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Increased orthodontic tooth movement using 100mg Reduced Glutathione (GSH) on rabbits

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Abstract: **Accelerating orthodontic tooth movement, within its acceptable limits, can prevent damage to the teeth and its surrounding structures that are usually caused by prolonged treatment. Recent studies have investigated new methods and techniques that can reduce treatment time. It has been reported that Glutathione can induce osteoclastic differentiation, potentially accelerating tooth movement. Thus, this study aimed to determine the effect of reduced glutathione (GSH) on orthodontic tooth movement in rabbits. This in-vivo study utilized twenty-six (26) 10-12 week old male rabbits that were divided into 3 groups: Control Group A (without treatment), Control Group B (with tooth movement only) and Experimental Group C (with tooth movement and GSH). A nickel-titanium (Ni-Ti) closed coil spring with a 56.7g force was inserted between the maxillary incisors and the first molar to allow tooth movement. Reduced glutathione (GSH) 100 mg was orally administered daily, one week prior to and after the installation of the appliance. After 14 days, the distance of tooth movement was measured. H&E staining was performed to determine osteoclastic activity and observed under a scanning electron microscope at 10X and 40X magnification. Results showed that the mean distance of orthodontic tooth movement (mm) among subjects without GSH was at 0.20mm while for those with GSH was at 0.41mm. The number of osteoclasts also differed between those without GSH which had 1-2 osteoclasts and those with GSH which had 3-4 osteoclasts. The correlation using Spearman Rho's test regardless of the groups was strongly positive at Spearman's rank correlation coefficient (r_s)= 0.95. Among those without GSH, it was found to be lower but still moderately positive at r_s = 0.67. Lastly, those treated with GSH also had a strongly positive correlation at r_s =0.84. All of the results were statistically significant at alpha =0.01. It can be concluded that there was an increase in tooth movement in the group that received 100mg GSH compared to the group without GSH.**

Keywords: **orthodontic tooth movement, reduced glutathione, osteoclastic activity.**

I. INTRODUCTION

Extended orthodontic treatment can have deleterious effects like gingival recession, root resorption, pain, pulpal changes, periodontal problems, and temporomandibular problems [30]. Thus, prolonged treatment is a major concern for orthodontic professionals. As a consequence of this, many have resorted to adjunctive procedures that can help decrease orthodontic treatment time. This includes techniques in accelerating tooth movement, within the allowable limits of the supporting tooth structures.

During orthodontic tooth movement, there is mechanical stimulation of the teeth and its supporting structures, which results in cellular responses, synthesis, and release of neurotransmitters, cytokines, growth factors, colony-stimulating factors, and metabolites of arachidonic acid [7]. Fundamentally, once there is force acting on the tooth, inflammation in the periodontal ligament (PDL) occurs. Subsequently, tissue remodeling transpires through resorption and deposition in the compression and tension areas of the PDL, respectively. Once necrotic tissues have been eliminated by osteoclasts, tooth movement begins and is followed by osteoblasts laying down new bone [20]. Over the years, there have been techniques that have been designed to alter or hasten these cellular responses. Their main goal is to accelerate tooth movement and reduce the orthodontic treatment time. These techniques include vibratory stimulation, low-level laser therapy, customized appliances, and surgical adjunct procedures like remote corticotomy [23]. These methods are based on the principle that when the bone is stimulated, an inflammatory cascade starts to increase the number of osteoclastic activities therefore increasing the rate of tooth movement [9]. Although they have been proven to be effective, these techniques can be more invasive, quite

expensive, and which not all patients are likely to agree with. Therefore, researchers and dental practitioners have been looking for non-invasive and low-cost procedures which can promote acceleration of tooth movement.

The use of pharmacological agents to accelerate orthodontic tooth movement has gained interest to reduce the total treatment time. It can be considered as a practical, effective, and inexpensive alternative. Various drugs have been studied for accelerating tooth movement and have garnered successful results but most of these have only been tested on animals. A very popular drug that is by far the most widely tested in orthodontic tooth movement is prostaglandin (PGE1 and PGE2). Studies have shown that PGE2 enhanced the rate of orthodontic movement by inducing osteoclast formation but consequently increased the amount of root resorption [19]. Another drawback of prostaglandin is the route of administration. Multiple injections are required because of its short half-life and are supposed to be mixed with local anesthesia. This is due to prostaglandin's noxious agents that can lead to hyperalgesia [17].

