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Research Article

Oral Mucosal Responses to Titanium and Composite Resin: An Immunohistochemical Study

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Abstract

Aims: The current study aimed to evaluate the healing process of the oral mucosa over a submucosal contact with Titanium and Composite resin.

Materials and Methods: 24 male New Zealand rabbits were subjected to this study. 12 received a titanium particle in the submucosal tissue, and the other 12 received a composite resin particle. using histological examination of the collected samples. the measuring parameters were the inflammatory cells infiltration, granulation tissue formation, reepithelization and two immunohistochemical tests using cluster of differentiation 31 and matrix metalloproteinase 3 expression in the collected samples to Determine the best material that permits for mucosal healing in contact with the examined two materials and assuring any complications that may arise during the healing of the mucosal soft tissue that is in contact with the mentioned materials.

Results: The results parameters showed similar results with a slight advantage to the titanium material. No significance was noted in the three and seven-day results, while 14-day results show statistical significance favoring Titanium in the parameters of granulation tissue formation, reepithelization, and matrix metalloproteinase 3 expression.

Conclusion: Titanium shows superior soft tissue healing to the composite resin. But the clear difference will start after 2 weeks

Keywords: Cluster of differentiation 31, Composite resin, Matrix metalloproteinase 3, Titanium.

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INTRODUCTION

Wound repair is a systematic biological process characterized by four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Oral wound healing is considered an ideal model of wound healing because it resolves rapidly and without scar formation (1).

Titanium is a chemical element with the symbol Ti and atomic number 22. Found in nature only as an oxide (2), a large number of studies have reported that the soft tissue integration (STI) quality of conventional smooth and bio-inert titanium-based transmucosal components is highly inferior to that of the natural teeth, which may hinder the long-term success of the implant restorations (3).

Dental composite resins are dental cements made of synthetic resins. Synthetic resins evolved as restorative materials since they were insoluble, of good tooth-like appearance, insensitive to dehydration, easy to manipulate, and inexpensive. Composite resins are most commonly composed of bisphenol A-glycidyl methacrylate (Bis-GMA) and other dimethacrylate monomers, achieved by formulating unique concentrations of each constituent (4). Dental resins are not inert in the oral environment and may release monomers and other substances such as Bisphenol-A (BPA) due to incomplete polymerization and intraoral degradation. Current research shows that various monomers present cytotoxic, genotoxic, proinflammatory, and even mutagenic effects. Of these eluting substances, the elution of BPA in the oral environment is of particular interest due to its role as an endocrine disruptor (5).

The cluster of differentiation (CD) designation refers to proteins found at the surface of cells. Each unique surface molecule is given a different number, which allows cell phenotypes to be differentiated. Surface expression of a particular CD molecule is beneficial for the characterization of cell phenotypes (6).

Platelet endothelial cell adhesion molecule (PECAM-1), also known as cluster of differentiation 31 (CD31), is a protein that in humans is encoded by the PECAM1 gene located on chromosome 17q23.3 (7). PECAM-1 is a cell-to-cell adhesion protein that interacts with other PECAM-1 molecules by homophilic interactions or with non-

PECAM-1 molecules through heterophilic interactions (8). It is normally located on endothelial cells, platelets, macrophages and Kupffer cells, granulocytes, lymphocytes (T cells, B cells, and NK cells), megakaryocytes, and osteoclasts.

CD-31, known as a transmembrane glycoprotein expressed on the endothelium, is commonly used as a measurement expresser of angiogenesis by calculating microvascular density (MVD) (9).

Matrix metalloproteinases (MMPs), also known as matrix metallopeptidases or matrixins, are metalloproteinases that are zinc-containing calcium, calcium-dependent endopeptidases (10). The principal biological function of MMPs is the degradation of ECM (extracellular matrix) proteins and glycoproteins, membrane receptors, cytokines, and growth factors. The MMPs are involved in numerous biologic processes, such as tissue repair and remodulation, cellular differentiation, morphogenesis, angiogenesis, cell proliferation and migration, wound healing, and apoptosis (11).

Stromelysin-1, also known as matrix metalloproteinase-3 (MMP-3), is an enzyme that in humans is encoded by the MMP3 gene. The MMP3 gene is part of a cluster of MMP genes that localize to chromosome 11q22.3.(NIH 2023) The MMP-3 enzyme degrades the collagen types II, III, IV, IX, and X, proteoglycans, fibronectin, laminin, and elastin (12). furthermore, MMP-3 can activate other MMPs such as MMP-1, MMP-7, and MMP-9, rendering MMP-3 crucial in connective tissue remodeling process (13). The enzyme is also thought to be involved in wound repair, progression of atherosclerosis, and tumor initiation. In addition to classical roles for MMP3 in the extracellular space, MMP3 can enter the cellular nuclei and control transcription (14).

