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INTEGRATED STUDY MASTER'S THESIS

A Literature Review of Low-Level Laser Therapy in Enhancing Accelerated Orthodontic Tooth Movement

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ABSTRACT

As the demand for orthodontic therapy increases, innovative technologies aim to assist the orthodontic community in achieving the most effective results. Low-level laser therapy is a relatively new non-surgical orthodontic acceleration technique. This literature review evaluated its effectiveness, by systematically examining existing literature, studies and reviews. The key points of this review are how and if low-level laser therapy can be used to enhance orthodontic treatment, examining its effect on the oral environment and comparing it to alternative orthodontic acceleration techniques.

Keywords: low-level laser therapy; photobiomodulation; accelerated orthodontics; laser; orthodontic tooth movement

Acronyms: Orthodontic tooth movement (OTM), Photobiomodulation (PBM), Light emitting diodes (LED), Light amplification by stimulated emission of radiation (laser), Enzyme-linked immunosorbent assay (ELISA), gingival cervical fluid (GCF), Orthodontically induced inflammatory root resorption (OIIRR), Periodontal ligament (PDL)

I. INTRODUCTION

The spotlight on orthodontic therapy and its effectiveness has intensified, garnering significant attention in recent literature as researchers delve into its intricacies and impact. A trend of heightened awareness within the population about the physical and psychological effects of dental misalignments has provided a surge in demand for orthodontic interventions over the past decade [1].

While the average treatment duration was found to be 31.3 months, it is dependent on several patient-, practitioner- and treatment-related factors [2,3]. In light of adverse outcomes such as caries, periodontitis and orthodontically induced root resorption as well as patient satisfaction associated with prolonged orthodontic treatment time, there arises a compelling interest in minimizing treatment duration to mitigate these potential negative impacts [4,5]. This can be accomplished via orthodontic acceleration techniques.

Orthodontic acceleration techniques are relatively new and can be categorized into surgical, non-surgical and pharmacological. While surgical techniques were the first to emerge side effects and invasiveness make non-surgical techniques attractive for many [6]. This review briefly discusses each orthodontic acceleration technique but targets one aspect of orthodontic acceleration - the role of low-level laser therapy.

Low-level laser therapy is a non-surgical orthodontic acceleration technique that has been hypothesized to decrease treatment time, decrease pain, stimulate cellular processes, promote tissue healing, and boost patient dissatisfaction [7].

By systematically reviewing existing literature the aim is to assess the homogeneity of the results, identify recurrent patterns and shed light on the limitations and gaps in research.
Ultimately the goal is to contribute an up-to-date and comprehensive review of the literature provided on low-level laser therapy and to identify the direction of future advancements in the research. To evaluate the effectiveness of low-level laser therapy in orthodontic environment the main research questions addressed will be: (1) What are the cellular and biological benefits of low-level laser therapy throughout orthodontic therapy? (2) How effective is low-level laser therapy in decreasing the rate of orthodontic tooth movement compared to other orthodontic acceleration techniques? (3) How can we implement low-level laser therapy into practice-based orthodontics?

For this purpose, this literature review follows a clear plan outlined as follows:

1. Historical theories of orthodontic tooth movement, and the biological and cellular mechanism involved.
2. The clinical methodology of low-level laser therapy explores how low-level laser therapy can be used in a clinical environment.
3. The effects of low-level laser therapy on cellular metabolism, pain relief, treatment time, bone remodelling, vascular changes and orthodontically induced root resorption are investigated with regards to other orthodontic acceleration modalities.
4. The disadvantages and side effects of low-level laser therapy in the orthodontic practice.
5. The limitations of the research as well as the difficulties faced throughout this review.

II. THEORY OF ORTHODONTIC TOOTH MOVEMENT

Even though this paper focuses on the effectiveness of low-level laser therapy (LLLT) and accelerated orthodontic tooth movement, it is important to understand the method of tooth movement and the cellular changes that occur through orthodontic treatment.

Orthodontic tooth movement is a result of forces applied to the tooth and periodontium provoking biological changes in the bone which result in bone remodelling, the biological activity is not fully understood yet, nonetheless there are theories describing the cellular changes throughout orthodontic tooth movement (OTM) [8].

2.1 CELLS INVOLVED IN ORTHODONTIC TOOTH MOVEMENT

Five cells respond to orthodontic tooth movement (OTM): osteoblasts, osteoclasts, osteocytes, osteoprogenitor cells, and bone lining cells [9].

The osteoblasts have the central role as the bone-forming cells, being differentiated from mesenchymal progenitor cells under the influence of several factors such as *bone morphogenic protein (BMPs), transforming growth factor ßI and II (TGF-ßI and II), insulin-like growth factor I and II (IGF-I and II), platelet-derived growth factor (PDGF),* and *fibroblast growth factor (FGF)* they synthesize and secrete the bones extracellular matrix [9]. Furthermore, the Osteoblast lining the bony socket directly reacts to the pressure of orthodontic movement, by the process of mechanotransduction [9].

Secondly, the process of bone resorption involved in orthodontic tooth movement (OTM) is carried out by osteoclasts [9]. Their differentiation from hematopoietic stem cells, is regulated by factors produced by osteocytes and osteoblasts, such as *colony-stimulating factor (CSF), receptor activator of nuclear factor-kappa B ligand (RANKL), osteoprotegerin (OPG), and bone morphogenic proteins (BMPs)*[10]. CSF, RANKL and RANK can promote osteoclast differentiation contrary OPG can inhibit osteoclast formation by binding to RANKL inhibiting its binding to its receptor RANK [9].

The osteocyte is, understood as being the mechanosensory cells of the bone, primarily responsible for proprioception and response, during OTM adaptation and loading patterns [11]. They are believed to be terminally differentiated osteoblasts, located in lacunae, and surrounded by bone matrix; their cytoplasmic process resides in canaliculi [11]. They communicate with nearby osteocytes and osteoblasts through ion exchanges via gap junctions [9].

The bone lining cell is also a terminally differentiated osteoblast, that are thinly extended over the bone surface, they are involved in propagating the activation signal that initiates bone resorption and remodelling [9,12].

Osteoprogenitor cells, located in the vicinity of blood vessels of the periodontal ligament, are the stem cells that generate osteoblasts [9].

2.2 THEORIES OF ORTHODONTIC TOOTH MOVEMENT

The bone bending theory by Farrar in 1888, describes that the force applied to the tooth creates tooth movement as the bone is elastic, thus the tooth will move in the pulled direction [13]. This explains why in paediatric patients with less dense bones the rate of orthodontic movement is faster when compared to older patients with denser bones [14].

In 1962 the biological electricity theory by Bassett and Becker proposed that the body regenerates electrical currents as the bone changes [15]. For orthodontics, this means that the deformation of the bone will send an electrical current to change the bone's metabolism leading to cellular differentiation and resulting in tooth movement [8,15].

The most accepted theory is the pressure-tension theory developed through classical histological studies, of Sandstedt in 1904, Oppenheim in 1911 and Schwarz in 1932 [8,16–18]. It describes

orthodontic tooth movement as it divides the periodontium into a pressure or compression and a tension side [9].

When orthodontic force is applied, histologically the compressed side, where the tooth root is pushed against the alveolar bone, shows a disruption and disorganization of the periodontal ligament (PDL) cells, the blood vessels appear compressed leading to a lack of oxygen and nutrition resulting in osteoclastogenesis, hyalinization, and cell death [9,19].

On the contralateral "tension" side, the PDL is being stretched, leading to bone deposition through osteogenesis [9,19]. The changes in equilibrium of the PDL, are followed by a chain of biochemical events via chemical messengers which lead to an activation of osteoclasts and osteoblast to restore balance [9]. Even though it is a well-accepted theory, it is believed to look at the tooth in a "2 dimensional" perspective [9].

A recent theory, known as the biphasic theory, divides OTM into two phases: the catabolic and anabolic phases [20]. Initially, the catabolic phase, dependent on osteoclastogenesis, resorbs the bone via osteoclasts at the compression and tension site, followed by the anabolic phase which restores the bone [19].

Wise's review explained why bone is osteogenic under loading forces and resorptive when force is released by two theories [21]. Firstly, the compressive force triggers tissue injury and therefore a resorptive inflammatory response occurs [21]. The second theory suggests that the loss of the functional strain at the compression site of the PDL triggers osteoclastic activity, while osteogenic activity is reenforced at the contralateral loading side [21]. Highlighting the crucial role of the PDL in sensing and initiating the necessary cellular and inflammatory responses [21].

