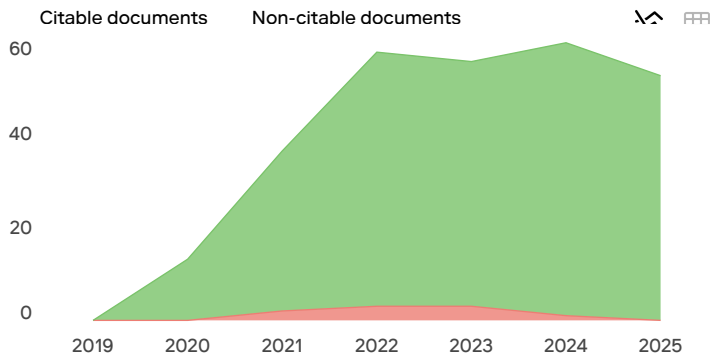
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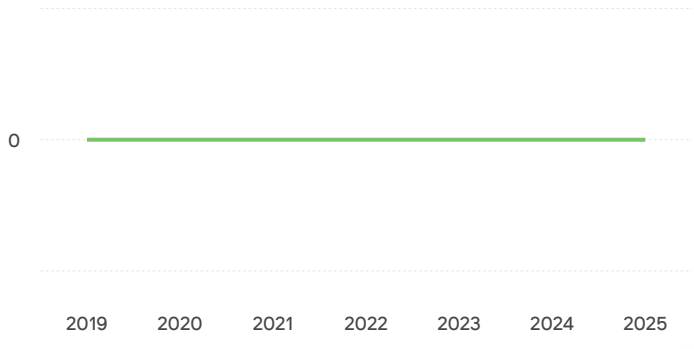








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# **1. Bukti undangan sebagai reviewer**



Rosalina Tjandrawinata &lt;rosalina@trisakti.ac.id&gt;

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## Biomaterial Investigations in Dentistry - Invitation to Review Manuscript ID IABO-2026-0137

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BIOMATERIAL INVESTIGATIONS IN DENTISTRY &lt;onbehalf@manuscriptcentral.com&gt;

Wed, May 13, 2026 at  
8:18 PMReply-To: anne.peutzfeldt@sund.ku.dk  
To: rosalina@trisakti.ac.id

13-May-2026

Dear Dr. Thandrawinata,

My name is Anne Peutzfeldt and I am Editor in Chief of the journal Biomaterial Investigations in Dentistry, which is owned by the not-for-profit organization Acta Odontologica Scandinavica Society, and which is now a Diamond Open Access journal with a CiteScore of 5.1.

Based on your background and expertise, I am contacting you to ask whether you would undertake to review the manuscript mentioned in my official reviewer invitation below. Your contribution would be highly valued.

Kind regards,  
Anne Peutzfeldt  
DDS, PhD, DrOdont  
Editor in Chief  
Biomaterial Investigations in Dentistry

Dear Dr Roslina Tjandrawinata:

The above manuscript, entitled "Engineering bioactive glass ionomer cement with tricalcium phosphate and translationally controlled tumor protein for enhanced physicochemical performance and mineral regeneration" has been submitted to Biomaterial Investigations in Dentistry.

I would be very grateful if you would kindly agree to act as a reviewer for this paper. The abstract appears at the end of this letter.

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Dr Anne Peutzfeldt  
Editor in Chief  
Biomaterial Investigations in Dentistry

## MANUSCRIPT DETAILS

**TITLE:** Engineering bioactive glass ionomer cement with tricalcium phosphate and translationally controlled tumor protein for enhanced physicochemical performance and mineral regeneration

### ABSTRACT:

**Objective:** To develop a bioactive glass ionomer cement (BIOGIC) incorporating tricalcium phosphate (TCP) and translationally controlled tumor protein (TCTP), and to evaluate its chemical characteristics, setting behavior, and mineral regeneration potential using micro-computed tomography (micro-CT).

**Materials and methods:** Conventional glass ionomer cement (GIC) was modified to produce BIOGIC, BIOGIC+TCP, BIOGIC+TCP supplemented with TCTP (3  $\mu$ g and 10  $\mu$ g), and BIOGIC containing 10% chlorhexidine (CHX).

Chemical structure was analyzed by Fourier transform infrared spectroscopy (FTIR), while setting and working times were determined using standardized methods. Mineral regeneration was assessed at 0, 7, 14, 21, and 28 days by measuring mineral volume fraction (MV/TV) and mineralized density. Statistical analyses included one-way and two-way ANOVA ( $p < 0.05$ ).

**Results:** FTIR analysis demonstrated comparable spectral profiles across all groups, with no peak shifts or new functional groups, indicating preservation of the fundamental chemical structure of GIC. All modified BIOGIC formulations exhibited significantly shorter setting and working times than conventional GIC ( $p < 0.05$ ), with no significant differences among modified groups. Micro-CT analysis revealed limited mineral formation in BIOGIC alone, whereas TCP incorporation significantly increased MV/TV and mineralized density. TCTP supplementation further enhanced mineral regeneration in a time- and dose-dependent manner, with BIOGIC+TCP+10  $\mu$ g TCTP showing the highest values at days 21 and 28. Significant effects of treatment, time, and their interaction were observed ( $p < 0.05$ ).

**Conclusions:** TCTP incorporation enhances the regenerative potential of TCP-modified BIOGIC while preserving chemical integrity and improving handling properties, supporting its application in advanced bioactive restorative materials.

## **2. Bukti menerima undangan sebagai reviewer**



Rosalina Tjandrawinata &lt;rosalina@trisakti.ac.id&gt;

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BIOMATERIAL INVESTIGATIONS IN DENTISTRY &lt;onbehalf@manuscriptcentral.com&gt;

Thu, May 14, 2026 at  
10:24 AMReply-To: anne.peutzfeldt@sund.ku.dk  
To: rosalina@trisakti.ac.id

13-May-2026

Dear Dr Roslina Tjandrawinata:

Thank you for agreeing to review the above manuscript, entitled "Engineering bioactive glass ionomer cement with tricalcium phosphate and translationally controlled tumor protein for enhanced physicochemical performance and mineral regeneration" for Biomaterial Investigations in Dentistry. The deadline for your review is 27-May-2026.