MATERIALS AND METHODS

This experiment was approved by the ethical committee of the College of Dentistry / University of Mosul / Department of Oral and Maxillofacial Surgery under ethical approval number (**Uom. Dent 29/23**). This experimental animal study was conducted at the experimental surgical center of Veterinary Teaching Hospital, the College of

Veterinary Medicine/the University of Mosul, Mosul, Iraq. The animals received their care in accordance with the institution's guidelines, with appropriate veterinary care and standard laboratory nutritional support throughout the study period.

Twenty-four New Zealand male rabbits with an age of around 6 months and a weight range of 1.3 kg +_ 200 grams were used in this study. They received a dose of Ketamine hydrochloride 10% at a 50 mg/kg dose, mixed with 2% Xylazine at a 5mg/kg dose as a muscular relaxant in order to achieve general anesthesia through intramuscular injection. They were divided into two groups with 12 rabbit in each: the first group received titanium implants at the muco -gingival fold just distally to the central incisor using a small surgical incision (4 mm) that closed with silk suture (size 5.0) in a primary intention, the second group received the customized composite resin implants and sutured also with the same size 5.0 silk, autopsies samples of excisional soft tissue that contains the embedded materials were collected from each group at the intervals of three, seven & fourteen days following the insertion process. The animals were sacrificed with an overdose of general anesthesia and a fixative solution.

RESULTS

The samples collected from the animals were examined blindly by the histopathologists. Each slide was examined using the light microscope that aims to evaluate the inflammatory cells infiltration (I.C.I), granulation tissue formation (G.T.F), re-epithelialization (Re-Ep), cluster of differentiation 31 (CD31), and matrix metalloproteinase 3 (MMP3) expression. With the three, seven, and fourteen-day period samples from four specimens (Figures 1-18). Table 1 shows the Mann-Whitney U test results significance levels of the examined groups at the 3 different intervals ($P \leq 0.05$).

Table (1): Mann-Whitney U test results significance levels of the tested groups at the 3 different periods, with (P ≤0.05)

Time	Groups compared	I.C.I. P ≤0.05	G.T.F. P ≤0.05	Re-ep. P ≤0.05	CD 31 P ≤0.05	MMP3 P ≤0.05
3 days	Composite - Titanium	0.617	0.495	0.495	1.000	1.000
7 days	Composite - Titanium	0.186	1.000	0.495	0.495	0.495
14 days	Composite - Titanium	0.495	0.022*	0.032*	0.061	0.032*

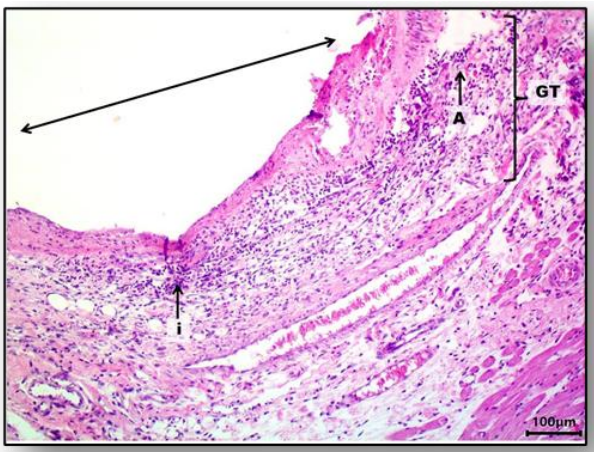

Figure (1): photomicrograph of rabbit oral mucosa of the Composite treated group (3 days) showing the site of pin (↔) with moderate inflammatory cells infiltration (score 3) (i), granulation tissue (score 1) (GT), with angiogenesis A). H&E stain, 10X.

