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ORIGINAL ARTICLE

# EVALUATION OF CYTOKERATIN-19 EXPRESSION AND OXIDATIVE STRESS STATUS ON GINGIVAL WOUND HEALING OF RABBITS TREATED WITH OMEGA-3

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**Summary**

**Background:** Gingiva is a delicate tissue that protects alveolar bone against external stimuli. Gingival breaks expose alveolar bone, and the fast wounds heal the betterment of the teeth frame. We aimed to compare the influence of omega-3 on the gingival healing period after trauma and the potential involvement of cytokeratin-19 protein expression.
**Methods:** A total of 18 rabbits were used, after trauma-induced, these rabbits were subdivided into three groups of 6 each. Group 1 is the control group that received normal saline only, the second group received omega 3 for 10 days before the trauma, while the third group received omega 3 supplements for 10 days before the gingival injury and continued receiving them for an additional 10 days afterwards. For each time point (third and seventh day of healing), 3 rabbits were sacrificed, and tissue was collected for total antioxidant capacity and malondialdehyde measurement. Tissue fixed for histopathology and immunohistochemistry analysis.
**Results:** Omega 3 has shown improvement in the healing process regarding the period of healing, antioxidant parameters, and intensity of cytokeratin-19 expression compared to the control group. Moreover, rabbit groups exposed to omega 3 before trauma has shown better healing response compared to those initiated therapy with trauma.
**Conclusion:** Omega 3 is notably beneficial when used for both prevention and treatment since it reduces oxidative stress and improves healing processes measured by increased expression of cytokeratin-19 in epithelial tissue. Omega 3 can therefore be thought of as a possible choice for the treatment of gingival wounds and gingivitis.

*Key words: CK19; Oxidative stress; Gingival wound; Omega-3; Rabbit*

## Introduction

The most significant budget constraint on the health care system and a challenge in daily clinical practice is the repair of wounds of diverse origins, particularly in hospitalized patients (1). On a molecular and subcellular

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level, wound healing is an intricate biochemical process that involves several intercellular interactions as well as the activation of many chemokines, cytokines, and growth factors. The three stages of wound healing always pass through proliferation (granulation), inflammation, and maturation (remodelling). Different cells and their byproducts are typical or dominant for each stage of healing, and their predominance overlaps (2).

Nutrition is one of the factors that affect the speed and quality of wound healing (3). Many micronutrients, including vitamins (4, 5) and minerals (6-8), have been examined for their impact on the healing process. Omega-3 modulates the production of pro-inflammatory cytokines (interleukin-1, interleukin-6, and tumour necrosis factor-alfa) by their final products (such as leukotrienes or prostaglandins), and as a result, exert dominant anti-inflammatory effects (9, 10).

Omega-3, however, have a more pro-inflammatory impacts (11). Several studies have looked at the preventive effects of omega-3 on the immune response, some neurological (12) and mental diseases, atherogenesis (13), lipidemia, and the vascular system. Because fatty acids may influence the rate of wound repair, their role ought not to be disregarded (14).

Animal models are also used in tissue repair research in addition to research trials. Topical application of essential fatty acid oil on skin wounds was shown to have both local and systemic effects in a rat models (15, 16). After supplementation with various dietary oils, variations in tissue response during the healing process in a rat model have recently been described (17, 18).

The long chains of fatty acids act as a precursor to a certain type of prostaglandins, and omega-6 or omega-3 are sources of arachidonic acid (19). When tissues are injured or infected, prostaglandins aid in the healing process by inducing pain and a rise in body temperature while also triggering the inflammatory response. When tissues are damaged in any way, white blood cells travel to the damaged tissues and subsequently prostaglandins are created there to promote healing (9, 10).

The intermediate filamentous protein keratin 19 is a member of the keratin family and is responsible for maintaining the structural integrity of epithelial cells. Only the periderms, the trans-surface layer that encloses the growing epidermis, contain it (20). Although the underlying biology is still poorly understood, cytokeratin (CK19) is primarily viewed as a marker of defective epithelial differentiation and is expressed in the simple epithelium and basal cells of the squamous epithelium. When cells are injured, they immediately begin to prepare for two opposing processes—the healing of the current damage and programmed cell death—by starting two contradictory pathways within seconds. They incorporate cues from the cellular death mechanism and the continuing repair process (21).