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Sincerely,  
Dr Anne Peutzfeldt  
Associate Editor  
Biomaterial Investigations in Dentistry

### **3. Bukti review artikel**

**Engineering bioactive glass ionomer cement with tricalcium phosphate and translationally controlled tumor protein for enhanced physicochemical performance and mineral regeneration**

Journal:	<i>Biomaterial Investigations in Dentistry</i>
Manuscript ID	IABO-2026-0137
Manuscript Type:	Original Article
Keywords:	Glass ionomer cement, Tricalcium phosphate, Mineral regeneration
Abstract:	<p><b>Objective:</b> To develop a bioactive glass ionomer cement (BIOGIC) incorporating tricalcium phosphate (TCP) and translationally controlled tumor protein (TCTP), and to evaluate its chemical characteristics, setting behavior, and mineral regeneration potential using micro-computed tomography (micro-CT).</p> <p><b>Materials and methods:</b> Conventional glass ionomer cement (GIC) was modified to produce BIOGIC, BIOGIC+TCP, BIOGIC+TCP supplemented with TCTP (3 <math>\mu</math>g and 10 <math>\mu</math>g), and BIOGIC containing 10% chlorhexidine (CHX). Chemical structure was analyzed by Fourier transform infrared spectroscopy (FTIR), while setting and working times were determined using standardized methods. Mineral regeneration was assessed at 0, 7, 14, 21, and 28 days by measuring mineral volume fraction (MV/TV) and mineralized density. Statistical analyses included one-way and two-way ANOVA (<math>p &lt; 0.05</math>).</p> <p><b>Results:</b> FTIR analysis demonstrated comparable spectral profiles across all groups, with no peak shifts or new functional groups, indicating preservation of the fundamental chemical structure of GIC. All modified BIOGIC formulations exhibited significantly shorter setting and working times than conventional GIC (<math>p &lt; 0.05</math>), with no significant differences among modified groups. Micro-CT analysis revealed limited mineral formation in BIOGIC alone, whereas TCP incorporation significantly increased MV/TV and mineralized density. TCTP supplementation further enhanced mineral regeneration in a time- and dose-dependent manner, with BIOGIC+TCP+10 <math>\mu</math>g TCTP showing the highest values at days 21 and 28. Significant effects of treatment, time, and their interaction were observed (<math>p &lt; 0.05</math>).</p> <p><b>Conclusions:</b> TCTP incorporation enhances the regenerative potential of TCP-modified BIOGIC while preserving chemical integrity and improving handling properties, supporting its application in advanced bioactive restorative materials.</p>

## Engineering bioactive glass ionomer cement with tricalcium phosphate and translationally controlled tumor protein for enhanced physicochemical performance and mineral regeneration

### Abstract

**Objective:** To develop a bioactive glass ionomer cement (BIOGIC) incorporating tricalcium phosphate (TCP) and translationally controlled tumor protein (TCTP), and to evaluate its chemical characteristics, setting behavior, and mineral regeneration potential using micro-computed tomography (micro-CT).

**Materials and methods:** Conventional glass ionomer cement (GIC) was modified to produce BIOGIC, BIOGIC+TCP, BIOGIC+TCP supplemented with TCTP (3  $\mu$ g and 10  $\mu$ g), and BIOGIC containing 10% chlorhexidine (CHX). Chemical structure was analyzed by Fourier transform infrared spectroscopy (FTIR), while setting and working times were determined using standardized methods. Mineral regeneration was assessed at 0, 7, 14, 21, and 28 days by measuring mineral volume fraction (MV/TV) and mineralized density. Statistical analyses included one-way and two-way ANOVA ( $p < 0.05$ ).

**Results:** FTIR analysis demonstrated comparable spectral profiles across all groups, with no peak shifts or new functional groups, indicating preservation of the fundamental chemical structure of GIC. All modified BIOGIC formulations exhibited significantly shorter setting and working times than conventional GIC ( $p < 0.05$ ), with no significant differences among modified groups. Micro-CT analysis revealed limited mineral formation in BIOGIC alone, whereas TCP incorporation significantly increased MV/TV and mineralized density. TCTP supplementation further enhanced mineral regeneration in a time- and dose-dependent manner, with BIOGIC+TCP+10  $\mu$ g TCTP showing the highest values at days 21 and 28. Significant effects of treatment, time, and their interaction were observed ( $p < 0.05$ ).

**Conclusions:** TCTP incorporation enhances the regenerative potential of TCP-modified BIOGIC while preserving chemical integrity and improving handling properties, supporting its application in advanced bioactive restorative materials.

**Keywords:** Glass ionomer cement; Tricalcium phosphate; Mineral regeneration; Micro-CT; Bone density

## Introduction

Glass ionomer cement (GIC) has been widely used in restorative dentistry for several decades due to its unique combination of physicochemical and biological properties, including chemical adhesion to enamel and dentin, sustained fluoride release with anticariogenic effects, thermal expansion coefficients comparable to tooth structure, and favorable biocompatibility [1,2]. Consequently, GIC has been applied in a broad range of clinical indications, such as atraumatic restorative treatment, cervical restorations, luting agents, and base or liner materials [2,3]. Despite these advantages, conventional GIC still exhibits inherent limitations that restrict its application in load-bearing and regenerative contexts.

One major limitation of conventional GIC is its relatively low mechanical strength, particularly fracture toughness and wear resistance, which may compromise long-term clinical performance under functional loading [4,5]. In addition, its setting reaction is technique-sensitive and influenced by environmental conditions, potentially affecting early mechanical stability and marginal integrity [3]. Moreover, although GIC is generally regarded as biocompatible, its intrinsic bioactivity remains limited, especially in terms of promoting mineralized tissue regeneration or integration with surrounding bone [6].

To overcome these shortcomings, various strategies have been proposed to modify GIC formulations, including altering glass composition, incorporating reinforcing fibers, adding antibacterial agents, and introducing bioactive fillers [4], [7]. Among these approaches, the incorporation of calcium phosphate-based materials has attracted increasing attention due to their chemical similarity to the mineral phase of bone and teeth. Tricalcium phosphate (TCP) is a well-established bioactive ceramic with excellent biocompatibility and osteoconductivity, capable of releasing calcium and phosphate ions that facilitate apatite nucleation and growth [6], [8].

Previous studies have demonstrated that TCP incorporation into dental materials enhances mineral deposition and improves biological responses at the material-tissue interface [9,10]. In GIC systems, TCP has been reported to promote ion exchange and apatite formation, thereby improving mineral integration [6]. However, TCP mainly acts as a passive osteoconductive scaffold, and its regenerative efficacy is largely dependent on the surrounding biological environment [8].

Recently, increasing emphasis has been placed on incorporating bioactive molecules into restorative materials to actively modulate cellular behavior and promote tissue regeneration [11,12]. Translationally controlled tumor protein (TCTP), also known as fortilin, is a multifunctional protein involved in cell growth, apoptosis inhibition, stress response, and immune regulation [13]. Importantly, emerging evidence indicates that TCTP plays a role in bone remodeling by promoting osteoblast differentiation, mineralized matrix formation, and angiogenesis [14,15].

Despite its biological relevance, the application of TCTP in dental restorative materials has not been extensively investigated. Incorporation of TCTP into GIC may represent a promising strategy to transform a traditionally passive restorative material into an active regenerative system. However, such modification must not compromise the fundamental chemical structure, setting behavior, or clinical handling properties of GIC [5], [16].