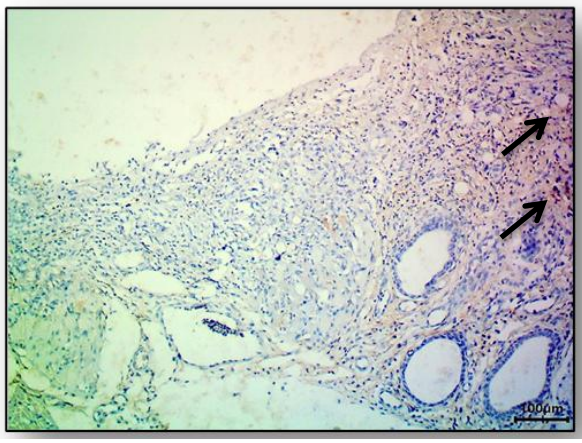

Figure (2): Immunohistochemistry expression of the CD31 in the Composite group (3 days) showing weak positive expression (score 1) pointed with arrows. Hematoxylin stain, 10X.

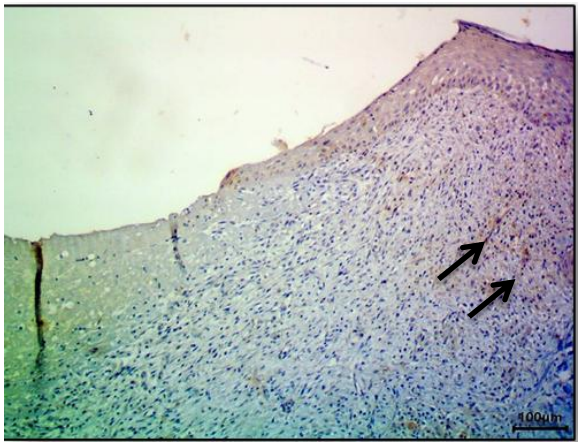

Figure (3): Immunohistochemistry expression of the MMP3 in the Composite group (3 days) showing moderate positive expression (score 2) pointed with arrows. Hematoxylin stain, 10X.

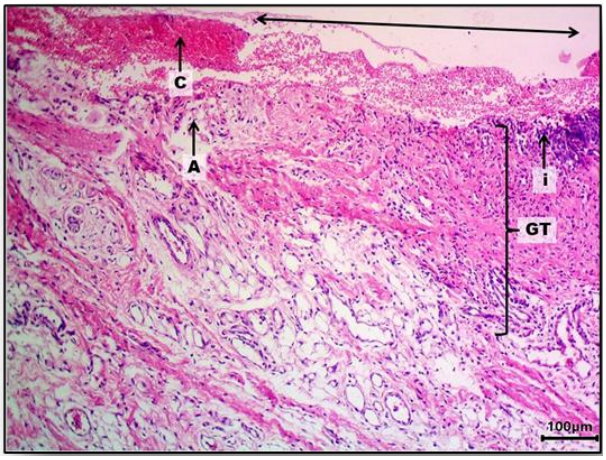

Figure (4): photomicrograph of rabbit oral mucosa of the Titanium treated group (3 days) showing the site of pin (↔) with blood clot formation (C), inflammatory cells infiltration (score 2) (i), high granulation tissue (score 1) (GT), with angiogenesis (A). H&E stain, 10X.

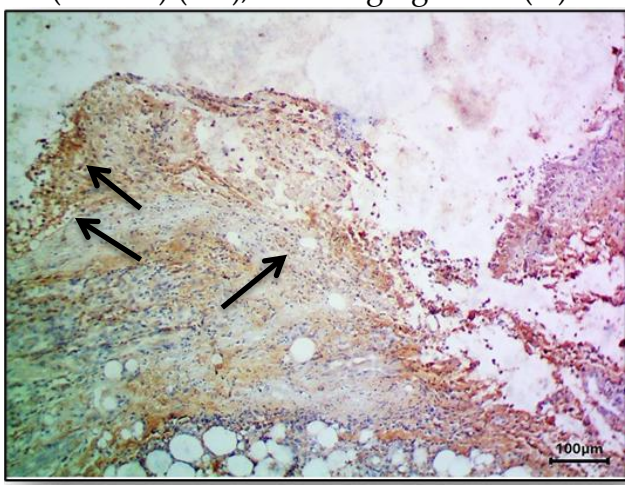

Figure (5): Immunohistochemistry expression of the CD31 in the Titanium group (3 days) showing moderate positive expression (score 2). (arrows). Hematoxylin stain, 10X.