III. THEORY OF LOW-LEVEL LASER THERAPY

3.1 METHODOLOGY OF LOW-LEVEL LASER THERAPY

The term "Laser" is an acronym for "light amplification by stimulated emission of radiation". Lasers are instruments designed to generate monochromatic, coherent, collimated, polarized, highly focused light [22]. They have been implemented in the medical field for therapeutic purposes over an extensive period [22]. Notably, the Nobel prize of 1903 was awarded to Niels

Finsen in recognition of his ground-breaking contribution to the application of ultraviolet light for the treatment of lupus vulgaris [22].

In a series of experiments to assess the safety of laser light, Mester et al. observed no side effects of laser other than increased hair growth [23]. However, their study did reveal a noteworthy phenomenon: Low-level lasers were observed to accelerate the process of wound healing which became known as Photobiomodulation [24].

Photobiomodulation (PBM) is the process by which red or near-infrared light is absorbed by the cells and can stimulate cellular function, usually, this is done by using low-level lasers but can also be accomplished by using Light emitting diodes (LED) devices [25]. LED light is almost monochromatic, but contrary to laser light it is not coherent, nor collimated nor polarized, therefore it is unclear if LED and lasers can be substituted, this can be seen in Figure 1 [22]. LEDs only require a minimal power source, and are safe to use at home, furthermore, they have no restriction of use in the European Union and are not bound by federal laser product standards in the United States, making LED use commercially attractive [22].

Through the different parameters and use of lasers and LED devices it is important to differentiate the two, this review will be focused on the PBM effect LLLT has on orthodontic acceleration.

Lasers, similar to light, behave as particles and a wave, the variables we may alter when applied in orthodontic acceleration are the number of application appointments, the wavelength which varies from 300 - 10 600 nm, the type of emission pattern which can be continuous or pulsating: pulse rate from 0 to 5000 Hz, the intensity from 10^{-2} to 10^{2} J/cm^{2} and electromagnetic spectrum ranging from 630 to 980 nm, the duration of application which vary for 30-60 seconds per point, each variable is dependant on the type of laser used [26–29].

The procedure of orthodontic acceleration with LLLT is operator-dependent as the application is performed manually by the movements of the operator [28]. Therefore, it is a highly technique-sensitive process for which the replication of application with each patient is not possible [28].

There are different handpieces able to produce laser; the most operator-dependent is the classic handpiece for which the effectiveness varies with the distance to the focal point, whereas the flat top handpiece can have the same focal spot even if there is a varying distance to the targeted area [28]. Notably, there are LED photo biomodulation devices that emit LED light independently of the operator, thus reproducing the same application per patient [28].

Clinically, the operator must place the correct parameters into the low-level laser device to gain optimal results [28]. Usually, throughout the studies, it is visible that the higher the parameters within the possible range, the higher the divergence of statistically significant effect to no effect within the results of the placebo versus the non-placebo group. Nonetheless, the optimal exposure, wavelength, and other exposure parameters have not been established yet.

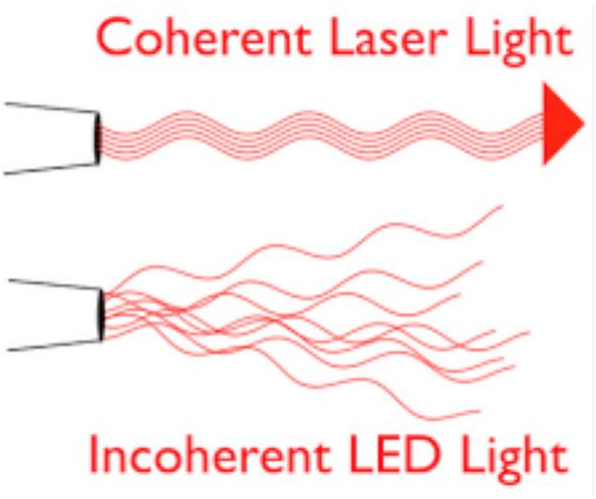

Figure 1 A schematic representation of the difference between a low-level laser beam and an LED beam [28].

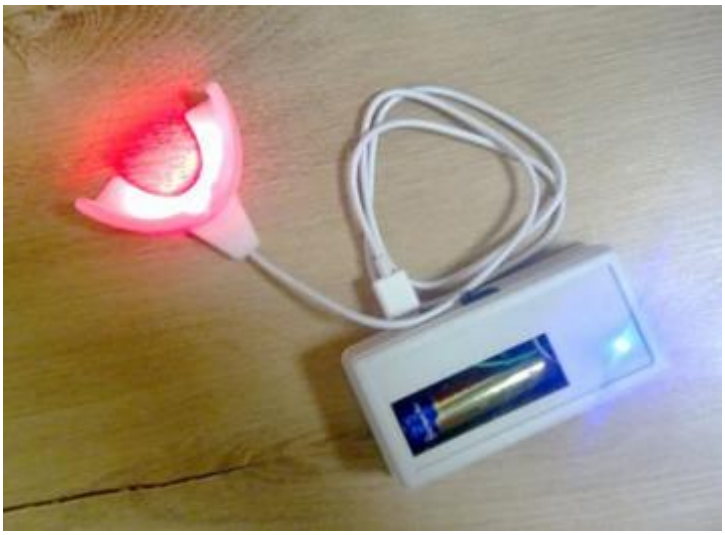

Figure 2 An intra-oral LED device used for orthodontic tooth movement acceleration [30].

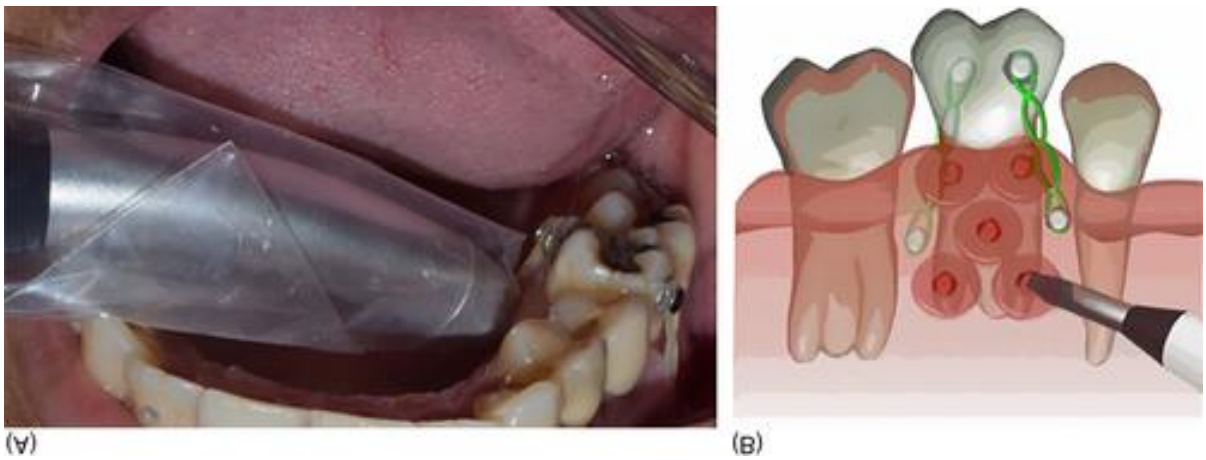

Figure 3 A) Real representation of LLLT device application B) Demonstrates a schematic view of the chosen points for LLLT application [31].

3.2 THE CELLULAR CHANGES INDUCED BY LLLT

There are several factors, such as the type of laser parameters, the force applied, and the position of the teeth, which influence the inflammatory reaction occurring during OTM, the cellular changes have been studied, and the differences occurring when PBM effects OTM are shown in this part of the review.

In the review by Xinyuan Wang et al. concerning the effect of PBM therapy on orthodontic treatment, the findings revealed that PBM has a notable effect on orthodontic therapy [7]. On a cellular level, the study revealed a positive effect on bone remodelling, reduced inflammatory root resorption, and modulated the cells involved in maintaining the balance of the bone structures [7].

There are several hypotheses on how PBM impacts cell proliferation and differentiation, angiogenesis, bone metabolism, collagen, and fibre formation.

One hypothesis is demonstrated by Figure 4, which shows that PBM influences the mitochondria where it targets the cytochrome c oxidase (Cox) as it is a photo acceptor [7]. This has a positive impact on the electron transport chain as it increases ATP production through ATP enzyme subunits (ATP synthase, COXIV, and complex I) increasing the energy supply and nucleic acid synthesis [7].