Therefore, the aim of this study was to develop a novel bioactive glass ionomer cement incorporating TCP and TCTP and to evaluate its chemical integrity, setting behavior, and mineral regeneration potential using micro-computed tomography (micro-CT) analysis.

## Materials and Methods

### *Materials Preparation and Experimental Groups*

This study received ethical approval from the Human Research Ethics Committee of the Faculty of Dentistry, xxx (NH6901-001).

A conventional GIC was used as the base material in this study. The powder and liquid components were prepared according to the manufacturer's instructions and served as the control group. To enhance the biological performance of GIC, a modified formulation (BIOGIC) was developed by incorporating bioactive components. Tricalcium phosphate (TCP) was added to the BIOGIC powder phase to obtain an osteoconductive composite (BIOGIC+TCP). In addition, translationally controlled tumor protein (TCTP) was incorporated into the BIOGIC+TCP formulation at concentrations of 3  $\mu\text{g}$  and 10  $\mu\text{g}$  per specimen, yielding BIOGIC+TCP+3  $\mu\text{g}$  TCTP and BIOGIC+TCP+10  $\mu\text{g}$  TCTP groups, respectively. A BIOGIC formulation containing 10% CHX was also prepared as a comparative group. Additionally, the invention titled "Material for the Release of Substances from Glass Ionomer Cement Modified with Chitosan" was granted a patent on January 31, 2023, under patent number 0501002755 in Thailand. Another related invention, titled "Resin Composition for Application in Glass Ionomer Cement and Its Manufacturing Method," was granted a patent on March 13, 2023, under patent number 1001001095 in Thailand.

All powder components were homogenized using mechanical mixing to ensure uniform distribution of TCP, TCTP, or CHX within the cement matrix. The liquid component was added immediately before specimen preparation, and mixing was performed under controlled conditions to minimize variability. All experimental groups were prepared using identical powder-to-liquid ratios to ensure comparability. [7], [11].

### *Fourier Transform Infrared Spectroscopy (FTIR) Analysis*

Fourier transform infrared spectroscopy (FTIR) was employed to evaluate potential changes in the chemical structure of GIC following material modification. Specimens from each group were prepared, allowed to set completely, and then finely ground into powder. FTIR spectra were recorded using a Fourier transform infrared spectrometer over a wavenumber range of 4000–400  $\text{cm}^{-1}$  with a resolution of 4  $\text{cm}^{-1}$ . Each spectrum was obtained by averaging 32 scans to improve signal-to-noise ratio.

Characteristic absorption bands corresponding to the carboxylate groups of polyacrylic acid, metal–polyacid salt formation, and glass network vibrations were analyzed. Comparisons were made between conventional GIC and modified formulations to determine whether incorporation of TCP, TCTP, or CHX altered the fundamental chemical structure of the cement. [5], [9].

### *Setting Time Measurement*

Initial and final setting times were determined in accordance with standardized testing procedures for glass ionomer cements. Freshly mixed cement was placed into standardized molds and maintained under controlled environmental conditions. Initial setting time was defined as the time elapsed from the start of mixing until the material exhibited resistance to a standardized indenter without visible surface disruption. Final setting time was defined as the time at which the material could withstand indentation without any visible deformation [3].

For each experimental group, setting time measurements were performed in triplicate. Mean values and standard deviations were calculated. Statistical comparisons among groups were conducted to evaluate the influence of bioactive additives on the setting behavior of the cement.

#### *Micro-Computed Tomography (Micro-CT) Analysis*

Quantitative micro-computed tomography (micro-CT) analysis was performed to assess mineral microarchitecture and mineralization within the defect region. Specimens were scanned using a high-resolution micro-CT system under standardized scanning parameters. Image reconstruction was performed using the manufacturer's software, and three-dimensional datasets were generated.

A region of interest (ROI) corresponding to the original defect area was defined for each specimen. Quantitative parameters were calculated using dedicated image analysis software. Mineral volume fraction (MV/TV) was used to quantify the proportion of mineralized tissue within the total volume. Mineralized density was determined by calibration with hydroxyapatite phantoms and expressed as milligrams of hydroxyapatite per cubic centimeter. All measurements were performed by a blinded investigator to minimize observer bias. Mean values were calculated for each group at each time point [6], [9].

#### *Statistical Analysis*

Statistical analysis was performed using dedicated statistical software. Data were expressed as mean  $\pm$  standard deviation. One-way analysis of variance (ANOVA) was used to compare initial and final setting times among the different material formulations. For micro-CT outcomes, two-way ANOVA was conducted with treatment group and time as independent factors to evaluate main effects and interaction effects. When significant differences were detected, Tukey's multiple comparison post hoc test was applied to identify pairwise differences among groups. A significance level of  $p < 0.05$  was adopted for all statistical analyses.

## **Results**

#### *FTIR analysis/ Setting time and working time*

FTIR analysis demonstrated that all restorative material groups exhibited similar spectral profiles, indicating comparable chemical compositions. No distinct differences in characteristic absorption bands or overall molecular structure were observed when compared with conventional GIC. These findings suggest that the incorporation of additional components did not alter the fundamental chemical structure of GIC, as shown in Fig.1.

As shown in Table 1, significant differences in both setting time and working time were observed among the tested materials ( $p < 0.05$ ). Conventional GIC exhibited the longest setting

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2  
3 time ( $163 \pm 5.57$  s) and working time ( $235.67 \pm 4.04$  s). In contrast, all modified BIO-GIC  
4 formulations demonstrated significantly shorter setting and working times compared with GIC,  
5 as indicated by different superscript letters. BIO-GIC, BIO-GIC+TCP, BIO-GIC+TCP+3  $\mu$ g  
6 TCTP, BIO-GIC+TCP+10  $\mu$ g TCTP, and BIO-GIC+10% CHX showed comparable setting  
7 times ranging from  $120.33 \pm 11.36$  to  $128 \pm 5.29$  s, with no statistically significant differences  
8 among these groups. Similarly, the working times of the modified materials were significantly  
9 reduced compared with GIC, ranging from  $175 \pm 6.24$  to  $186 \pm 8.54$  s, while no significant  
10 differences were detected among the modified groups themselves.

### 11 12 13 **Mineralized density and Mineral volume fraction (MV/TV)**

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15  
16 At baseline (day 0), the GIC group exhibited a consistently high MV/TV (>93%), reflecting  
17 the dense nature of the mineral volume fraction (MV/TV) of all six experimental groups is  
18 presented in Fig. 2. At baseline (day 0), the GIC group exhibited the highest MV/TV values  
19 (>93%), reflecting the dense and highly mineralized nature of the material. In contrast, BIOGIC  
20 alone showed significantly lower MV/TV values (~78%), indicating limited initial  
21 mineralization. The incorporation of TCP into BIOGIC resulted in a significant increase in  
22 MV/TV compared with BIOGIC alone at all evaluated time points.