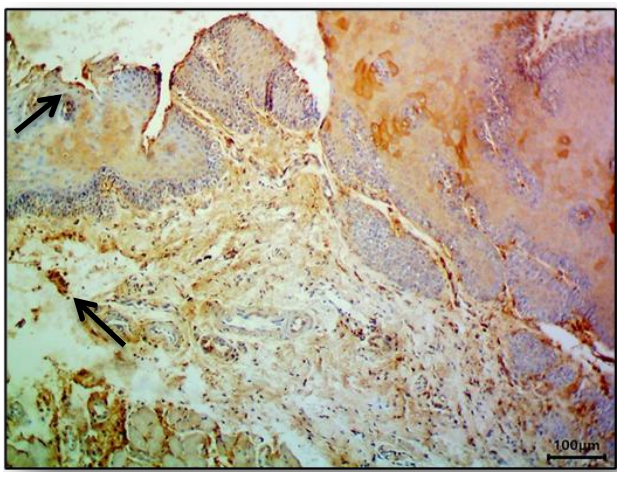

Figure (6): Immunohistochemistry expression of the MMP3 in the Titanium group (3 days) showing moderate positive expression (score 2), pointed with arrows. Hematoxylin stain, 10X

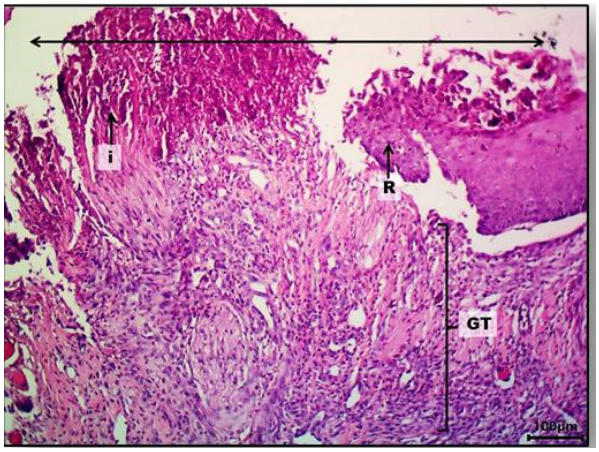

Figure (7): photomicrograph of rabbit oral mucosa of the Composite treated group (7 days) showing the site of pin (↔) with inflammatory cells exudation (score 2) (i), high granulation tissue (score 3) (GT), and re-epithelialization (score 2) (R). H&E stain, 10X.

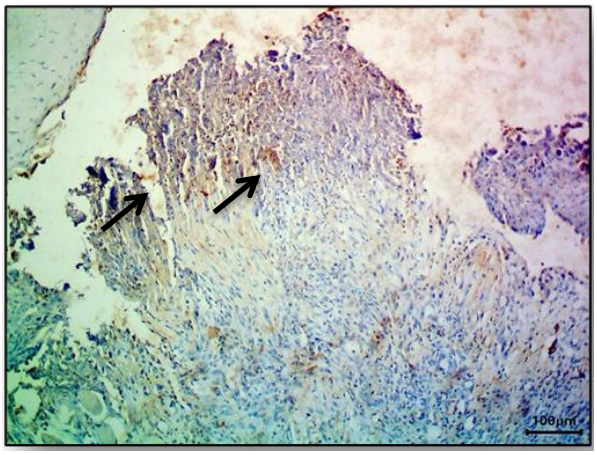

Figure (8): Immunohistochemistry expression of the CD31 in the Composite group (7 days) showing weak positive expression (score 1) pointed with arrows. Hematoxylin stain, 10X

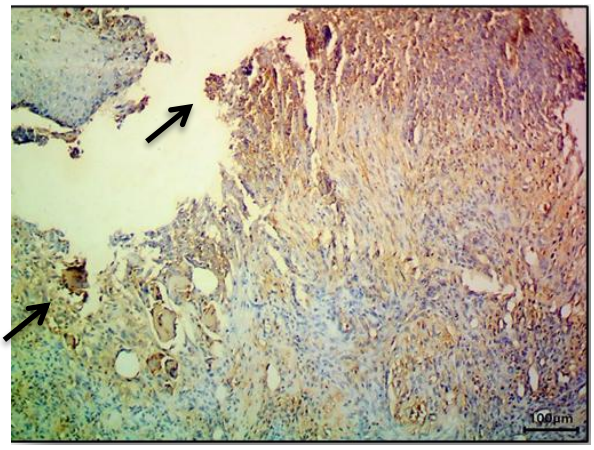

Figure (9): Immunohistochemistry expression of the MMP3 in the Composite group (7 days) showing weak positive expression (score 1) pointed with arrows. Hematoxylin stain, 10X.