Simultaneously, it has been proposed that PBM mitigates Nitric oxide (NO) via photodissociation [7]. NO binds to COX which is harmful to cellular respiration as it competes

with oxygen and reduces necessary enzymatic activity, therefore this would be a favorable outcome of PBM [7]. This hypothesis has been made as the studies have shown an increase in the level of NO, when PBM was applied, indicating its release from cox or an upregulation of cox [7,32]. This increases ATP and cytokine synthesis in a process called “retrograde mitochondrial signaling” proposed by Karu, seen in Figure 4 [33].

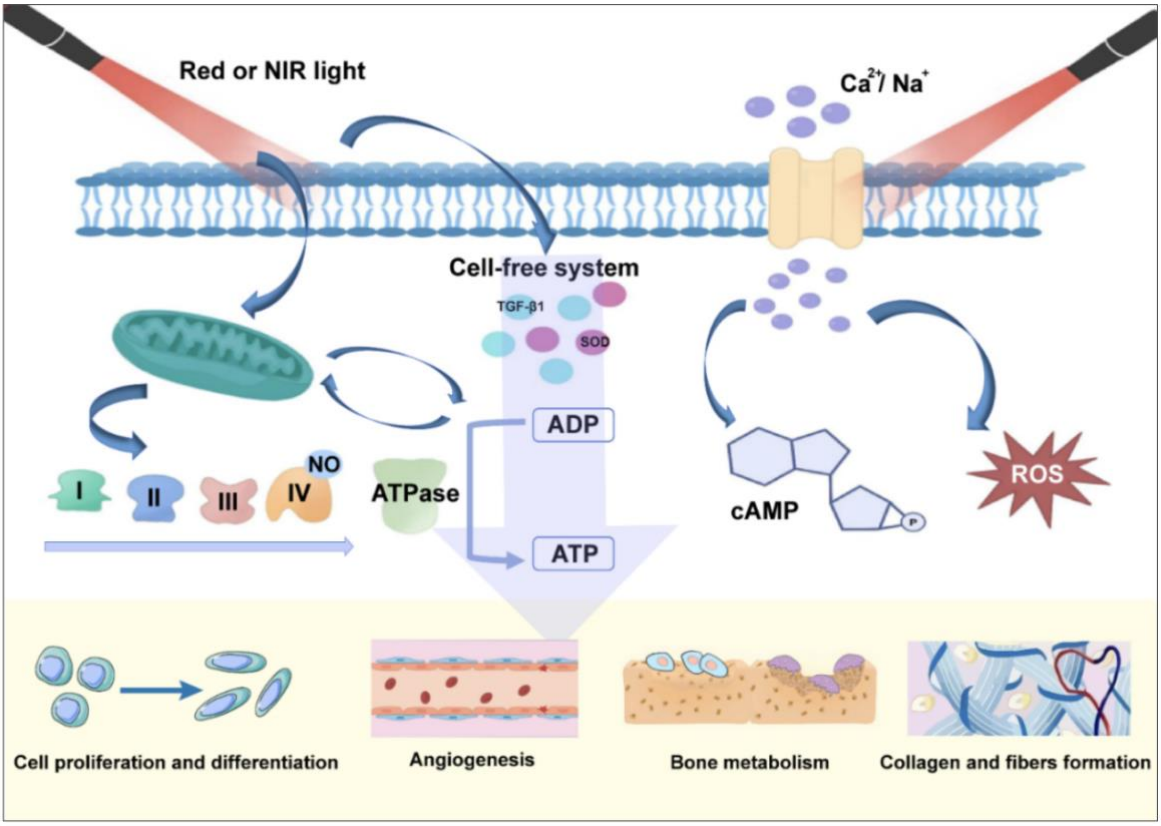

Figure 4 A schematic representation of the photobiomodulation action on the mitochondria, cAMP and ROS as well as on the cell-free system [7].

The second hypothesis states that when PBM is applied there is an increase in cAMP and calcium concentration in the cellular matrix, caused by the activation of light-sensitive ion channels, affecting osteogenic differentiation indicators, which allow calcium to enter the cell [7,32]. The increased calcium and cAMP concentration together with ROS and NO will trigger signaling pathways that activate transcription factors which enhance gene-related protein synthesis, cell migration, cell proliferation, anti-inflammatory signaling, anti-apoptotic proteins, and antioxidant enzymes [7,32]. Additionally, PBM might enhance bone healing by controlling sodium channels [7].

PBM has been shown to activate TGF-ß1 and superoxide dismutase within the cell-free system to improve stem cell differentiation and help the regeneration of dental tissue [7].

It is speculated that PBM could increase angiogenesis, as an increase in the expression of growth factors such as vascular endothelial growth factor (VEGF), basic fibroblastic growth factor (bFGF), and angiogenic genes, were observed [7].

Some studies hypothesize that PBM could be able to regulate inflammatory cytokines such as the reactive oxygen species (ROS) and TGF-ß1 response, as their result reveals that a wavelength of approximately 623 - 660 nm shows an increase in the ROS and TGF-ß1 levels, whereas a higher wavelength of 970 nm has shown a decrease the ROS level in neutrophil polymorphonuclear (PMN) granulocytes, thus the wavelength is the factor affecting the level of ROS in different cells [7]. An increase in ROS level would aid in the accelerated ATP production throughout the OTM process seen in Figure 4 [7].

PBM could increase the pro-inflammatory effect during OTM, as it may be able to increase macrophage activity by aiding the differentiation of monocytes into macrophages [7].

Some studies found an increased interleukin-1ß (IL-1ß) in the gingival cervical fluid of the compression side after PBM which is beneficial for bone remodelling [7]. Some studies, however, hypothesized that the increased IL-1ß is due to the stretched periodontal ligament rather than from the PBM [7].

PBM has been shown to decrease critical regulators of nociceptors including PGEs and IL-1ß [7]. If the correct duration of application is applied, this would cause pain relief [7].

PBM could improve wound healing as it has been shown to impact collagen synthesis and fibrogenic-related processes [7]. Studies have shown that PBM inhibits plasminogen activator (PA) activity, during orthodontic treatment to prevent tissue damage, as PA can promote plasmogen transition into plasmin which is seen when the PDL is under stress [7]. Furthermore, PBM may be able to enhance signaling pathways which play an important role in fibroblast proliferation and gene transcription to positively affect wound healing [7].

Through animal studies, it was seen that PBM has demonstrated an enhanced effect on non-mineralized tissue generation, as there was an up-regulation of RANKL and matrix metalloproteinase-13 (MMP-13) and an increase in fibroblasts [7]. Through histological staining, there was a visibly heightened basic fibroblast growth factor (bFGF) in the periodontal ligament of rabbits after PBM [7]. There was an increase in type I collagen and elastin expression and a more even collagen distribution post-PBM, all this suggesting a potential for promoting tissue healing and regeneration via PBM [7].

3.3 THE EFFECT OF LLLT ON BONE REMODELLING

Bone remodelling is the basis for tooth movement and controls the rate at which tooth movement occurs [8]. This intricate phenomenon is a result of an inflammatory process as orthodontic forces are applied to the teeth, where chemical mediators such as cytokines, interleukins, growth factors, RANKL receptors, and osteoprotegerin play a major role [8]. It is imperative for orthodontists to be aware of the impact certain medications wield on the bone remodelling rate. Notable examples include NSAIDs, bisphosphonates, exogenous thyroxine, and steroids each of which should be carefully considered in the orthodontic context, nonetheless will not be taken into investigation in this review [34].

As previously discussed, bone remodelling is a continuous process throughout orthodontic treatment where pressure by orthodontic forces causes osteoclasts to break down bone whilst osteoblasts rebuild the bone, which guides the tooth into its new position, a schematic representation of the process can be seen in Figure 5 [35].

Significantly, osteoblast differentiation is being mediated by osteoprogenitor cells under the influence of bone morphogenic protein (BMPs), transforming growth factor (TGF-ßI and II), insulin-like growth factor (IGF-I and II), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), while osteoclasts differentiation is influenced by colony-stimulating factor (CSF), receptor activator of nuclear factor-kappa B ligand (RANKL), osteoprotegerin (OPG), and bone morphogenic proteins (BMPs) [9].