23  
24  
25 Among the TCP-containing groups, the addition of TCTP further enhanced mineral formation  
26 in a time-dependent manner. Both BIOGIC+TCP+3  $\mu$ g TCTP and BIOGIC+TCP+10  $\mu$ g TCTP  
27 demonstrated significantly higher MV/TV values than BIOGIC alone at days 21, and 28 ( $p <$   
28 0.05). Notably, the BIOGIC+TCP+10  $\mu$ g TCTP group achieved the highest MV/TV at day 28,  
29 suggesting improved mineral maturation and more effective defect filling. The BIOGIC+CHX  
30 group exhibited moderate increases in MV/TV over time but remained lower than the TCTP-  
31 supplemented groups at later time points.

32  
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34 Two-way ANOVA revealed significant main effects of treatment and time, as well as a  
35 significant interaction between these factors ( $p < 0.05$ ), indicating that changes in MV/TV were  
36 dependent on both material composition and the duration of observation.

37  
38  
39 Mineralized density analysis revealed distinct differences in mineralization kinetics among the  
40 experimental groups (Fig. 3). BIOGIC alone exhibited relatively low mineralized density  
41 values with minimal increases over time, indicating limited mineral deposition. The  
42 incorporation of TCP into BIOGIC resulted in a moderate enhancement of mineralized density,  
43 particularly at the mid and late observation periods.

44  
45  
46 The addition of TCTP significantly accelerated mineralization. Both BIOGIC+TCP+3  $\mu$ g  
47 TCTP and BIOGIC+TCP+10  $\mu$ g TCTP groups showed significantly higher mineralized  
48 density values compared with BIOGIC and BIOGIC+TCP at multiple time points, with the  
49 most pronounced differences observed at days 21 and 28 ( $p < 0.05$ ).

### 50 51 **Qualitative micro-CT structural observations and morphometric analysis**

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54 Micro-CT morphometric analysis provided additional insight into the internal structural  
55 characteristics of the six experimental groups and further supported the findings obtained from  
56 MV/TV and mineralized density measurements. Conventional GIC consistently exhibited the  
57 highest object volume fraction (Ob.V/TV, 93.35–96.25%), the lowest porosity (3.75–6.65%),  
58 and the highest apparent and object densities (Ap.D: 2446.15–2563.55 mg HA/ccm; Ob.D:  
59 2577.73–2665.46 mg HA/ccm) throughout the observation period. This group also showed  
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3 relatively low object number (Ob.N, 3.45–5.77 1/mm) but markedly greater object thickness  
4 (Ob.Th, 0.349–0.604 mm), indicating a dense and continuous internal structure with limited  
5 void space. The persistently high Ob.V/TV and density values of conventional GIC should be  
6 interpreted as intrinsic characteristics of the material itself rather than newly formed mineral  
7 deposition [19].  
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10 In contrast, BIOGIC alone demonstrated the least favorable microstructural profile among the  
11 modified formulations. This group maintained low Ob.V/TV values (76.75–80.66%), high  
12 porosity (19.34–23.25%), and relatively low density values (Ob.D: 1776.58–1932.65 mg  
13 HA/ccm) throughout the study period. A progressive increase in object number from 8.38 to  
14 11.17 1/mm, together with a reduction in object thickness from 0.160 to 0.118 mm by day 28,  
15 suggested the presence of numerous small and relatively thin mineralized domains without  
16 effective structural consolidation. These findings are consistent with the lower MV/TV and  
17 mineralized density values observed in this group and support the presence of a fragmented  
18 and heterogeneous internal architecture.  
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22 The incorporation of TCP into BIOGIC improved the morphometric profile compared with  
23 BIOGIC alone. BIOGIC+TCP exhibited higher Ob.V/TV values (81.15–82.63%), lower  
24 porosity (17.37–18.85%), and higher density values, with Ob.D reaching 2261.14 mg HA/ccm  
25 at day 21. In addition, object volume increased from 51.86 to 55.69 mm<sup>3</sup> over the 28-day  
26 period, indicating greater mineral occupancy within the scanned volume. However, this group  
27 still displayed relatively high object number values (8.66–10.20 1/mm) and only modest object  
28 thickness (0.144–0.166 mm), suggesting that TCP alone improved mineral filling and packing  
29 but was less effective in promoting the formation of thicker and more continuous mineralized  
30 structures.  
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33 BIOGIC+TCP+10 µg TCTP showed the clearest evidence of late-stage structural maturation.  
34 By day 28, this group achieved the highest Ob.V/TV among all modified formulations  
35 (86.86%) and the lowest porosity (13.14%). In parallel, object number decreased from 9.22 to  
36 8.18 1/mm over time, while object thickness increased from 0.160 to 0.193 mm. Both apparent  
37 density and object density also increased from baseline to day 28, indicating progressive  
38 densification of the internal structure. From a morphometric perspective, the combination of  
39 fewer objects, greater thickness, lower porosity, and higher density suggests a transition from  
40 a dispersed mineral phase toward fewer, thicker, and more mature mineralized domains. These  
41 observations are in agreement with the high MV/TV and mineralized density values recorded  
42 for this group, particularly at days 21 and 28.  
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46 BIOGIC+10% CHX exhibited an intermediate but dynamic pattern. This group started with  
47 one of the lowest baseline Ob.V/TV values (78.18%) and the highest porosity (21.82%), but  
48 showed marked improvement over time, reaching 86.08% Ob.V/TV at day 21 and 82.54% at  
49 day 28, while porosity decreased to 17.46%.  
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## 52 Discussion

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54 Chemical characterization using FTIR revealed that all modified formulations retained the  
55 characteristic absorption bands associated with the acid–base reaction between polyalkenoic  
56 acid and fluoroaluminosilicate glass, which is the defining chemical mechanism of GIC. The  
57 absence of peak displacement or additional functional groups indicates that incorporation of  
58 TCP, TCTP, or chlorhexidine did not disrupt the cement's core chemical framework. This  
59 finding is consistent with previous studies reporting that bioactive fillers and biological  
60

additives can be incorporated into GIC matrices without compromising their chemical integrity [5], [7]. Preservation of chemical structure is of critical importance, as it underlies essential clinical properties including adhesion to tooth structure, fluoride release, resistance to dissolution, and long-term stability [1], [2].