Any anomaly in the underlying tissue system causes oxidative stress, which is caused by an imbalance between antioxidants like glutathione, catalase, and superoxide dismutase, as well as the status of total antioxidants, like total antioxidant capacity (T-AOC) and oxidants such as malondialdehyde (MDA) (22). The epithelium is vulnerable to shifts in the oral cavity due to the numerous frictions and irritations that occur there (23). A few biochemical factors like (T-AOC and MDA) were paired with CK19, as a biomarker for the existence of wound regeneration and wound healing, to examine the impact of curative and preventative omega-3 therapies on periodontal wound healing (22).

The purpose of the current study was to assess how omega-3 could hasten healing by reducing the time to complete resolution, oxidative stress, and protein keratin's role in the healing process using a rabbit model.

## Materials and Methods

**Chemicals**: Materials used in the present study are outlined in Table 1.

| Materials | Manufacturer | Origin | Cat. No. |
|---|---|---|---|
| **Omega-3** | Beauty and Health CO | Ukraine | |
| **MDA kit** | Elabscience | USA | E-BC-K025-S |
| **T-AOC kit** | Elabscience | USA | E-BC-K136-S |
| **Monoclonal Antibody-CK19 (Clone RCK108)** | DAKO CO. | Denmark | IR61561-2 |

**The animals:** A total of 18 mature domestic rabbits (weight 0.5-1 kg; age 1- 4 months), settled in ground cages with proper environmental conditions, including temperature, lighting, cleanliness and free access to water and food. The animals were divided into three groups )6 each):

- Group 1: received daily normal saline
- Group 2: received 300 mg/rabbit of omega-3 for roughly 10 days before gingival incision.
- Group 3: received 300 mg omega-3 per rabbit for 10 days before the periodontal wound and continued for another 10 days.

**Sample collection:** A sterilized knife was used to cut a 0.5 cm incision from the gingival in each group. For comparison, three rabbits were sacrificed at 3rd and 7th day of healing. After 3 and 7 days after the gingival surgery, tissue samples were collected from the wound site. Some of the wound tissue was frozen at -20 °C, and other portions of them were placed in neutral formalin to analyze the expression of CK19.

**Histological analysis:** According to manufacturer instructions, MDA and T-AOC were measured using tissue samples derived from the site of injury.

CK19 was evaluated by incubation with the RCK108 primary antibody for 20 min. Samples were incubated with Dako® EnVision™ FLEX as secondary antibodies for 20 min (13). The immunostaining of CK19 in this work was done with a FLEX Monoclonal Mouse Anti-Human Oncoprotein, Clone 124, Ready-to-Use (Link), Code IR614, for use with Dako EnVision FLEX detection system and Autostainer Link equipment. The staining procedure parts of the detecting system's instructions were followed exactly.

**Statistical analysis:** Duncan's test assessed data at a significance level of less than 0.05, using a one-way ANOVA and Kruskal–Wallis test.

## Results

After 7 days of treatment with omega-3, the T-AOC (u/ml) revealed that the serum concentration of T-AOC has significantly ($p<0.05$) increased compared to the control group or pre-post normal saline treatment. Moreover, pre-post-treatment with omega-3 has even induced betterment of T-AOC than pre-treatment alone (Figure 1). Conversely, after 7 days of treatment with omega-3, the MDA (nmol/ml) revealed that the serum concentration of MDA has significantly ($p<0.05$) decreased as compared to the control group or pre-post normal saline treatment. Moreover, pre-post-treatment with omega-3 has even induced a greater reduction of MDA than pre-treatment alone (Figure 2).

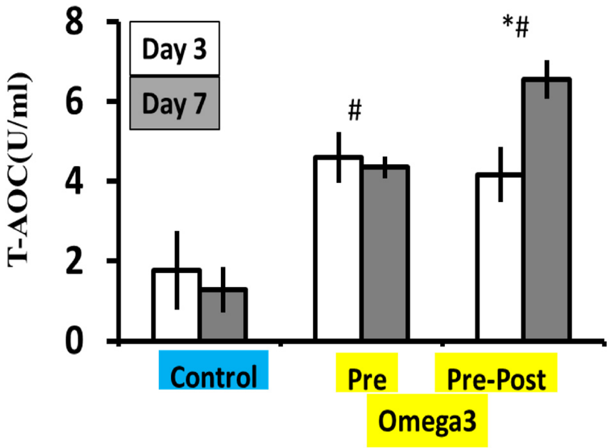


**Figure 1.** Total antioxidants capacity (T-AOC) concentrations in the rabbit's gingival wound of the experiment of all groups based on two-time points at day 3 and day 7 pre- or pre-post-omega 3 therapy versus normal saline-treated or control groups. Data Expressed as mean±SD. *$p<0.05$ as compared to other groups even with different time points.