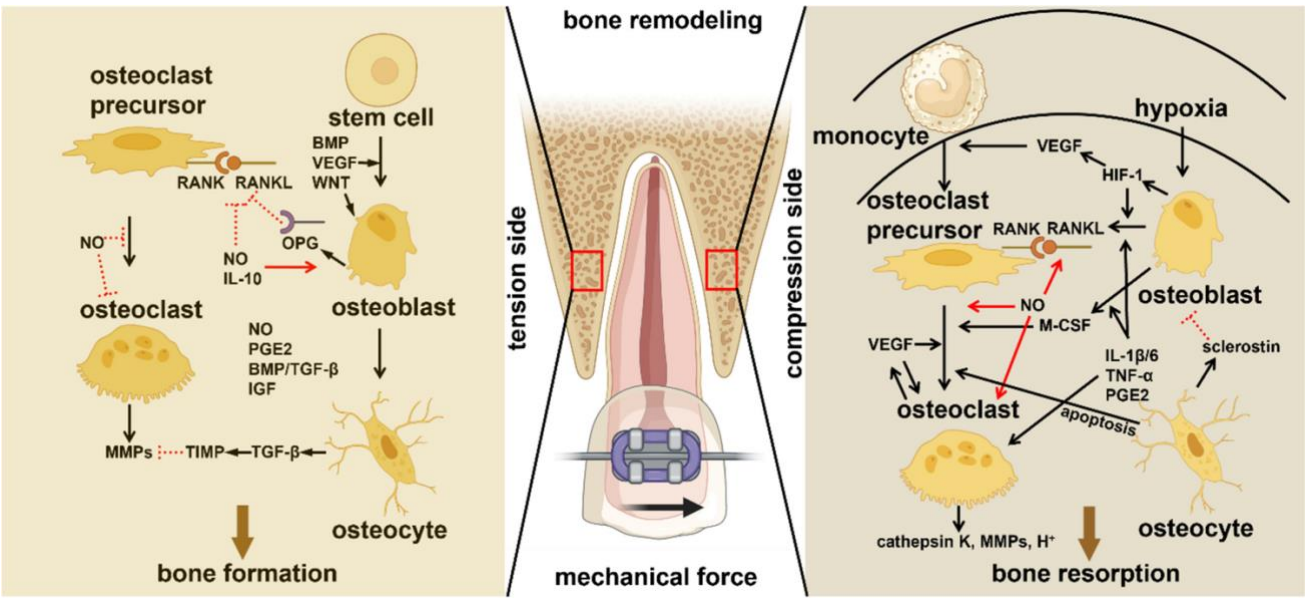

Figure 5 Schematic representation of the process of bone remodelling through orthodontic force [35].

To assess bone remodelling on a cellular level most of the studies analyse the cytokines level in the gingival cervical fluid (GCF), using paper pointers which are then analysed using the Enzyme-linked immunosorbent assay (ELISA) method [31,36–40]. The main cytokines studied are RANKL, IL-1ß, IL-6, IL-8 and OPG [38].

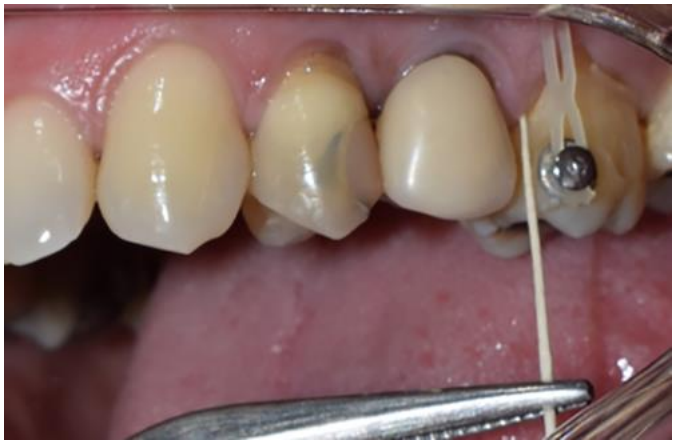

Figure 6 A representation of cervicular fluid sampling [31].

RANKL or receptor activator of nuclear factor kappa beta (NFkB ligand) is a part of the membrane-associated tumor necrosis factor ligand family [29]. It is anchored in the cellular membrane and works as a biomarker for the regulation of osteoclastogeneses [29]. RANKL aids in the activation and production of osteoclasts [29]. Therefore a higher RANKL concentration would mean a higher bone resorption leading to accelerated OTM [29].

OPG on the other hand plays a central biological role as it binds to RANKL and interferes with its binding to other receptors which stops the differentiation and activation of osteoclasts and thus halters bone to break down [29]. Therefore, it is advantageous to have a lower concentration of OPG if you want to have a high osteoclast concentration [29].

The ratio of RANKL/OPG is commonly used to present bone resorption. This is associated with root resorption both in an orthodontically and functionally induced way [29].

IL-1ß is a pro-inflammatory cytokine that is released by different cells as a reaction in the presence of mechanical stress and is therefore the most studied [29,38]. It is associated with the efficiency at which the alveolar bone is rebuilt, as RANKL- expression stimulates the differentiation

of osteoclast-like cells [29]. This process can be detected from the beginning of the OTM to the end [29].

IL-8 and IL-6 are other cytokines regularly studied throughout orthodontic tooth movement [29]. IL-6 is active in immunoreactive areas and inflammations, it induces osteoclast production that aids in bone resorption [29]. IL-8 on the other hand participates in the differentiation of osteoclasts, in areas of orthodontic stress [29]. It also aids in angiogenesis by affecting the migration, invasion, and proliferation of endothelial cells via their receptors [29].

In a study by Fernandez et al., 2019 to assess the rate of orthodontic tooth intrusion throughout LLLT, the study used a low-power diode laser of 808 nm, 100 mW and a density of 25 J/cm^2 to measure the amount of tooth movement [31]. The GCF was analysed monthly for inflammatory mediators namely IL-6, IL-8, and IL-1ß [31]. The extraction of GCF was done using paper pointers in the gingival sulcus, which were then assessed using the enzyme-linked immunosorbent assay (ELISA) [31].

The findings showed a 34% faster tooth movement when using LLLT in comparison to the conventional orthodontic extrusion [31].

Throughout the study as the orthodontic force was applied, there was a constant increase in the cytokine levels of both the placebo and the laser group, the results can be seen in Figures 7, 8 and 9 [31]. The results show higher IL-1ß levels in the laser group when compared to the control group, which were especially present at day 30 [31]. Throughout the study, there was a decrease in the IL-1ß concentration in the laser and the non-laser group [31].

IL-6 and IL-8 levels were also constantly higher in the laser group when compared to the non-laser group and we can see that there was a constant increase in IL-6 and IL-8 levels in both the laser and non-laser group [31].

The findings suggest that LLLT enhances bone metabolism as the cytokine analysis indicates differences in inflammatory mediators between the laser and non-laser groups.

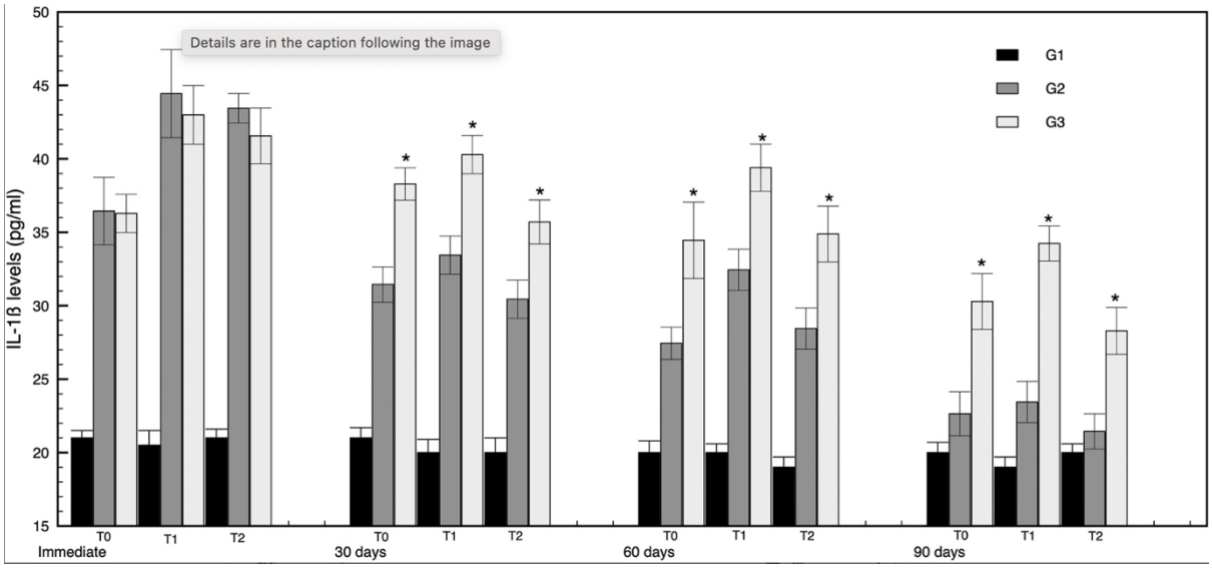

*Figure 7 Shows the different concentration levels of IL-1ß for the control group (G1), the group with orthodontic appliance but without LLLT (G2) and the group with orthodontic appliance and LLLT (G3), the * symbol represents a statistically significant difference determined by intragroup analysis* [31].