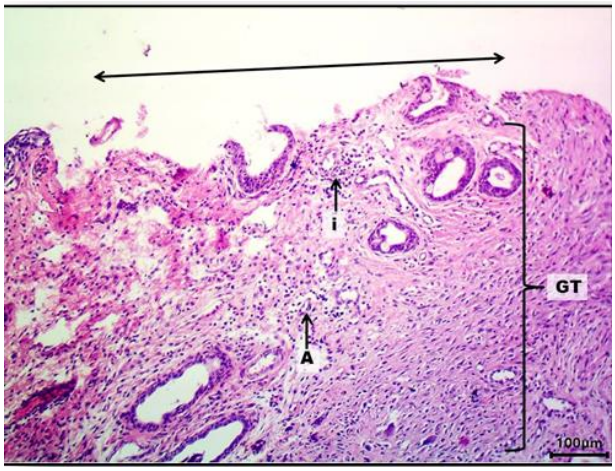

Figure (10): photomicrograph of rabbit oral mucosa of the Titanium treated group (7 days) showing the site of pin (↔) with inflammatory cells infiltration (score 1) (i), granulation tissue (score 1) (GT), with angiogenesis (score 2) (A). H&E stain, 10X.

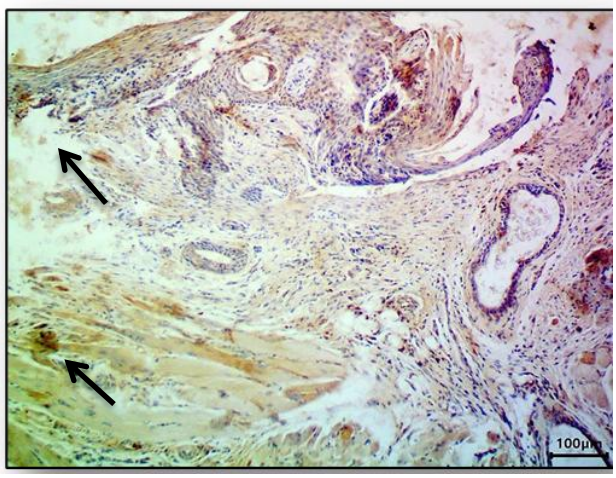

Figure (11): Immunohistochemistry expression of the CD31 in the Titanium group (7 days) showing weak positive expression (score 1). Hematoxylin stain, 10X.

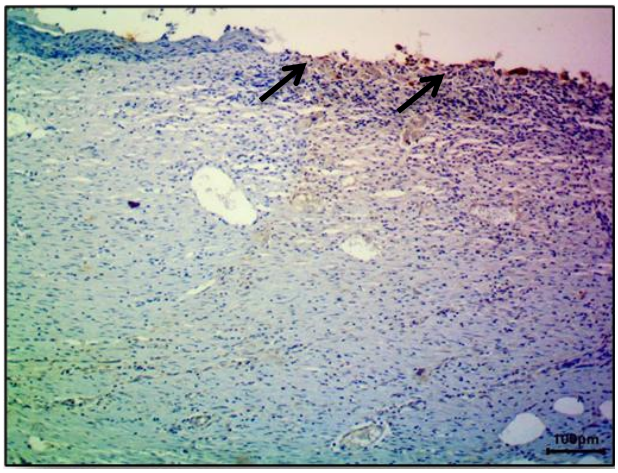

Figure (12): Immunohistochemistry expression of the MMP3 in the Titanium group (7 days) showing moderate positive expression (score 2). Hematoxylin stain, 10X.

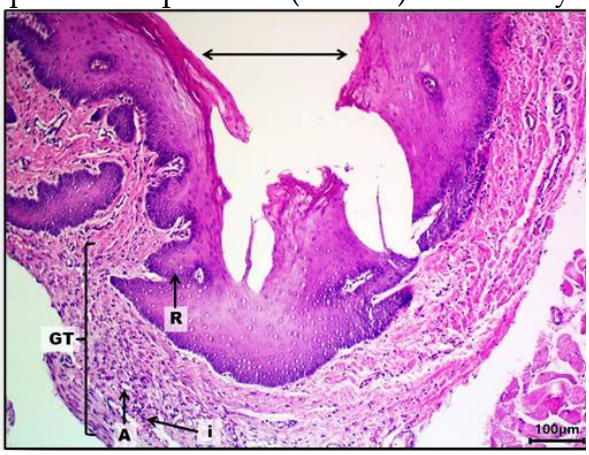

Figure (13): photomicrograph of rabbit oral mucosa of the composite treated group (14 days) showing the site of pin (↔) without inflammation (score 0), high granulation tissue (score 3) (GT), angiogenesis (A) and re-epithelialization (score 2) (R). H&E stain, 10X.