Setting behavior is a key determinant of clinical usability and early restoration success. In the present study, all BIOGIC-based formulations exhibited significantly shorter setting times than conventional GIC, while remaining within clinically acceptable limits. Similar reductions in setting time have been reported following incorporation of calcium phosphate phases or bioactive glass fillers, which may increase the availability of multivalent cations and accelerate cross-linking of the polyacid matrix [9], [10]. From a clinical perspective, shortened setting time is advantageous because it reduces the vulnerability of the material to moisture contamination, improves handling efficiency, and enhances early mechanical stability. Importantly, the lack of significant differences in setting time among the modified BIOGIC formulations suggests that the addition of TCTP did not adversely affect working predictability, supporting its feasibility for clinical translation [3]. Micro-CT analysis provided quantitative insight into the mineral regeneration potential of the tested materials. BIOGIC alone demonstrated limited mineral formation over time, confirming that conventional or minimally modified GIC possesses low intrinsic osteogenic activity. This observation is in agreement with previous reports describing GIC as a material that is primarily biocompatible but only weakly bioactive in terms of mineralized tissue regeneration [6]. The incorporation of TCP resulted in a significant increase in mineral volume fraction and mineralized density, supporting its established role as an osteoconductive filler capable of releasing calcium and phosphate ions that promote apatite nucleation and growth [8], [9].

Nevertheless, TCP alone did not achieve optimal mineral regeneration, highlighting an important limitation of passive osteoconduction. While TCP provides a favorable ionic and structural environment for mineral deposition, it does not actively regulate cellular behavior. Bone regeneration is a complex biological process requiring not only an appropriate scaffold but also active modulation of cell proliferation, differentiation, and matrix maturation. The modest regenerative outcomes observed in the BIOGIC+TCP group underscore the need for biologically active signals to complement osteoconductive materials [6].

In contrast, supplementation with TCTP resulted in a pronounced enhancement of mineral regeneration in both a time- and dose-dependent manner. The significant increases in mineral volume fraction and mineralized density observed in TCTP-treated groups, particularly at later healing stages, indicate that TCTP plays an active role in promoting bone formation and maturation. These findings are consistent with previous *in vitro* studies demonstrating that TCTP enhances osteoblast survival, proliferation, and differentiation, as well as mineralized matrix formation [13], [14], [15]. The delayed but progressive nature of the regenerative response suggests that TCTP primarily influences osteogenic differentiation and matrix mineralization rather than early inflammatory or provisional phases of healing. The superior mineralized density observed in the BIOGIC+TCP+10  $\mu$ g TCTP group further indicates a dose-dependent biological effect. Increased mineral density is closely associated with improved bone quality, mechanical competence, and long-term stability of regenerated tissue. This dose-dependent response suggests that TCTP exerts threshold-sensitive effects on osteogenic pathways, potentially through regulation of apoptosis resistance, cytoskeletal organization, and cellular stress responses, which are critical for sustained osteoblast function during bone remodeling. Although the molecular mechanisms were not directly examined in

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3 this study, the observed outcomes align well with the multifunctional biological roles attributed  
4 to TCTP in previous investigations [14], [15].  
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7 The enhanced regenerative performance of the BIOGIC+TCP+TCTP composite highlights the  
8 importance of multifunctional material design. In this system, BIOGIC provides a clinically  
9 established adhesive and biocompatible matrix, TCP functions as an osteoconductive scaffold  
10 and ionic reservoir, and TCTP serves as a biologically active signaling molecule that directly  
11 modulates cellular behavior. The synergistic interaction among these components enables  
12 simultaneous structural support, ion-mediated mineral nucleation, and biologically driven  
13 tissue regeneration. This integrative strategy reflects an emerging paradigm in biomaterials  
14 research, in which restorative materials are designed not only to replace lost tissue but also to  
15 actively participate in the healing process [9], [18]. Representative micro-CT cross-sectional  
16 images (Fig. 4) qualitatively supported the quantitative findings for MV/TV and mineralized  
17 density. Conventional GIC exhibited a relatively dense and homogeneous radiopaque structure  
18 throughout the observation period, with minimal visible temporal change. In contrast, BIOGIC  
19 alone showed a more heterogeneous internal architecture, characterized by irregular radiopaque  
20 distribution and more apparent internal voids or low-density regions, consistent with its lower  
21 MV/TV and mineralized density values. The incorporation of TCP into BIOGIC was associated  
22 with a broader distribution of radiopaque areas, a more compact internal structure, and partial  
23 filling of internal void spaces compared with BIOGIC alone. These structural changes became  
24 more evident with TCTP supplementation. In particular, BIOGIC+TCP+3  $\mu\text{g}$  TCTP showed a  
25 more uniform mineralized architecture and reduced structural heterogeneity than  
26 BIOGIC+TCP, whereas BIOGIC+TCP+10  $\mu\text{g}$  TCTP exhibited the densest and most  
27 continuous radiopaque network, with fewer visible internal voids, especially at days 21 and 28.  
28 These qualitative observations were consistent with the higher MV/TV and mineralized density  
29 values observed in the TCTP-containing groups. In comparison, BIOGIC+10% CHX  
30 maintained a relatively heterogeneous internal structure and did not exhibit the same degree of  
31 internal densification or mineral continuity as the TCP- and TCTP-containing groups. A more  
32 pronounced improvement in microstructural organization was observed in the TCTP-  
33 containing groups. BIOGIC+TCP+3  $\mu\text{g}$  TCTP showed consistently high Ob.V/TV values  
34 among the modified materials and reached 86.78% at day 28, while porosity decreased to  
35 13.22%. This group also exhibited the highest final object volume (Ob.V = 63.06 mm<sup>3</sup>) and  
36 one of the largest total volumes (TV = 72.61 mm<sup>3</sup>), indicating substantial volumetric filling of  
37 the internal structure. Its object thickness remained relatively stable at a level higher than that  
38 of BIOGIC and BIOGIC+TCP (0.145–0.188 mm), whereas object number remained lower than  
39 in the BIOGIC and TCP groups at later time points. Together, these findings suggest a more  
40 integrated and less fragmented mineral architecture, consistent with the observed increase in  
41 MV/TV and mineralized density [20-21].  
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48 Apparent and object densities also increased over time. Nevertheless, the CHX-containing  
49 formulation retained relatively high object number values (9.66–10.68 1/mm) and  
50 comparatively low-to-moderate object thickness values (0.110–0.157 mm), indicating that its  
51 internal structure remained composed of relatively fine and discontinuous mineralized units  
52 [18-21]. Thus, although CHX incorporation appeared to improve densification compared with  
53 BIOGIC alone, the resulting architecture remained less consolidated than that observed in the  
54 TCTP-containing groups.  
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57 Overall, the micro-CT morphometric data demonstrated that the materials differed not only in  
58 mineral volume fraction and mineralized density, but also in their patterns of internal  
59 organization. Conventional GIC represented a compact and continuous reference structure,  
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3 whereas BIOGIC alone showed a porous and fragmented architecture. TCP improved mineral  
4 occupancy and reduced porosity, while TCTP, particularly at 10  $\mu\text{g}$ , appeared to promote a  
5 more mature and integrated mineralized structure characterized by lower porosity, greater  
6 object thickness, lower object number, and higher density. These findings further support the  
7 potential role of TCTP in enhancing not only mineral deposition but also structural maturation  
8 within the modified glass ionomer system. Despite the encouraging results, several limitations  
9 should be acknowledged. First, the molecular and cellular mechanisms underlying TCTP-  
10 mediated enhancement of mineral regeneration were not directly investigated. Future studies  
11 should examine the expression of osteogenic markers such as RUNX2, alkaline phosphatase,  
12 osteocalcin, and collagen type I, as well as signaling pathways involved in osteoblast  
13 differentiation and mineralization. Second, angiogenic coupling, which plays a critical role in  
14 bone regeneration, was not assessed and warrants further investigation. Finally, long-term in  
15 vivo studies evaluating mechanical performance, degradation behavior, and biological safety  
16 are necessary to confirm the translational potential of TCTP-modified GIC formulations.  
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## 20 **Conclusions**