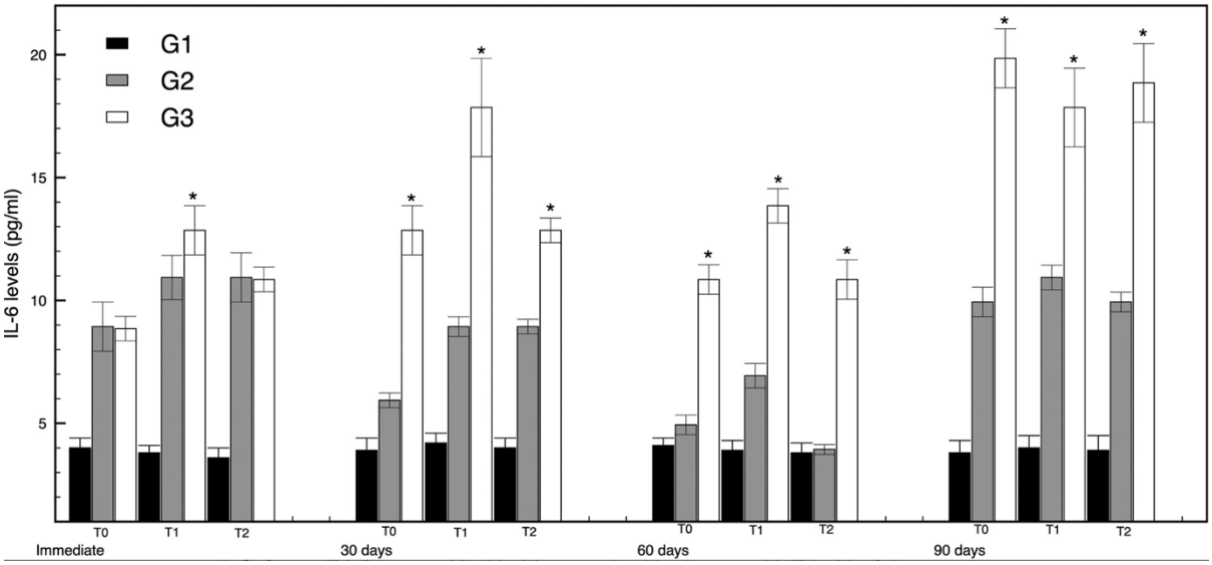

*Figure 8 Shows the different concentration levels of IL-6 for the control group (G1), the group with orthodontic appliance but without LLLT (G2) and the group with orthodontic appliance and LLLT (G3), the * symbol represents a statistically significant difference determined by intragroup analysis* [31].

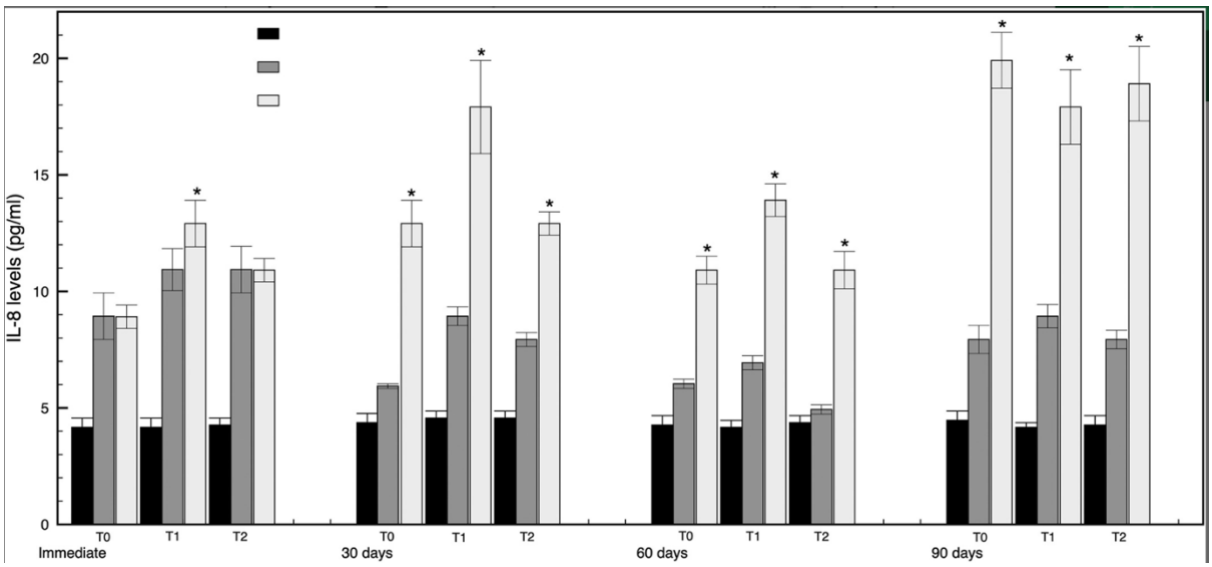

*Figure 9 Shows the different concentration levels of IL-8 for the control group (G1), the group with orthodontic appliance but without LLLT (G2) and the group with orthodontic appliance and LLLT (G3), the * symbol represents a statistically significant difference determined by intragroup analysis* [31].

On the contrary, a similar study was done by Murakami-Malaquinas-Silva et al. which showed different results [36]. They assessed the differences of orthodontic tooth movement with the laser of 808 nm wavelength and 100 mW power, they also used the ELISA method for analysing the cytokines, while only applying the laser 5 times throughout the study, which is a 40% lower application when compared to Fernandes et al. [31,36]. Throughout the study they wanted to evaluate the cytokine levels in the GCF of TNF-α, IL-6 and IL-1ß levels [36].

Their results showed low expressions for the TNF-α and IL-6 so that they could not be taken into account, they suggest this might have been due to the high radiation exposure where higher doses (>2 J/cm^2) may have an inhibitory effect on IL-6, while smaller dosages (<2 J/cm^2) have the potential to increase the IL-6 concentration [36]. As they were using a 25 J/cm^2 they would fall into this category, nonetheless, Fernandes et al. were using the same 25 J/cm^2 density and found results for the expression of IL-6 [31,36].

When analysing the IL-1ß levels, the results showed a statistically significant difference in the levels of IL-1ß when comparing the placebo to the laser group [36]. The differences were visible after 72h when the laser group showed a stable value for the IL-1ß cytokine, and the placebo group showed a steady increase [36]. Some studies suggest that this shows a controlled inflammation which is beneficial to bone remodelling and pain control, regardless the results of this study show that there

was no statistically significant impact on pain observed [36]. However, the laser group had a 10% faster OTM velocity compared to the control group [36].

These findings show the controverse results in the different LLLT studies. They are indicating that the parameters and in this case the frequency of application can have drastic impacts on the velocity and cytokine levels when LLLT is used during orthodontics.

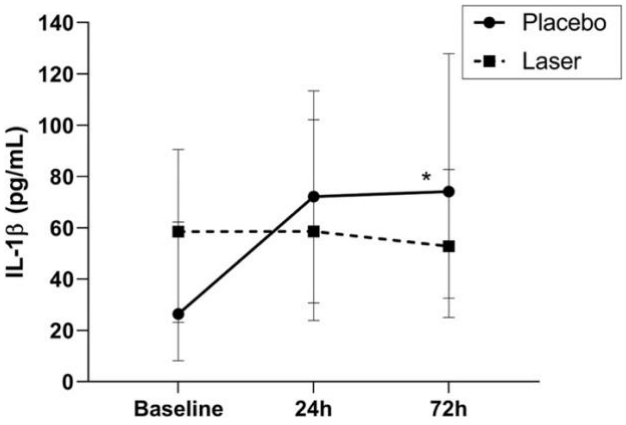

Figure 10 Shows the results of the IL-1ß level in the placebo group and the laser group, in the study of Mukrami-Malaquias-Silva et al. [36].

In a different study by Domínguez et al. which measured the RANKL and OPG concentration in the GCF via the ELISA, they used a different laser as the previous 2 studies discussed [37]. This study used a diode laser device operating at continuous wave, 670 nm wavelength, 200 mW power output, and 6.37 W/cm2 energy density [37]. Their results showed statistically significant differences regarding the OTM rate as there was an approximately 37.6% faster tooth movement in the laser group when compared to the control group, indicating an increased bone resorption [37]. No statistically significant difference between the two groups was noted in the values of RANK and OPG [37].