Living a healthy lifestyle can help prevent chronic diseases and long-term illness. Maintaining good health is important for better self-confidence and self-image. Vitamins and supplements have been recognized to help achieve these. Glutathione is one of the supplements that can be very beneficial to one's overall health. It is a known antioxidant present in almost every cell in the body. Studies show that it plays a role in the detoxification of drugs and xenobiotics and maintains redox homeostasis in the body [10]. Glutathione exists in two interconvertible forms, reduced glutathione (GSH) and oxidized glutathione (GSSG). GSH is a predominant compound with a biologically active sulfhydryl group which acts as the active part of the molecule. The thiol group (-SH) of glutathione reduces the number of free radicals by binding to the un-shared electrons of free radicals formed as a result of oxidative stress [18]. This sulfhydryl group also allows for interaction with a variety of biochemical systems, hence the abbreviation "GSH" for its active form [8]. GSH is most commonly used in glutathione dietary supplements, is inexpensive, and the core behind other forms of active glutathione.

The highest glutathione concentration is found in the liver due to the liver's ability to remove and detoxify toxins and it is also found in the lung epithelial lining [5]. Decreased amounts of GSH may contribute to oxidative stress and may be a contributing factor to many diseases [31]. Therefore, GSH dietary supplements are being taken to help with the improvement of liver abnormalities and lessen diabetic complications. Furthermore, it is used as a protection against viral infections, acts on anti-tumor activity and may help manage autism [26]. GSH can also lighten skin color which makes it appealing to people who want to whiten their skin thus making GSH popular in the world of cosmetics [3].

GSH is usually administered orally and intravenously. For the intravenous route, a recommended dose of 600-1200 mg injected once or twice weekly is needed to have skin-lightening effects while the suggested dosage for oral intake ranges from 250-1000 mg/day depending on the manufacturer's instruction [29]. Drugs converted to animal dose use the dose-factor method, this utilizes the no observed adverse effect levels (NOAEL) of the drug. The equivalent human dose of GSH in animals, specifically in rabbits, ranges from 50-100 mg depending on their weight [22]. Based on the National Center for Biotechnology's compound summary of 2021, the lethal dose of GSH in mice is 5000 mg/kg for the oral route and 2238 mg/kg for the intravenous route making GSH non-toxic and safe.

Antioxidants are part of the body's innate defense mechanism and many occur naturally in the saliva. GSH, a known antioxidant, is able to fight free radicals and oxidative stress that may occur in the oral cavity [25]. GSH is slowly being incorporated in dental-related studies and might be beneficial when used as a supplement to help accelerate the healing process and prevent chronic periodontitis. In other studies [6], it was shown that there is a decrease of GSH in the saliva in patients with periodontal disease. This is possibly because of the excessive quantity of free radicals and ROS due to the presence of infection and inflammation that GSH tries to neutralize.

There are no studies relating GSH to Orthodontics. However, GSH is said to have an importance during physiologic bone remodeling wherein GSH induces osteoblastic activity and decreases osteoclastic differentiation [13],[28]. Interestingly, Fujita et al in 2019 [11], studied the effect of exogenous GSH when injected on mouse bone cells. Although no orthodontic tooth movement was involved in this study, it was suggested that GSH can accelerate osteoclast activity. It is possible that orthodontic patients who care about their image may coincidentally also be taking GSH as a supplement. Unfortunately, no studies have been done to test if GSH has an effect on orthodontic tooth movement in relation to osteoclastic activity.

II. MATERIALS AND METHODS

Samples

Twenty-six (26) 10-12- week old, 1-1.8kg male rabbits were randomly divided into 3 groups: 2 test subjects for Control Group A (without any treatment - as reference point), 12 subjects for Control Group B (with tooth movement only) and 12 subjects for the Experimental Group (with tooth movement and GSH).

Subject Preparation

Control Group A (without treatment - as reference point) - two (2) subjects did not receive GSH and no force was applied to its teeth, but subjects were still housed and fed daily for 3 weeks. These subjects were used as the baseline reference for the osteoclastic activity.

Control Group B (with tooth movement only) - twelve (12) subjects underwent tooth movement using a closed NiTi coil spring with eyelets. A ligature wire, with a diameter of .08mm was used to attach the spring at both ends (i.e., the mandibular central incisor to the first premolar). These were secured by means of a light-cured bonding material and a force of 56.7g [12] was applied using a tension gauge.

Experimental Group (with tooth movement and GSH) - twelve (12) subjects received 100mg of GSH every day for 21 days. GSH was given orally one week prior to the installation of the orthodontic appliance. One hundred mg (100mg) of GSH was diluted in 2 ml of water and was administered orally using a syringe. These 12 subjects underwent tooth movement using a closed NiTi coil spring with eyelets. A ligature wire, with a diameter of .08mm was used to attach the spring at both ends (i.e., the mandibular central incisor to the first premolar). These were secured by means of a light-cured bonding material and a force of 56.7g [12] was applied using a tension gauge.

Methodology

Subject preparation for the orthodontic device

In order to install the orthodontic appliance, both the Control Group B and Experimental Group were anesthetized via intramuscular injection with Zoletil 0.5-2 mg/kg.