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22 In summary, this study demonstrates that incorporation of TCTP into a TCP-modified bioactive  
23 glass ionomer cement significantly enhances mineral regeneration in a dose-dependent manner  
24 while preserving essential chemical integrity and handling properties. These findings support  
25 the potential application of TCTP as a bioactive additive for the development of next-  
26 generation glass ionomer cements with improved regenerative functionality and broaden the  
27 scope of GIC from a conventional restorative material toward an advanced bioactive platform.  
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## 30 **Declarations**

### 31 **Funding**

32 None.

### 33 **Conflicts of interest/Competing interests**

34 The authors declare that they have no conflicts of interest.

### 35 **Availability of data and material**

36 The data will be made available as per requirement.

### 37 **Code availability**

38 Not applicable.

### 39 **Ethics approval**

40 This study received ethical approval from the Human Research Ethics Committee of the  
41 Faculty of Dentistry, xxx (NH6901-001).  
42

### 43 **Consent to participate**

44 Not applicable.

### 45 **Consent for publication**

46 Not applicable  
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**Table 1 Setting time and working time**

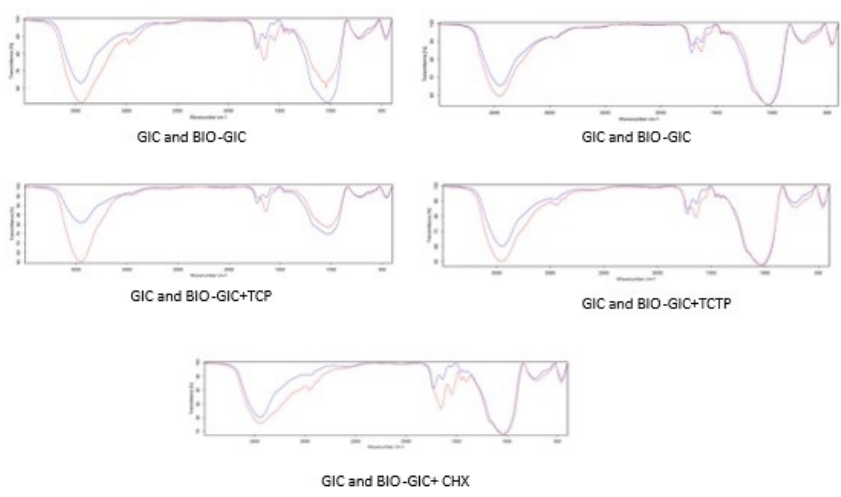
Group	Setting time (sec)	Working time (sec)
GIC	163±5.57 <sup>a</sup>	235.67±4.04 <sup>a</sup>
BIOGIC	120.33±11.36 <sup>b</sup>	181.33±7.51 <sup>b</sup>
BIOGIC+TCP	121.67±7.02 <sup>b</sup>	179±9.64 <sup>b</sup>
BIOGIC+TCP+3µg TCTP	128±5.29 <sup>b</sup>	175±6.24 <sup>b</sup>
BIOGIC+TCP+10µg TCTP	127.67±4.51 <sup>b</sup>	179±10.12 <sup>b</sup>
BIOGIC+10% CHX	127±7.00 <sup>b</sup>	186±8.54 <sup>b</sup>

Superscript lowercase letters (a, b) shown within the same column indicate statistically significant differences, as determined by one-way ANOVA followed by Scheffé's post hoc comparison at  $p < 0.05$  (mean ± SD,  $n = 5$ ).

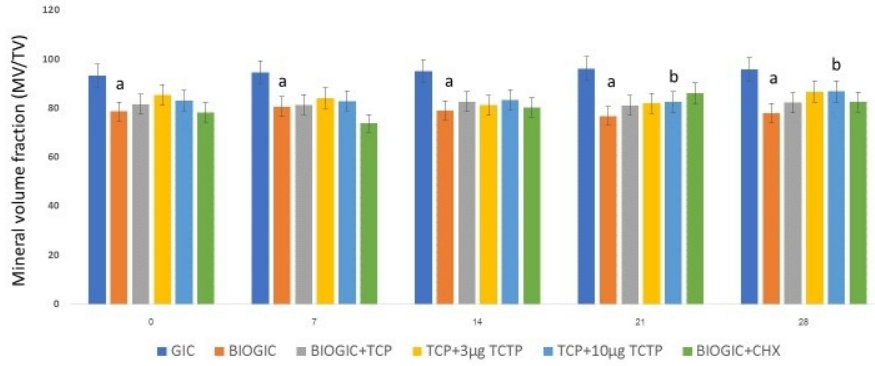
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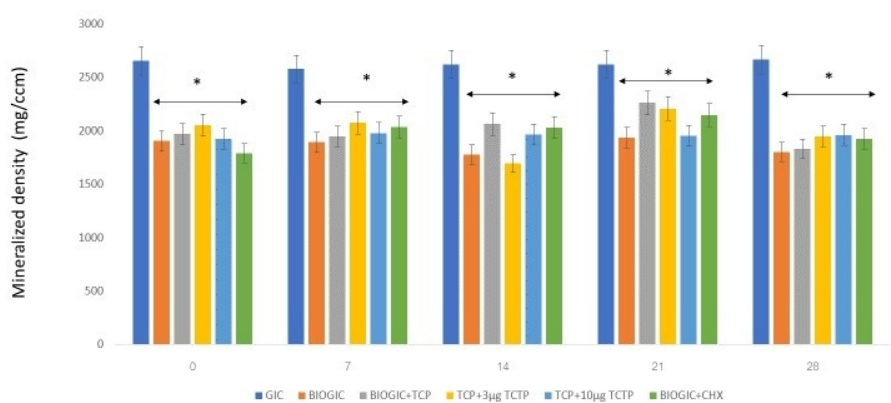