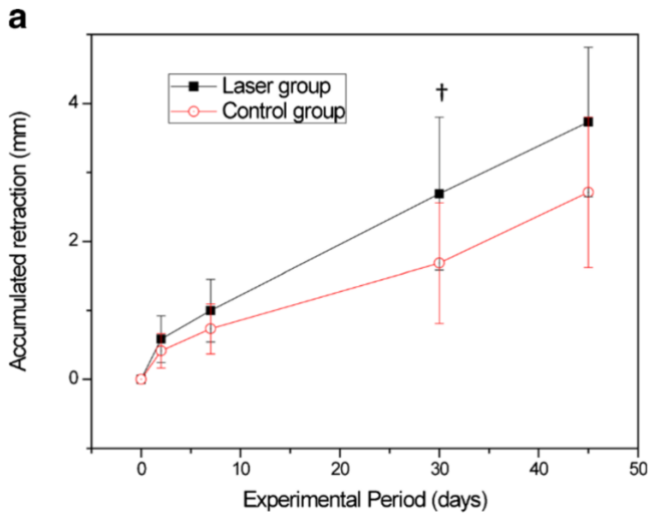

Figure 11 Representing the retraction measurements in the laser and control group. It is visible that the laser group has a constantly faster retraction when compared to the control group [37].

Another research by Zeng and Yang in 2021 used the semiconductor diode laser where the parameters were a wavelength of 810 nm, a power output of 100 mW and an energy density of 6.29 J/cm^2 in continuous wave mode [38]. Similarly to the other studies it was seen that the laser group had a higher rate of OTM, with a 35% faster retraction rate of OTM in the laser group when compared to the placebo group [38].

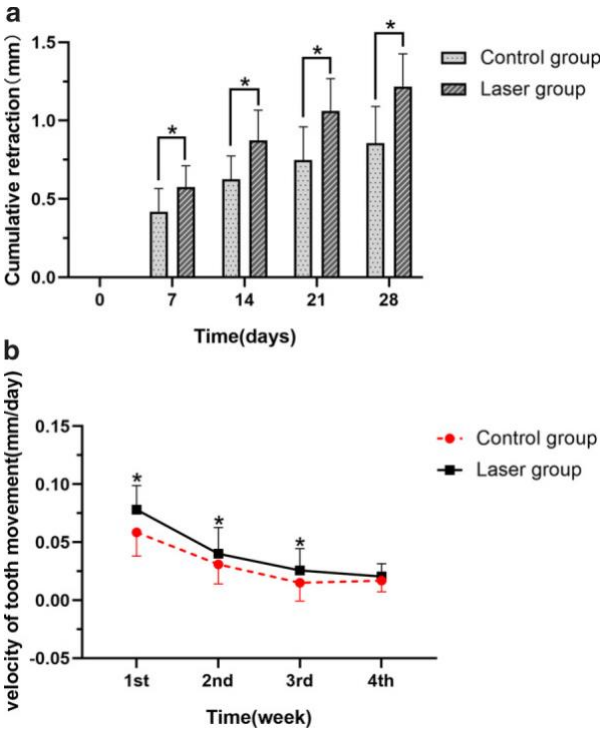

Figure 12 Shows the movement and velocity of the laser group and the placebo group, there was a statistically significant difference found when the groups were compared [38].

Throughout the study Zheng and Yang also measured the OPG, RANKL, and IL-1ß levels, the results can be seen in Figure 13 [38]. When looking at the RANKL values there was a statistically significant difference between the control and the laser group, the RANKL values were constantly increased in the laser group, when compared to its baseline with a peak RANKL level at day 21 [38]. The control group on the other hand had practically constant RANKL values [38]. The findings suggest that the application of laser had a noticeable effect on the RANKL level in the GCF [38].

The OPG concentration levels were statistically significantly different on day 7 of the trial as there was a much larger decrease seen in the laser group when compared to the control group [38]. As well as this the IL-1ß levels were statistically significant as there was a higher increase in IL-1ß levels seen in the laser group when compared to the control group [38].

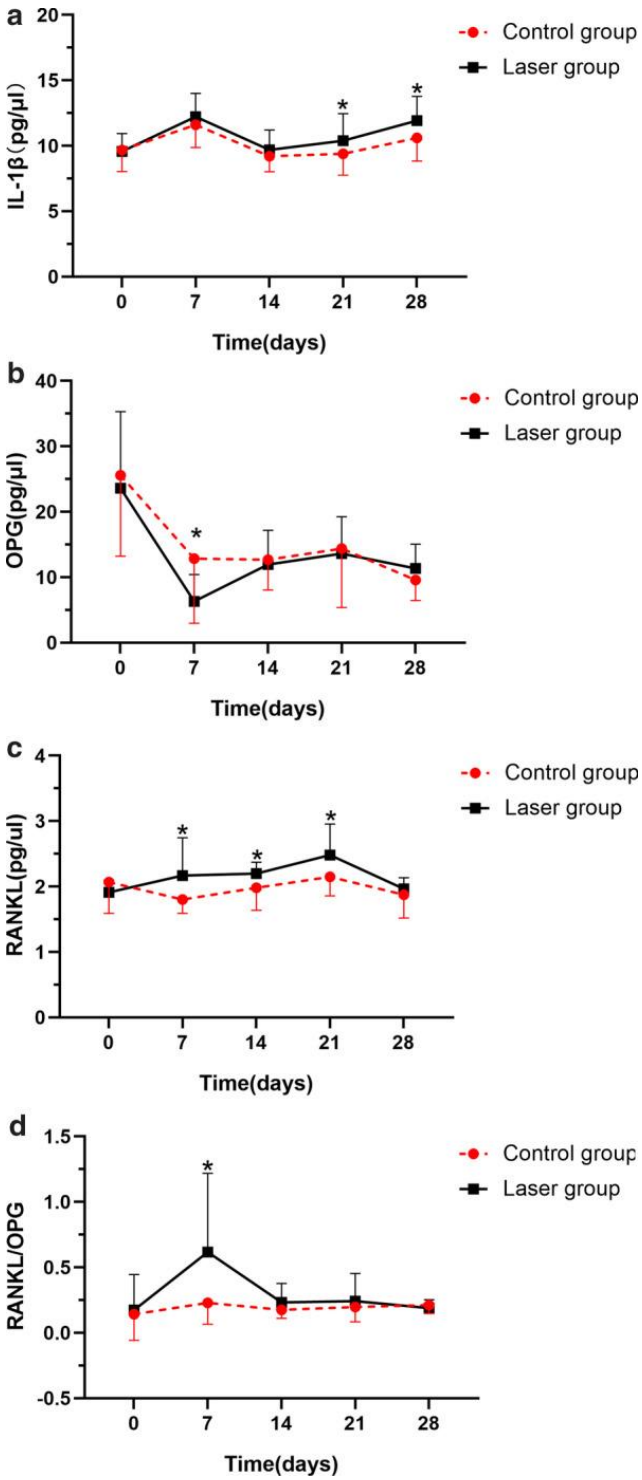

*Figure 13 The graphs show the different cytokine levels in the GCF in the control and laser group: a) shows the IL-1ß level, b) the OPG level and c) the RANKL level in the GCF, d) shows the RANKL/OPG ratio, the * shows where there was a statistically significant difference* [38].

Similarly, a study conducted by Üretürk et al., which focused on the analysis of LLLT during canine distalization assessed the IL-1ß concentration in the GCF and demonstrated a statistically significant increase in the IL-1ß at the compression side [39]. Nevertheless, the tension side showed no significant difference in IL-1ß levels when comparing the control to the laser group [39].

Likewise, significantly higher IL-1ß concentrations in the GCF were revealed in the study by Varella et al., who used a diode laser with a wavelength of 940 nm, an energy density of 8 J/cm2 and a power output of 100 mW, to assess the effect LLLT has on the rate of OTM [40].

The review by Reis et al. studied the PBM effect on OTM, by systematically evaluating various studies which assessed the cytokines concentration in the GCF after LLLT or LED application [29]. They observed inconsistent results in the IL-6, RANKL and OPG levels of the GCF post PBM treatments [29].

Their results revealed a consistent trend of the PBM effect on bone remodelling through LLLT as most studies indicated an increase of the IL-1ß, IL-8, osteopontin (OPN) and Prostaglandin E2 (PGE2) levels [29].

Interestingly, the IL-1ß levels were statistically significant in the LLLT studies having constant higher results, contrarily the only study which did not result in increased IL-1ß levels was by Ekieser et al. who used an LED device to achieve a PBM effect [41]. This suggests that the biomolecular effect exerted on IL-1ß is higher in LLLT than that of LED devices.