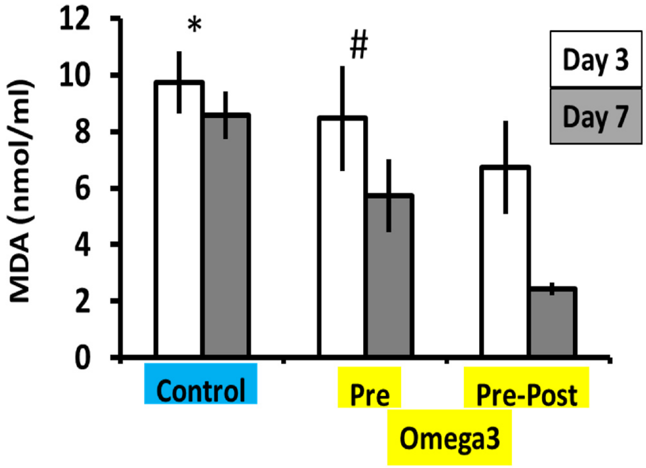


**Figure 2.** Malondialdehyde (MDA) concentrations in the rabbit's gingival wound of the experiment of all groups based on two-time points at day 3 and day 7 pre or pre-post-omega 3 therapy versus normal saline-treated or control groups. Data Expressed as mean±SD. *p<0.05 as compared to other groups even with different time points.

The immunohistochemistry staining for rabbit gingival mucosal epithelial cells revealed that after 7 days of treatment with omega-3, the cytokeratin 19 (CK19) expression revealed a higher CK19 expression ($p<0.05$) compared to lower intensity in the control negative group or pre-post normal saline treatment. Moreover, pre-post-treatment with omega-3 has even induced a higher intensity of CK19 expression than pre-treatment alone (Figure 3, Figure 4).

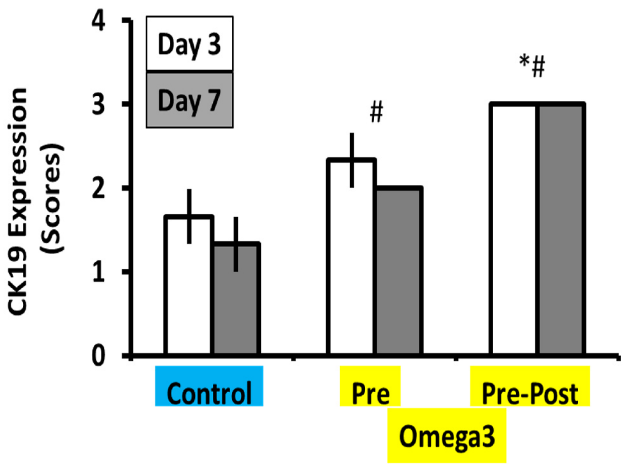


**Figure 3.** Immunohistochemical intensity scores of Cytokeraten 19 (CK19) expression in the epithelial cells of rabbits gingival mucosa based on two-time points at day 3 and day 7 pre or pre-post-omega 3 therapy versus normal saline-treated or control groups. Data Expressed as mean±SD. *p<0.05.

An immunohistochemistry stain for the CK19 protein demonstrated mild visceral phenotypes in the epithelial cells of the mucosa in the positive control group on the third day of healing (brown colour, Figure 4A1). The immunohistochemistry stain for CK19 protein in the positive control group on the seventh day of healing demonstrates modest visceral patterns in the mucosal epithelial cells (brown colour, Figure 4A2).

The Omega-3 pre-treatment group on the third day of healing shows a strong cytoplasmic pattern of expression of CK19 protein in the epithelial cells of mucosa (brown colour; score 3). Whereas the seventh day of healing shows mild CK19 protein cytoplasmic patterns expression in the epithelial cells of mucosa (brown colour; score 1; Figure 4B).