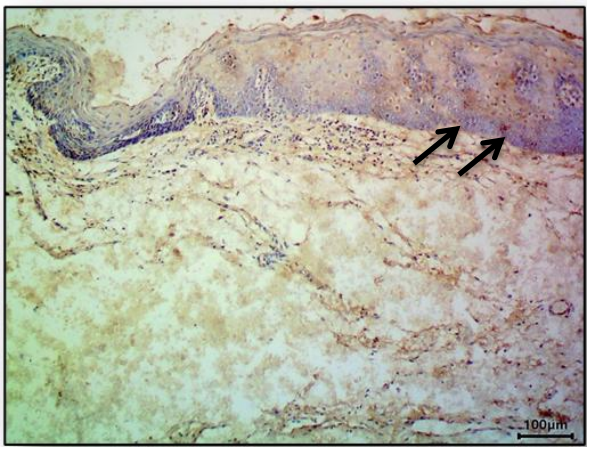

Figure (14): Immunohistochemistry expression of the CD31 in the Composite group (14 days) showing weak positive expression (score 1). Hematoxylin stain, 10X.

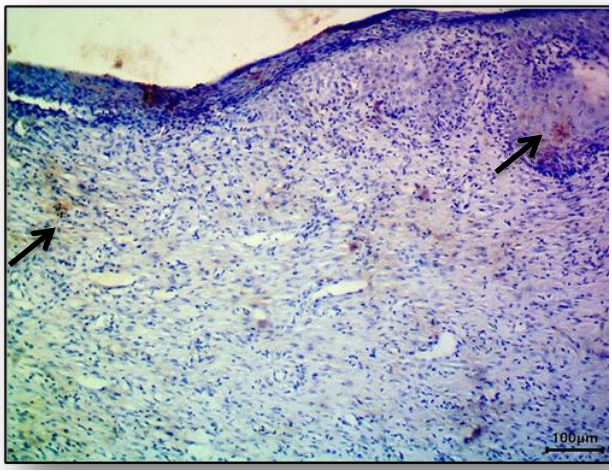

Figure (15): Immunohistochemistry expression of the MMP3 in the Composite group (14 days) showing moderate positive expression (score 2). Hematoxylin stain, 10X.

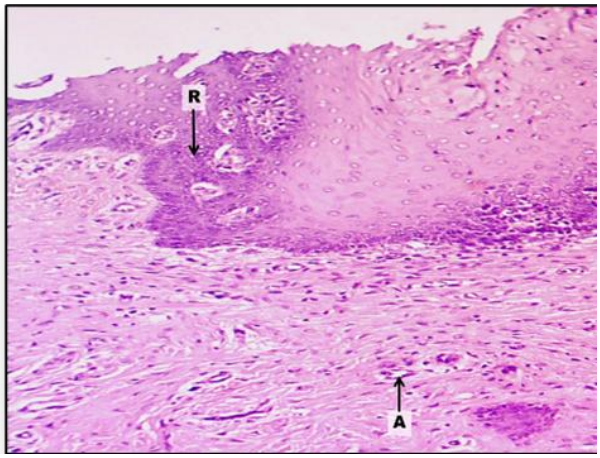

Figure (16): photomicrograph of rabbit oral mucosa of the Titanium treated group (14 days) showing the site of pin without inflammation (score 0), and granulation tissue (score 0), angiogenesis (score 3) (A) and well-developed re-epithelialization (score 3) (R). H&E stain, 10X.

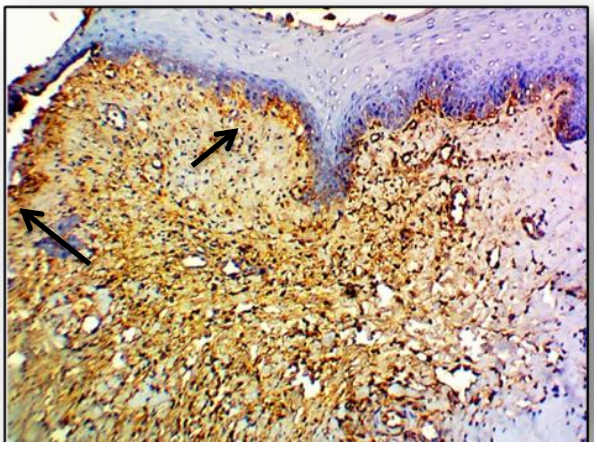

Figure (17): Immunohistochemistry expression of the CD31 in the Titanium group (14 days) showing moderate positive expression (score 2). Hematoxylin stain, 10X.