Through the persistent divergence in the results of studies, the question remains: What are the underlying factors contributing to the variations in results? An inconstant variable throughout all studies was the laser parameters namely: the type of laser its wavelength, power output, etc. Another factor may be the type of tooth movement studied. Consequently, this creates difficulty when establishing a direct comparison of results.

Regardless, several studies had similar observations: *the increase in orthodontic tooth movement velocity and increased cytokine levels of the GCF post-LLLT.*

Based on these observations it becomes apparent that further studies must be available, to establish unanimous statistically significant results when assessing the impact of LLLT on bone remodelling via the cytokine levels in the GCF. Furthermore, it is important to state that the results should be handled with caution due to the low evidence base.

3.4 THE EFFECTIVENESS OF LLLT ON TREATMENT TIME

Throughout orthodontic treatment there are several side effects such as root resorption, caries, gingivitis and alveolar bone loss which are dependent on the treatment time [4]. Reducing the treatment time can establish a smoother and less side-effect-prone orthodontic therapy, as well an increase in patient satisfaction [5].

Bone remodelling, tooth movement, and treatment time are all intertwined and somewhat in direct correlation. If there is an increased tooth movement due to increased bone remodelling there is a decreased treatment time. How much LLLT impacts the treatment time throughout OTM will be discussed in this part.

The study by Qamruddin et al. and the study by Varella et al. found a 2 times higher tooth movement rate in the laser group when compared to the control group [40,42]. Fernandes et al. observed a 34% faster tooth movement, while Murakami-Malaquias-Silva et al. only a 10% increase was measured [31,36]. Domínguez et al. observed a faster OTM which was not statistically significant [37]. Zeng and Yang reported a 35% increase in OTM in their laser group, and Üretürk et al. found a 40% increase in velocity of OTM in the laser group [38,39]. It is important to identify every parameter used in each of the studies to be able to establish a better comparison of results. The different parameters of each study assessed in this review are shown in Table 1.

A review by Chintavalakorn et al. assessed 25 studies for the acceleration of tooth movement [43]. Their results showed that 21 studies showed a positive impact of LLLT in the acceleration of tooth movement [43]. Similarly, Fini et al. had come to the same conclusion: most articles they had studied described a significant positive impact on accelerated tooth movement when LLLT was applied [27].

Most studies and reviews point to an accelerated tooth movement when LLLT is applied [27,43]. Nonetheless, there is no homogeneity in the results that can be caused by the different parameters and study environments [31,36–40,42].

Table 1 Comparison of study parameters and tooth movement velocity.

Study	Increase in velociy	Laser wavelength	Laser power output / Energy density	Type of laser	Output	Output	Application frequency
Qamruddin et al.	100%	940 nm	7.5 J/cm2	Gallium-aluminum-arsenic diode laser	100 mW	continous wave	baseline and repeated after 3 weeks for 2 more consecutive follow-up visits
Murakami-Malaquias-Silva et al.	10%	808nm	25 J/cm^2	infrared diode laser	100 mW	continous wave	Immediately, 24 h, 72 h, 1 month, and 2 months after activation
Fernandes et al.	34%	808nm	25 J/cm2	Low-power diode laser	100 mW		Immediately, 3 days, and 7 days after force application
Domínguez et al.	37,64%	670nm	6.37 W/cm²	diode laser device	200mW	continous wave	Days 0, 1, 2, 3, 4, and 7 in the laser group
Zheng and Yang	35%	810nm	6.29 J/cm^2	diode laser device	100 mW	continous wave	days 0, 7, 14, and 21
Üretürk et al.	40%	820nm	5 J/cm2	Gallium- aluminium AlAs diode low-level laser	20 mW	continous wave	day 0, 3rd, 7th, 14th, 21st, 30th, 33rd, 37th, 60th, 63rd, and 67th days)
Varella et al.	100%	940 nm	8 J/cm²	Gallium-aluminum-arsenide semiconductor diode laser	100 mW		Applied immediately after spring activation, Three consecutive days at specific intervals: Start of canine retraction, 4 weeks later, 8 weeks late

Various surgical, pharmacological and non-surgical techniques have also been proven effective in accelerating OTM and their comparison to LLLT is important for the understanding of the overall effect it has throughout orthodontic treatment [44].

Surgical techniques for accelerating orthodontic tooth movement and decreasing treatment time have shown positive results [45].

Corticotomy is one of the most used orthodontic acceleration procedures, which has been consistently studied [46]. It consists of small cuts or perforations in the cortical bone to accelerate orthodontic tooth movement by inducing a regional acceleration phenomenon (RAP) associated with perfusion and bone turnover increasing and decreasing bone density [46]. The review conducted by Gasparro et al. evaluated surgical acceleration techniques and showed a notably accelerated orthodontic tooth movement rate through corticotomy, ranging from 2- 4 times faster when compared with conventional treatment methods [6]. In comparison to LLLT cortictomies demonstrated an overall faster tooth movement rate [6]. The negative aspects of cortictomies is having frequent side effects such as pain, swelling and dentin hypersensitivity [6].

Piezoexcision, an orthodontic acceleration method that uses specialized instruments to make small incisions through the soft tissue using copious amounts of irrigation, was found to have low-quality evidence so that no statistically significant difference in treatment time could be determined [6]. Most systematic reviews studied showed a short-term effect of piezoexcision where treatment time was only effectively decreased within the first 1-3 months of treatment [6].

Microosteoperfortation (MOP) is a surgical orthodontic tooth movement acceleration method that consists of pinhole perforation made around the tooth which needs orthodontic tooth movement [6]. Most systematic reviews showed no statistically significant increase in OTM by microsteoperforation when compared to conventional orthodontic treatment [6].

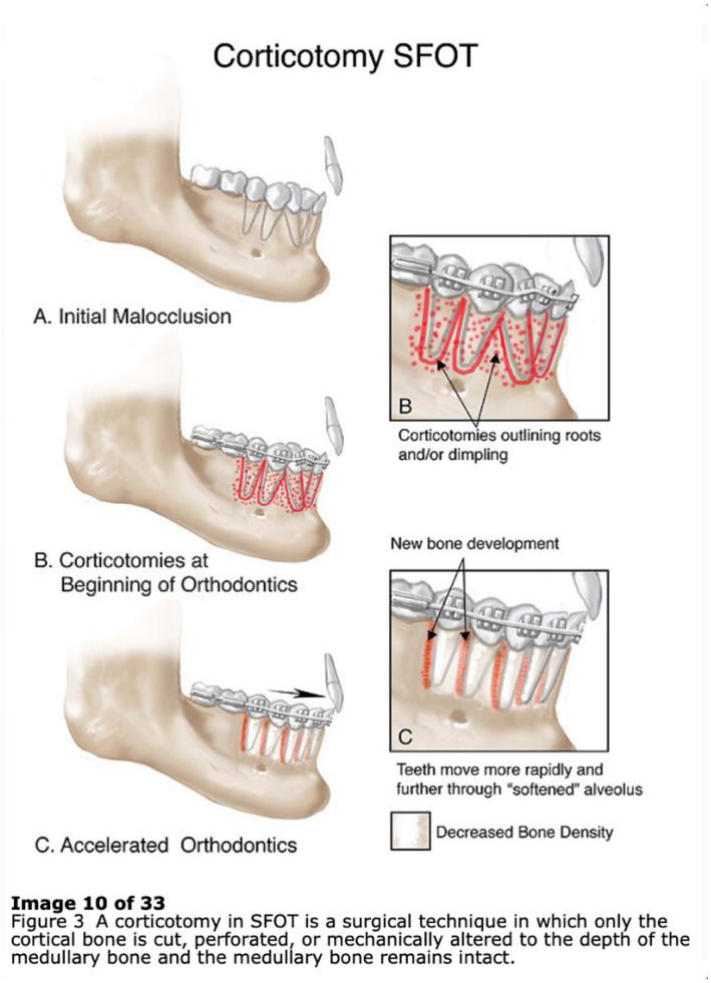

Figure 14 A schematic representation of a corticotomy [47].