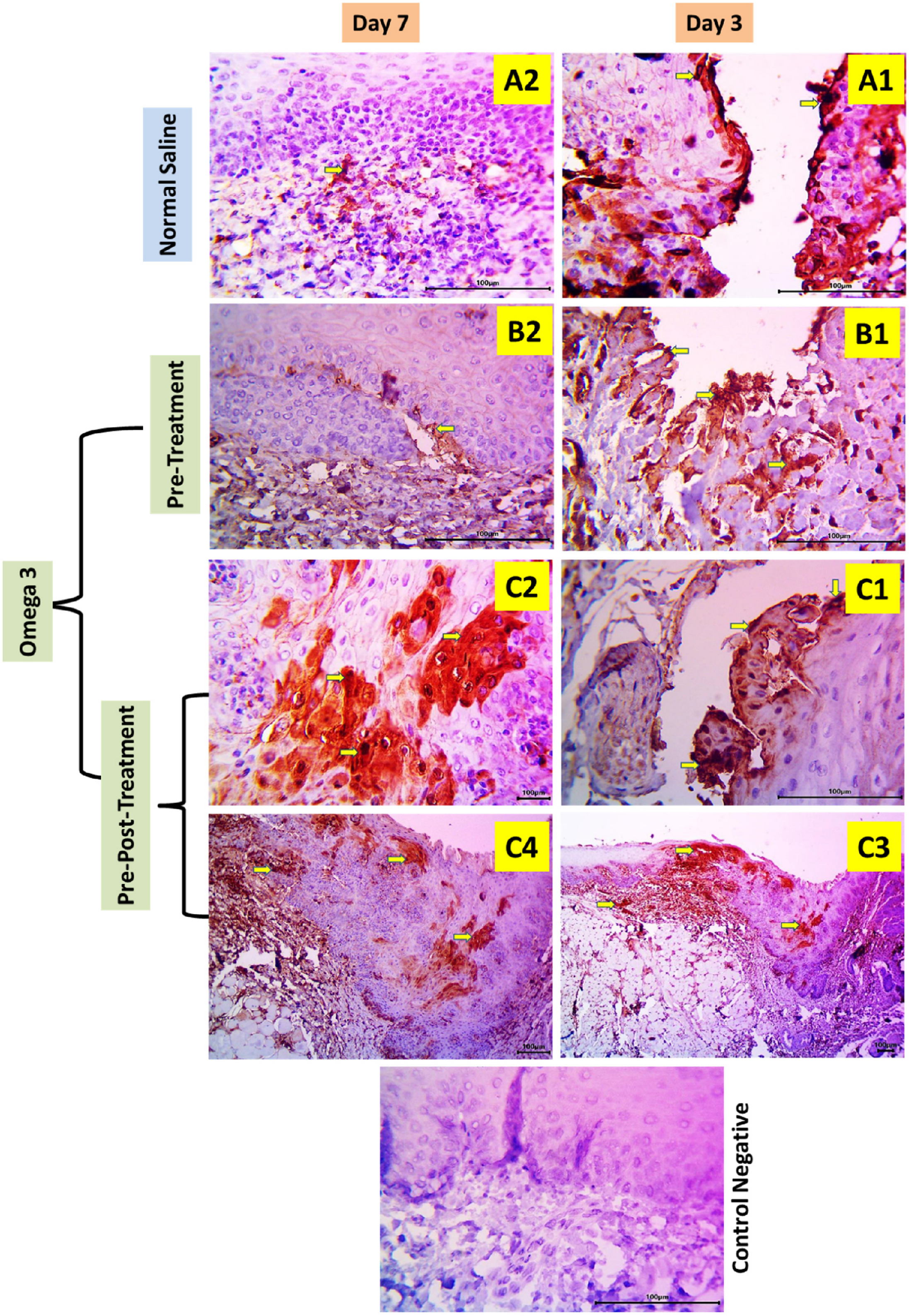


**Figure 4.** Representative images for IHC study of the stain of CK19 protein rabbit gingival wounds following either treatment with Normal saline or omega 3. Hematoxylin; Scalebar = 100µm, (A=normal saline treated, B=Omega3 pretreated, C=Omega3-pre-post-treated).

The Omega-3 pre and post-treatment group on the third day of healing shows strongly the immunohistochemical staining for CK19 protein at cytoplasmic patterns expression in the epithelial cells of mucosa (brown colour; score 3; Figure 4C). The Omega-3 pre and post-treatment group on the seventh day of healing shows a strong immuno-histochemical stain of CK19 protein (brown colour; score 3), more clearly revealed at cytoplasmic patterns expression in the epithelial cells of mucosa or cytoplasmic membrane (Figure 4C).