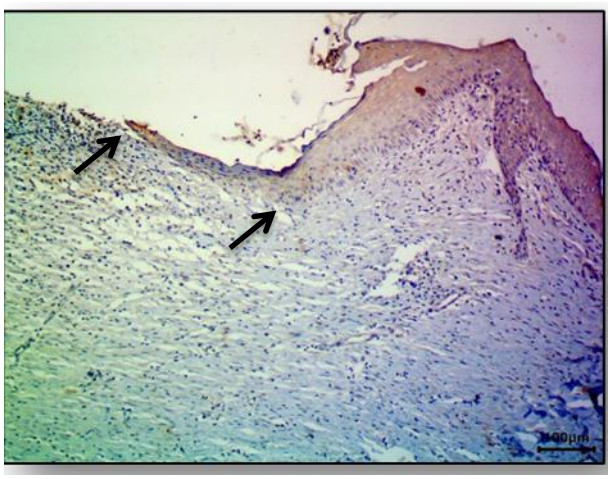

Figure (18): Immunohistochemistry expression of the MMP3 in the Titanium group (14 days) showing moderate positive expression (score 2). Hematoxylin

DISCUSSION

The original purpose of this study was to get more detailed information regarding the healing process taking place in the oral mucosa following the insertion of a certain type of biomaterial. Although titanium is considered the gold standard in osseous tissue integration in dental implants (15), there were questions about the soft tissue healing around the implant and whether zirconia is a better alternative.

Three days

This study suggests that after three days of the insertion of the mentioned materials, there was a slightly higher inflammatory response in the Composite resin group compared to the other group. Resin-based dental materials in direct contact with the oral mucosa can cause adverse reactions. TEGDMA (triethylene glycol dimethacrylate) based composite resin, in particular, caused significant damage to the oral mucosal models (16). Regarding the granulation tissue formation in the first three days, there was also no obvious difference. The re-epithelialization process showed a similar score with a slight advantage to the Titanium group. while the Composite group showed a lower score, but with no statistical significance. This may be due to the release of the bisphenol A (PBA) that increases the proinflammatory pathways and upregulates the expression and release of certain cytokines, such as IL6, IL1β, and TNFα (17).

Regarding the immunohistochemistry, the 3-day scores for the cluster of differentiation 31 gave similar results with a slight advantage to the Titanium group, with no mentioned significance. While the matrix metalloproteinase 3 (MMP3) results gave a negative score for both groups. This is due to the fact that the MMP 3 acts during the advanced stage of the healing process, as angiogenesis and modification of the extracellular matrix (ECM) (18), which is yet to be initiated at this stage.

Seven-day

After 7 days, the inflammatory cell infiltration scores were higher at the composite resin groups with a 1.75 mean score, while the titanium group showed a lower score at 1.25. These findings correspond with Milinkovic et al. (19), who found soft tissue response around titanium healing abutments to trigger a low-intensity inflammatory response that is dominated by B- B-lymphocytes. Studies also mention that eluted monomers are toxic to fibroblasts and macrophages, which also contribute to affecting the healing process at this stage (20). The granulation tissue formation at 7-day period showed a similar mean of 1.5 for both groups. The reepithelialization mean scores were 1.5 for titanium compared to a 1.25 mean for the composite group.

CD 31 expression for the titanium group scored a (1.5) mean. The composite group scored less with a (1.25) mean, but still with no statistical significance from these results. For 7 days is still an early time for the non-polymerized monomers to show their hindering effect on the healing process.

The MMP 3 expression was starting to appear but still in a weak expression since the role of the MMPs in remodeling and collagen type 3 degradation to be replaced by the firmer collagen type 1 is still early at this stage. the mean scores for the titanium were (0.75), while the composite group gave (0.5) mean score, it is obvious that these results lack any statistical significance.

Fourteen days

At this period, it is normal to observe a regression in the inflammatory process to allow the healing proliferation phase to take place. So, the inflammatory cells

infiltration mean score was (0.5) for the composite group and (0.25) for the titanium group; these results hold no statistical significance.