The orthodontic appliance consisted of a NiTi closed coil spring with eyelets, the diameter of which was 0.30.mm and a coil gap of 0.10mm (Ormco, USA).The appliance was placed between the mandibular incisors and mandibular first premolar and was fixed with a ligature wire 0.08mm and light-cured bonding material. The coil spring was measured and standardized using a tension gauge in order to produce a 56.7g force.

Measurement of tooth movement

Fourteen (14) days after installation of the orthodontic appliance, test subjects (Control Group B and Experimental Group) were euthanized by inhalation of 5% isoflurane to minimize suffering.

The space created distal of the first premolar were measured with three (3) consecutive thickness gauges that could get into the space. The moderately fitting ones that were selected were again measured with a digital caliper for accurate and final measurement.

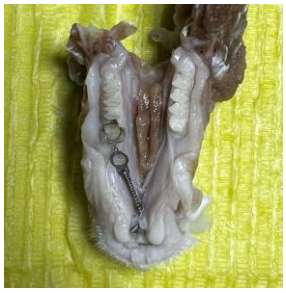


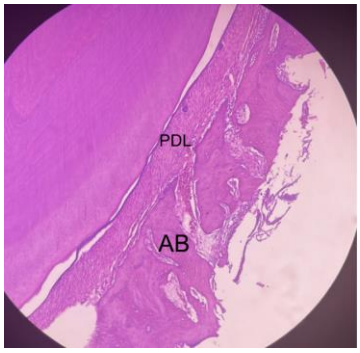
Fig. 1. Lower jaw with appliance

Fig. 2. Measurement of distance using thickness gauge

Histological Preparation and analysis

Following euthanasia, the mandible was removed and fixed in 4% paraformaldehyde for 24 hours at room temperature. The mandible was demineralized in 10% ethylenediaminetetraacetic acid (EDTA) for 10 days at 4°C. The samples were embedded in paraffin and sectioned at 4µm for histological analysis. The vertical sections of the mesial side of the mesial root were prepared since the mesial side was the pressure side during tooth movement. These sections were used to count the number of osteoclasts after staining with hematoxylin and eosin.

Cells were considered as osteoclasts if they were multinucleated and were located on the bone surface. The number of osteoclasts were counted. All samples were observed under 10X and 40X magnifications using a scanning electron microscope.



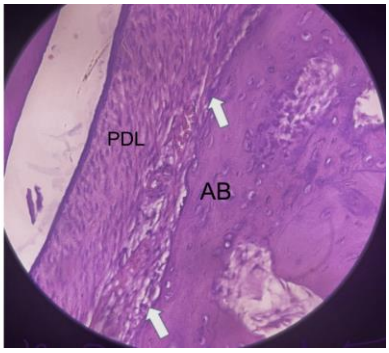
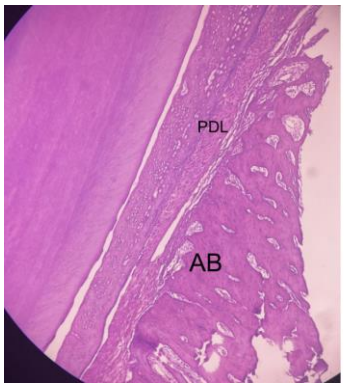


Fig. 2. Group without GSH at 10X magnification **Fig. 3. Group without GSH at 40X magnification**



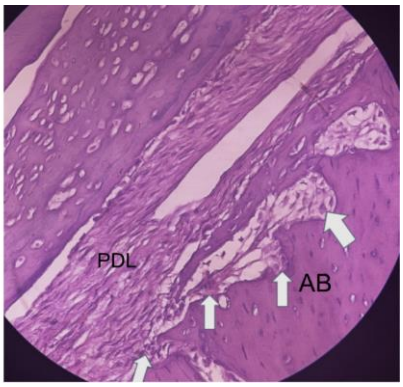


Fig. 4. Group with GSH at 10X magnification **Fig. 5. Group with GSH at 40X magnification**

III. RESULTS AND DISCUSSION

TABLE 1. Baseline Characteristics

		without GSH	with GSH	Statistic	p-value
	n	12	12		
Orthodontic tooth movement (mm)				17.45	2.95
	Mean	0.2	0.41		
	Median	0.2	0.41		
	Mode	0.21	0.41		
	Standard Deviation	0.01	0.01		
	Range	0.04	0.04		
	Minimum	0.18	0.39		
	Maximum	0.22	0.43		
Number of osteoclasts				18.45	1.74
	Minimum	1	3		
	Maximum	2	4		
	Range	1	1		
	Mode	2	3 and 4		
**Sig. at 0.10, **Sig. at 0.05, ***Sig. at 0.01*					

The mean distance of tooth movement (mm) among subjects without GSH was at 0.20mm (SD=0.01) while for those with GSH was at 0.41mm (SD=0.01). The difference was highly significant at alpha = 0.01. It can be noted that although the distance for those with GSH were higher, the spread was similar to those without GSH; standard deviations were both equal to 0.01 and ranges at 0.04.