**Discussion**

The present study has confirmed that omega-3 use systemically might have a potential role in shortening the duration of healing perhaps as a result of the reduced oxidative stress represented by increased T-AOC plasma levels and reduced MDA plasma levels alongside increased expression of cytokiratin19, increasing healing site tissue integrity.

Trauma or injury started with the initiation of an inflammatory reaction commenced by neutrophils. Neutrophils, which are key players in the healing process, are the first cell type to be drawn to the inflamed region (24). In the present study, omega-3 has potentially reduced the healing duration following the induction of a wound. In an experiment conducted on Wistar rats administered with linoleic acid to examine the effects of linoleic acid (as a source for omega-3 and fatty acids) on neutrophil recruitment, an air pouch was generated into the dorsal region. Four hours later, the exudate was taken, and the cells were quantified. The results reported in the wound tissue were corroborated by linoleic acid increasing neutrophil infiltration to the pouches (25). The induction of adhesion molecules like L-selectin on neutrophil surfaces can be used to explain this influence on migration (26). Rolling, activation, adhesion, and transmigration are at least four phases in the highly regulated process of neutrophil trafficking. It was found that linoleic acid also increased leukocyte-endothelium interaction (rolling and adhesion) by the intravital microscopy assay (26).

Our findings are consistent with those of comparative studies utilizing omega-3 as an antioxidant, anti-inflammatory, and wound-healing aid, one of which found that omega-3 supplementation is a straightforward technique for improving long-term periodontitis treatment (27). According to another analysis of the research, using omega-3s as a treatment can greatly boost periodontal tissue regeneration while reducing bleeding during the inspection.

Neutrophils release cytokines, chemokines, ROS, and other chemicals that intensify the inflammatory reaction after they have reached the wounded area (24). In the present study, omega-3 has greatly reduced the oxidative stress at the site of injury represented by reduced MDA and increased T-AOC in the tissue site, particularly on day 7. Hatanaka *et al.* (28) found that linoleic acid increased anion superoxide and H2O2 in a dose-dependent approach when assessing intra or external ROS generation. During tissue rupturing owing to ischemia, ROS generation is the first event that happens in the context of wound healing (29). Low levels of H2O2 are crucial for supporting tissue repair (30) because ROS affect gene expression (31) and cellular activities like migration (32) and cytokine production (33) in addition to disinfecting the wounded area.

The analysis of healing status was followed with regards to the expression level of CK19 in epithelial tissues and immunohistochemistry sections, revealing that omega-3 treatment before and after the wounding procedure had a clear positive effect on wound healing. The expression of CK19 increased dramatically in tissues obtained from the wound site, especially after 7 days of treatment, compared to the rest of the treated groups, indicating re-epithelialization, granulation tissue formation, angiogenesis, and the absence of inflammation at the wound site. This was the best of the results from various tissue slices. Fibroblasts, endothelial cells, and keratinocytes produce growth factors that direct vessel reconstruction and cause wound contraction during the proliferation and remodelling phases (34). In comparison to the other treated rabbits, the injection of omega-3 before and after a wound in the gums results in a faster wound healing rate and an increase in the expression of CK19, which could be due to increased collagen. Omega-3 was discovered to be a new therapeutic target in the current study to heal gingival wounds. In this regard, Rojo et al. (35) reported that lucuma nut oil had a promigratory impact on human fibroblasts that was correlated with an increase in vinculin expression. Vinculin is a focal adhesion protein necessary for fibroblasts to interact with the ECM (36), which is implicated in the contraction of wounds. The reasons for the failure of therapy could be linked to the presence of surrounding tissue factors released in response to local oxygen supply (37) or due to inflammatory cellular response (38).

## Conclusion

Omega-3 polyunsaturated fatty acids have fastened wound healing by reducing duration. The parameters of wound healing have improved including oxidative stress parameters, cytokeratin expression, and histopathological findings.

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## Conflict of interest

The authors declare no conflict of interest concerned in the present study.

## Adherence to Ethical Standards

The study was approved by the Research Ethical Committee and Scientific Committee in the Department of Dental Basic Science of the College of the Dentistry/ University of Mosul with approval number UoM.Dent/A.L.9/22.

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