There was a statistically significant difference between the composite resin group and the titanium group (0.022 significance) in granulation tissue formation, (0.032 significance) for re-epithelialization, and (0.032 significance) in MMP3 expression. There was also an (almost) statistically significant (0.061 significance) difference in CD 31 expression.

Demirel et al. (21) examined the monomer release from different Composite Resins. After bleaching, the released monomers were analyzed by HPLC (high-performance liquid chromatography) at predefined time intervals: 1, 7, and 28 days. Results: The monomers were released at all times from all composite specimens. The monomer release was increased over time. The highest monomer release was detected on day 28. (21)

CONCLUSIONS

Within the limitations of the current study, it is possible to conclude that:

Composite resin showed an acceptable healing process but is far inferior to the Titanium; the differences in all the healing monitored results between the composite and titanium appear to be directly proportional to time passage (all the statistically significant results were recorded at the 14-day interval).

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Authors' Contribution

Conceptualization: Khaleel AF, Al-Wattar WT, Mahmood AS. Formal analysis: Khaleel AF, Al-Wattar WT, Mahmood AS. Funding acquisition: Khaleel AF, Al-Wattar WT. Investigation: Khaleel AF, Al-Wattar WT. Methodology: Khaleel AF, Al-Wattar WT, Mahmood AS. Project administration: Al-Wattar WT, Mahmood AS. Resources: Khaleel AF, Al-Wattar WT, Mahmood AS. Software: Khaleel AF. Supervision: Al-Wattar WT, Mahmood AS. Validation: Al-Wattar WT, Mahmood AS. Visualization: Khaleel AF, Al-Wattar WT, Mahmood AS. Writing–original draft: Khaleel AF, Al-Wattar WT. Writing–review editing: Al-Wattar WT, Mahmood AS. All authors have read and approved the final manuscript.

Funding: This study is self-funded

Ethical statement: This experiment was approved by the ethical committee of the College of Dentistry / University of Mosul / Department of Oral and Maxillofacial Surgery under ethical approval number (**Uom. Dent 29/23**).

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript

Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declaration of Generative AI and AI-assisted technologies

During the preparation of this work, the authors used Grammarly software to edit and proofread the text. The authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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دراسة مناعية نسيجية للاستجابات المخاطية للفم للتيتانيوم والراتنج المركب

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الملخص

الأهداف: تهدف الدراسة الى تقييم عملية الاستشفاء للنسيج الضام المخاطي الفموي الذي يكون بتماس مع التيتانيوم او المركب الراتنجي. **المواد وطرائق العمل**: 24 من ذكور الارانب النيوزلندية تم استخدامها في هذا البحث وضع في 12 منها جسم تيتانيوم في الطبقة التحت مخاطية فيما تلقى ال 12 ارنب اخر جسم مصنوع من المركب الراتنجي. وباستخدام الفحوص النسيجية للعينات المجمعة. كانت معايير القياس تشمل تسرب الخلايا الالتهابية، تكوين النسيج الضام، اعادة بناء نسيج الظهارة بالإضافة الى فحصين للكيمياء المناعية هما فحص كتلة التمايز 31 وفحص انزيم المذيب لبروتين التمعدن البين خلوي 3 لتحديد أفضل مادة تسمح باستشفاء النسيج الضام الذي يكون بتماس مع المواد المذكورة وقياس اي مضاعفات يمكن ان تنشا خلال عملية الاستشفاء للنسيج الضام المتماس مع المواد المذكورة. **النتائج**: معطيات النتائج اظهرت نتائج متشابهة ولكن بأفضلية طفيفة لمادة التيتانيوم. لم تسجل اي فوارق ذات جدوى احصائية خلال فترة 3 و7 ايام، فيما اظهرت نتائج ال 14 يوم فروقات ذات جدوى احصائية لصالح مادة التيتانيوم فيما يخص قراءات تكوين النسيج الضام، اعادة نسيج الظهارة وفحوصات انزيم المذيب لبروتين التمعدن البين خلوي 3. **الاستنتاجات**: اظهرت مادة التيتانيوم تفوقا فيما يخص الاستشفاء للنسيج الرخو مقارنة بالمركب الراتنجي. لكن النتائج الملموسة تبدأ بعد اسبوعين

الكلمات المفتاحية: مجموعة التمايز 31، راتنج مركب، ميتالوبروتينيز المصفوفة 3، تيتانيوم.