TABLE 2.1. Distribution of number of osteoclast in subjects without GSH

Number of osteoclasts	n	%
1	5	26.3%
2	7	73.7%
Total	12	100.0%

TABLE 2.2. Distribution of number of osteoclast in subjects with GSH

Number of osteoclasts	n	%
3	6	42.9%
4	6	57.1%
Total	12	100.0%

The number of osteoclasts also differed between those without GSH and those with GSH. The former had 1-2 osteoclasts while the latter had 3-4. The difference was also significant at alpha= 0.01.

For the group without GSH, 73.7% of the subjects had two (2) osteoclasts while the rest had only one. On the other hand, the experimental group (with GSH) found half of the subjects with three (3) osteoclasts and the other half, four (4).

TABLE 3. Correlation between OTM and number of osteoclasts

Group	Spearman's Rho	p-value
All	0.95***	3.50E-12
Without GSH	0.67***	1.62E-02
With GSH	0.84***	6.84E-04
**Sig. at 0.10, **Sig. at 0.05, ***Sig. at 0.01*		

The correlation between the distance of tooth movement and number of osteoclasts was measured regardless of the group and in each group using the Spearman's Rho. Disregarding the groups, the correlation was strongly positive at 0.95. Among those without GSH, it was found to be lower but still moderately positive at 0.67. Lastly, those treated with GSH also had a strongly positive correlation at 0.84. All of the results were statistically significant at alpha =0.01.

IV. CONCLUSION

Orthodontic tooth movement (OTM) occurs when there is mechanical stress directed to the periodontium which then activates cellular differentiation that causes breaking down and creating new bone [20]. The force applied during OTM initiates osteoclastogenesis or osteoclast formation. During this phenomena, tissue damage occurs and alveolar process deformation takes place [15] subsequently, osteoclasts start to appear at the compression sites [27][32]. Interleukins and Tissue Necrosis Factor- alpha are also produced, which suggests the importance of inflammation during tooth movement [1]. Once all necrotic tissue has been removed by macrophages, giant cells, and osteoclast cells, this is when the tooth will start to move [16][4]. An increase in osteoclast activity has made it the hallmark of tooth movement in many studies [24][21]. Prolonged orthodontic treatment can lead to potential risks and damage in the soft and hard tissues. It can cause gingival recession, root resorption, pain, pulpal changes, periodontal problems, and temporomandibular problems [30].

Reduced Glutathione (GSH) is a known antioxidant in the body. Oral supplements are gaining popularity because of GSH's increased ability to reduce oxidative stress, help repair damaged cells, boost the immune system [2], and maintain redox homeostasis [10]. There is limited research on GSH relating to tooth movement. On the other hand, there are studies that suggest that GSH helps in bone remodeling under physiological conditions. Several studies suggest that orthodontic tooth movement can induce oxidative stress. Oxidative stress has the ability to alter bone remodeling process which results in an unbalance between osteoclasts and osteoblasts. Consequently, this activates osteoclastogenesis thus increasing bone resorption and prolonged bone resorption can lead to metabolic bone diseases or bone loss.

The role of GSH is that it reduces oxidative stress and has the ability to induce formation of osteoblasts and suppress osteoclast activity [28] by decreasing RANKL and suppressing TNF-α, respectively. However, results from this present experimental study showed that there is an increase in the number of osteoclasts in the GSH group compared to the group that did not receive any GSH during orthodontic tooth movement. The histologic results of this experiment conform with the study by Fujita et al (2019) [11], that exogenous GSH contributes to the increase in bone resorption because GSH promoted TNF-α which increased the number of osteoclasts when GSH was administered to a rat's bone marrow. The authors suggested that GSH enhances osteoclastogenesis under the pathological conditions of inflammation. Another study by Huh et al (2005) [14], pretreated bone mouse marrow with GSH for 15 hours and found that GSH promoted osteoclast differentiation. It is speculated that the reason for this discrepancy is due to the difference in experimental conditions and the fact that GSH is said to have a biphasic effect on osteoclast activity or differentiation depending on the concentration of GSH or how GSH was used in the experiment [11][14]. With an increased number of osteoclasts, there is an increase in bone resorption and consequently an increase in orthodontic tooth movement which coincides with the results of the study where the distance of tooth movement in the group with Glutathione is greater than the group without. Findings from this present study suggest that an increase in the number of osteoclasts may be directly proportional to an increase in tooth movement. However, it is important to note that the effect of GSH on osteoblasts and bone remodeling were not part of the present study. Regardless, if there was an increase in tooth movement when exposed to GSH, there is still no evidence that can determine a successful orthodontic tooth movement.

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