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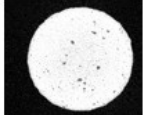
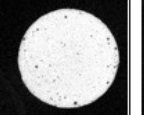
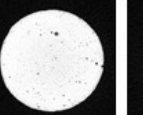
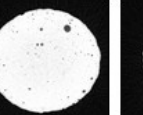
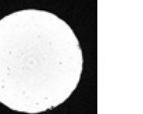
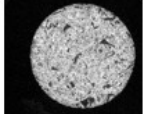
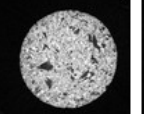
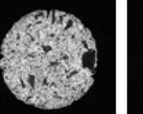
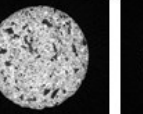
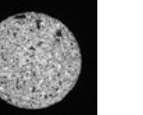
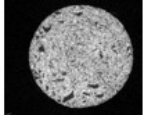
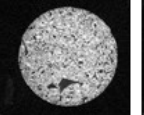
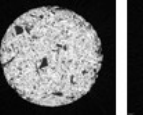
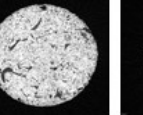
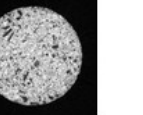
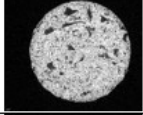
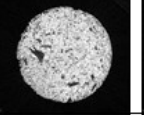
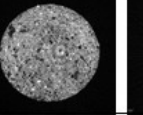
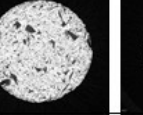
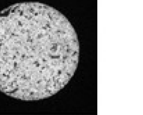
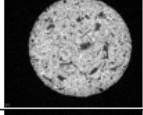
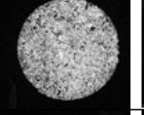
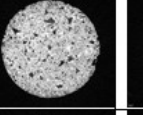
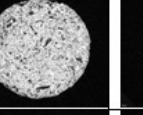
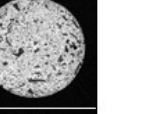
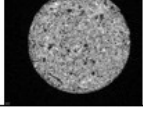
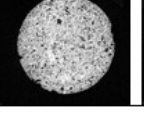
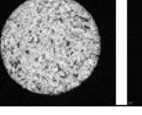
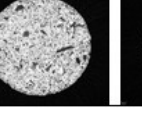
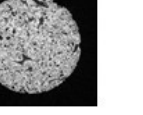


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67x38mm (300 x 300 DPI)

Group	Time intervals				
	Day 0	Day 7	Day 14	Day 21	Day 28
GIC					
BIOGIC					
BIOGIC+TCP					
BIOGIC+TCP+3 μg TCTP					
BIOGIC+TCP+1 0μg TCTP					
BIOGIC+ 10% CHX					

61x53mm (300 x 300 DPI)

## Figure legend

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- Figure 1 Comparative FTIR spectra of conventional GIC and modified BIOGIC formulations, including BIOGIC+TCP, BIOGIC+TCP+3 $\mu$ g TCTP, BIOGIC+TCP+10 $\mu$ g TCTP and BIOGIC+10% CHX. The spectra showed similar characteristic absorption bands among all groups, indicating that the incorporation of additional components did not alter the fundamental chemical structure of GIC.
- Figure 2 Mineral volume fraction (MV/TV) of the six experimental groups at days 0, 7, 14, 21, and 28. Data are presented as mean  $\pm$  SD (n = 5). Two-way ANOVA revealed significant effects of treatment, time, and their interaction (p < 0.05). a significant compared to GIC and b significant compared to BIO-GIC group
- Figure 3 Mineralized density progression. Two-way ANOVA revealed significant effects of treatment, time, and their interaction (p < 0.05).
- Figure 4 Representative micro-CT cross-sectional images showing mineral changes of conventional GIC and experimental BIOGIC formulations at different time intervals.

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For Peer Review Only

Dear Editor,

Thank you for offering me the opportunity to become a reviewer of the manuscript entitled “*Engineering bioactive glass ionomer cement with tricalcium phosphate and translationally controlled tumor protein for enhanced physicochemical performance and mineral regeneration*” submitted to *Biomaterial Investigations in Dentistry*.

This manuscript presents the development of a modified bioactive glass ionomer cement (BIOGIC) incorporating tricalcium phosphate (TCP) and translationally controlled tumor protein (TCTP), with evaluation of physicochemical behavior and mineral regeneration potential using FTIR, setting-time analysis, and micro-CT. The topic is relevant and timely because regenerative restorative biomaterials are of increasing interest in restorative dentistry and biomaterials science.

The strengths of this study are:

- Novel incorporation of TCTP into GIC-based system
- Clinically relevant biomaterial topic
- Inclusion of time-dependent mineralization analysis
- Use of micro-CT for quantitative assessment
- Generally coherent discussion linking biomaterial behavior and regeneration concepts
- The findings suggest enhanced mineralization without disruption of the core chemical structure
- Recent and mostly appropriate references

However, several methodological, analytical, and presentation-related issues should be addressed before publication. In its current form, the manuscript requires **major revision** to improve scientific rigor, reproducibility, and clarity.

### **Content / major comment:**

#### **1. Insufficient methodological detail regarding material composition**

The manuscript does not adequately describe the composition and preparation protocol of the experimental materials. Critical information is missing, including:

- Brand/manufacturer of the base GIC
- Exact concentration or weight percentage of TCP
- Molecular characteristics/source/purity of TCTP
- Preparation protocol of BIOGIC
- Powder-liquid ratio
- Whether TCTP was incorporated into powder or liquid phase
- Mixing duration and environmental conditions

Without these details, the study cannot be reproduced reliably. This is a major weakness.

Relevant sections: Materials and Methods

#### **Recommendation**

Provide a detailed formulation table including:

- Material source/manufacturer
- Composition
- Concentration (% wt or  $\mu\text{g/mL}$ )
- Mixing protocol
- Specimen dimensions
- Number of specimens per test

#### **2. Lack of sample size justification**

The manuscript states that measurements were performed in triplicate for setting time, while Table 1 reports  $n = 5$ , creating inconsistency. Additionally, no power analysis or sample size calculation was provided despite citing a methodological reference for sample size determination.

### **Recommendation**

Clarify:

- Actual sample size per group
- Biological vs technical replicates
- Statistical power calculation

### **3. Biological relevance of mineralization model is unclear**

The manuscript discusses “bone regeneration” and “osteogenesis,” but the study appears to involve only material-based micro-CT mineral assessment without:

- Cell culture
- Simulated body fluid (SBF)
- Animal model
- Osteogenic markers

Thus, the claim of “regeneration” may be overstated.

### **Recommendation**

The authors should:

- Clearly define what was scanned in micro-CT
- Explain how mineralization was induced
- Avoid overinterpreting acellular mineral deposition as true biological regeneration
- Replace terms like “bone regeneration” with “mineral deposition” or “mineralization potential” unless biologically validated

### **4. Micro-CT methodology lacks critical technical parameters**

The micro-CT section is incomplete. Missing parameters include:

- Scanner model
- Voltage/current
- Voxel size
- Exposure time
- Thresholding protocol
- Reconstruction settings
- ROI dimensions
- Calibration procedure details

These parameters are essential for reproducibility and interpretation.

### **Recommendation**

Provide complete micro-CT acquisition and analysis settings.

### **5. Overinterpretation of FTIR findings**

The statement that no structural changes occurred based solely on absence of new peaks is too strong. FTIR alone cannot fully confirm preservation of chemical integrity.

### **Recommendation**

Modify wording to:

“FTIR spectra suggested preservation of the principal chemical features of GIC.”

Additional characterization techniques (XRD, SEM-EDS, Raman spectroscopy) would strengthen the conclusions.

### **6. Absence of mechanical property evaluation**

The manuscript claims improved physicochemical performance, yet no mechanical testing was performed. Essential properties such as:

- Compressive strength
- Flexural strength
- Hardness

Bond strength  
Wear resistance  
were not evaluated.

**Recommendation**

Either:

Add mechanical testing data, or revise claims throughout manuscript to avoid overstating physicochemical enhancement.

**7. Ethical approval appears unnecessary or insufficiently explained**

The study is purely material-based with no clear involvement of humans, animals, or biological tissues. Yet ethical approval is reported.

**Recommendation**

Clarify:

- Why ethical approval was required
- Whether biological materials/cells were used

**Writing / minor comment:**

**1. Language and grammar require editing**

Several sentences are repetitive, overly long, or grammatically awkward. Examples include:

“mineral volume fraction (MV/TV) of all six experimental groups is presented...”

followed by duplicated baseline description

Missing punctuation in Discussion section

Inconsistent spacing around citations

**Recommendation**

Professional English editing is recommended.

**2. Inconsistent terminology**

The manuscript alternates between:

BIOGIC

BIO-GIC

modified BIOGIC

**Recommendation**

Use one standardized term consistently.

**3. Figures are inadequately presented in the PDF**

The uploaded version appears to contain missing or improperly rendered figures/pages.

Several pages only show image dimensions rather than visible figures.

**Recommendation**

Ensure all figures are properly embedded and legible.

**4. Statistical reporting should be improved**

The manuscript reports only p-values without:

F-values

Degrees of freedom

Effect size

Confidence intervals

**Recommendation**

Provide fuller statistical reporting.

**5. Patent statements disrupt scientific flow**

The patent information in the Materials and Methods section appears unrelated to the present experimental formulation and interrupts readability.

**Recommendation**

Move patent-related statements to Acknowledgments section

**6. Some references appear only loosely connected**

Certain references supporting micro-CT morphometric interpretation involve antimicrobial chitosan studies rather than mineral architecture.

**Recommendation**

Please ensure all citations are directly relevant.

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**Recommendation**

Please ensure all citations are directly relevant.

## **4. Bukti review diterima oleh pengelola jurnal**

**IABO-2026-0137 - [View Abstract](#)**

Engineering bioactive glass ionomer cement with tricalcium phosphate and translationally controlled tumor protein for enhanced physicochemical performance and mineral regeneration

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Yes

No

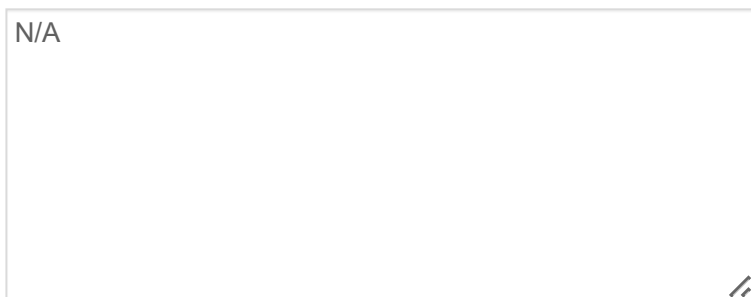
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\* If you co-reviewed or were part of a mentorship programme during this review, please provide details of your co-reviewer/mentor (if not applicable, type N/A):

N/A



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### Would you be willing to review a revision of this manuscript?

Yes

No

### \* Recommendation

Accept

Minor Revision

Major Revision

Reject & Resubmit

Reject

### Confidential Comments to the Editors

ΩSpecial Characters

Dear Editor, Thank you for offering me the opportunity to become a reviewer of the manuscript entitled "Engineering bioactive glass ionomer cement with tricalcium phosphate and translationally controlled tumor protein for enhanced physicochemical performance and mineral regeneration" submitted to Biomaterial Investigations in Dentistry. This manuscript presents the development of a modified bioactive glass ionomer cement (BIOGIC) incorporating tricalcium phosphate (TCP) and translationally controlled tumor protein (TCTP), with evaluation of physicochemical behavior and mineral regeneration potential using FTIR, setting-time analysis, and micro-CT. The topic is relevant and timely because regenerative restorative biomaterials are of increasing interest in restorative dentistry and biomaterials science. The strengths of this study are: Novel incorporation of TCTP into GIC-based system Clinically relevant biomaterial topic Inclusion of time-dependent mineralization analysis Use of micro-CT for

quantitative assessment Generally coherent discussion linking biomaterial behavior and regeneration concepts The findings suggest enhanced mineralization without disruption of the core chemical structure Recent and mostly appropriate references However, several methodological, analytical, and presentation-related issues should be addressed before publication. In its current form, the manuscript requires major revision to improve scientific rigor, reproducibility, and clarity.

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Rosalina Tjandrawinata &lt;rosalina@trisakti.ac.id&gt;

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## Thank you for submitting your review of Manuscript ID IABO-2026-0137 for Biomaterial Investigations in Dentistry

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**BIOMATERIAL INVESTIGATIONS IN DENTISTRY** <onbehalf@manuscriptcentral.com>

Thu, May 14, 2026 at 9:19 PM

Reply-To: anne.peutzfeldt@sund.ku.dk

To: rosalina@trisakti.ac.id

14-May-2026

Dear Dr Roslina Tjandrawinata:

Thank you for reviewing the above manuscript, entitled "Engineering bioactive glass ionomer cement with tricalcium phosphate and translationally controlled tumor protein for enhanced physicochemical performance and mineral regeneration" for Biomaterial Investigations in Dentistry.

We greatly appreciate the voluntary contribution that each reviewer gives to the Journal. We hope that we may continue to seek your assistance with the refereeing process for Biomaterial Investigations in Dentistry, and hope also to receive your own research papers that are appropriate to our aims and scope.

Sincerely,  
Dr Anne Peutzfeldt  
Associate Editor  
Biomaterial Investigations in Dentistry

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