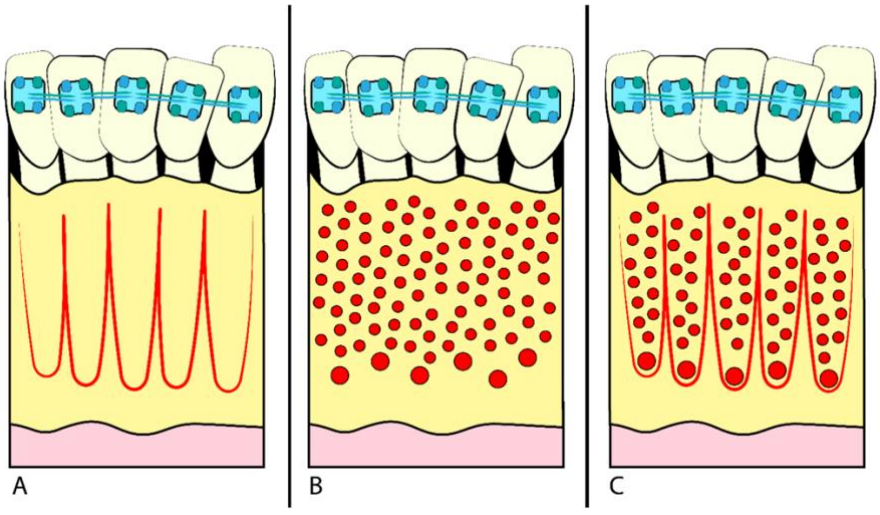

Figure 15 A schematic representation of A) Corticotomies B) MOP and C) Corticotomies combined with MOP [48].

There are several hormones such as growth hormone, beta-2-adrinergic, thyroxine and vitamin D which have been used to accelerate orthodontic tooth movement and stimulate cellular processes [44,49].

Growth hormone (GH) increases osteoblast proliferation and differentiation [44]. It induces protein synthesis and mineralization [44]. Therefore it was used to accelerate orthodontic tooth movement in rats, nonetheless it did not show promising results as even though the osteoclast number increased, bone angiogenesis was decreased [50]. The synchronization and metabolism of bone remodelling were disturbed, and GH did not show effective results for the clinical environment of orthodontic therapy [44,50].

Parathormone (PTH) intake results in an increase of osteoblasts, RANKL and activates osteoclasts as it binds to osteoblast receptors which produce insulin-like growth factor 1 (IGF-1) [51]. It was found in animal studies that intermittent PTH intake can be effective in OTM [52–54]. Nonetheless there is a lack of consistent evidence to show the effectiveness of PTH in orthodontic acceleration [52–54].

Vitamin D also activates osteoclasts and aids in their differentiation [44]. Animal studies have shown an effective decrease of orthodontic tooth movement time after vitamin D administration which varies from a 23 – 60 % increase in the rate of OTM [44]. More studies are necessary, to have evidence-based scientific results [44].

Thyroxine has been shown to decrease orthodontic treatment time in animal studies, an increased concentration of IL-1ß was detected after thyroxine intake [55]. Even though thyroxine may be able to aid in orthodontic acceleration the health-related changes that induce metabolic disease are not worth compromising for an accelerated treatment time [44,55]. It is noteworthy to consider thyroxine intake if patients with hypo- or hyperthyroidism undergo orthodontic therapy [44].

Beta-2-adrenergic antagonists stimulate osteoblasts to undergo osteoclastogenesis through a complex process, that could be used to decrease orthodontic treatment time [44].
However, no clinical trials are proving a statistically significant effectiveness in orthodontic acceleration with the use of beta-2-adrenergic antagonists [44].

Vibration therapy has been shown to prevent or minimize bone loss in individuals, especially post-menopausal woman suffering from osteoporosis, it has been shown to restore bone density [56].

The impact of high-frequency vibrations (HFV) in orthodontic acceleration is determined by the orthodontic force exerted and its corresponding load towards the alveolar bone and the periodontal ligament, where the effects can be anabolic or catabolic [57]. Intraorally high-frequency vibrations are above or equal to 90 Herz and low-frequency vibrations above or equal to 45 Herz [57]. The catabolic effect is increased via HFV in response to an orthodontic compressive force [58]. It enhances the recruitment, differentiation and proliferation of osteoclast cells crucial for tooth movement [58]. In the review by Fernanda et al. to determine the effectiveness of vibrations on orthodontic acceleration there were divergent results mainly indicating no statistically significant impact of vibration therapy on orthodontic acceleration [57]. The majority of studies are working with different vibrations making a direct comparison difficult [57]. Thus there is no conclusive result as more studies are needed to have a qualitative and quantitative conclusion of the effectiveness of vibrations on OTM [57].

LED works similarly to LLLT, a recent study comparing LLLT to LED found that only LLLT had a statistically significant impact on the rate of OTM, with up to 60.8% faster tooth movement in the LLLT group compared to the control group [30]. The LED group had a 26% increased OTM rate compared to the control group [30]. Different studies using different LED devices have been shown to have an even higher rate of OTM acceleration, where OTM could be accelerated up to 60%, by a LED device [30].

Amongst various orthodontic acceleration modalities corticotomy and LLLT have been shown to yield consistently positive results concerning the rate of orthodontic treatment time. Notably, corticotomy has been particularly efficient in increasing the rate of OTM. However, it is crucial to acknowledge the side effects and invasiveness of the procedure which may leave orthodontists and patients sceptical about its convenience.

3.5 THE EFFECT OF LLLT ON ROOT RESORPTION

Orthodontically induced inflammatory root resorption (OIIRR) is a common side effect throughout orthodontic treatment that may be unavoidable [59]. It affects approximately 90% of orthodontic patients [59].

OIIRR is the pathological loss of tooth structure induced by the inflammatory response during orthodontic tooth movement. In most cases it is clinically insignificant as there is only a minimal

amount of OIIRR [60]. OIIRR depends on risk factors which can be divided into patient factors as well as treatment-dependent factors [61].

The treatment factors include the

- duration of orthodontic treatment [60,61]
- orthodontic forces for which stronger forces have shown a higher risk for OIIRR [60,61]
- orthodontic appliances used affect the force on the respective tooth and therefore must be considered [60,61]
- type or amount of tooth movement required can affect the biological mechanical factors so that some tooth movements are more prone to OIIRR [60,61]

The patient risk factors include [60,61]

- the genetics as some patients are more prone to OIIRR than others [60,61]
- anatomical shape of the tooth- some tooth root shapes are more prone to root resorption than others [60,61]
- history of traumatic injury to the tooth- teeth affected by previous trauma have been found more prone to root resorption [60,61]
- allergies [60,61]

As there has been a correlation of treatment time and OIIRR, it is understandable that LLLT may impact the amount of OIIRR.

In the review by Yamaguchi and Fukasawa discussing the importance and downsides of the inflammatory reactions occurring during orthodontic treatment, they found that inflammation causes accelerated OTM as well as OIIRR [61]. Therefore it is vital to understand the importance of a well-balanced inflammatory reaction throughout orthodontic therapy [61].

The research showed that there is a lack of homogeneity in the study results concerning the positive impact of LLLT on root resorption and reported no statistically significant effect of LLLT on OIIRR [61]. Chatakovska et al. noted no clear evidence for an effective decrease in OIIRR during orthodontic treatment accelerated via LLLT, as only recent studies report a positive effect on OIIRR by LLLT [43]. Similarly, Michelogiannakis et al. who reviewed the influence of LLLT on OIIRR concluded a heterogeneity in results and therefore no statistically significant effectiveness of LLLT in diminishing OIIRR [60]. It may be important to note that the review included animal and human studies [60].

Contrarily, the influence of RAP seen through surgical orthodontic acceleration techniques was found effective in decreasing OIIRR [61]. Concluding, that surgical methods for orthodontic

tooth acceleration- such as corticotomy- have been researched in aiding the reduction of OIIRR than LLLT [61].

3.6 THE EFFECT OF LLLT ON VASCULATURE AND BLOOD CIRCULATION

Angiogenesis is thought to be the first change occurring through LLLT [7]. It is the basis for building the vascular supply of bone remodelling [7]. Animal trials have discovered that LLLT could promote angiogenesis [7,62,63]. It is suggested that LLLT stimulates angiogenesis-related Src/ERK/STAT3 signaling pathways, which lead to an up-regulation of thrombopoietin and vascular endothelial growth factor (VEGF) as they increase reactive oxygen species (ROS) levels [7].

The “hypofunctional condition” seen in patients with malocclusion refers to the narrow periodontal ligament and lower bone mineral density causing a lower basic fibroblastic growth factor (bFGF) and VEGF [7]. In animal studies it was shown that the bFGF and VEGF levels were at a normal level post orthodontic treatment and LLLT [7].

Interestingly a study by Vitor et al. found that PBM using LLLT has a stimulatory effect on pulp angiogenesis via angiogenetic protein secretion through fibroblast [64]. Namely the study found an increase in VEGF-A, VEGF-C and VEGFR1 and a significant up-regulation of BMP-9 post LLLT [64].

Overall studies suggest a correlation between increased CCO concentrations and HbO, which have the effect of an improved mitochondrial oxygen consumption rate post-LLLT [7]. The pathway is schematically represented by Figure 16.

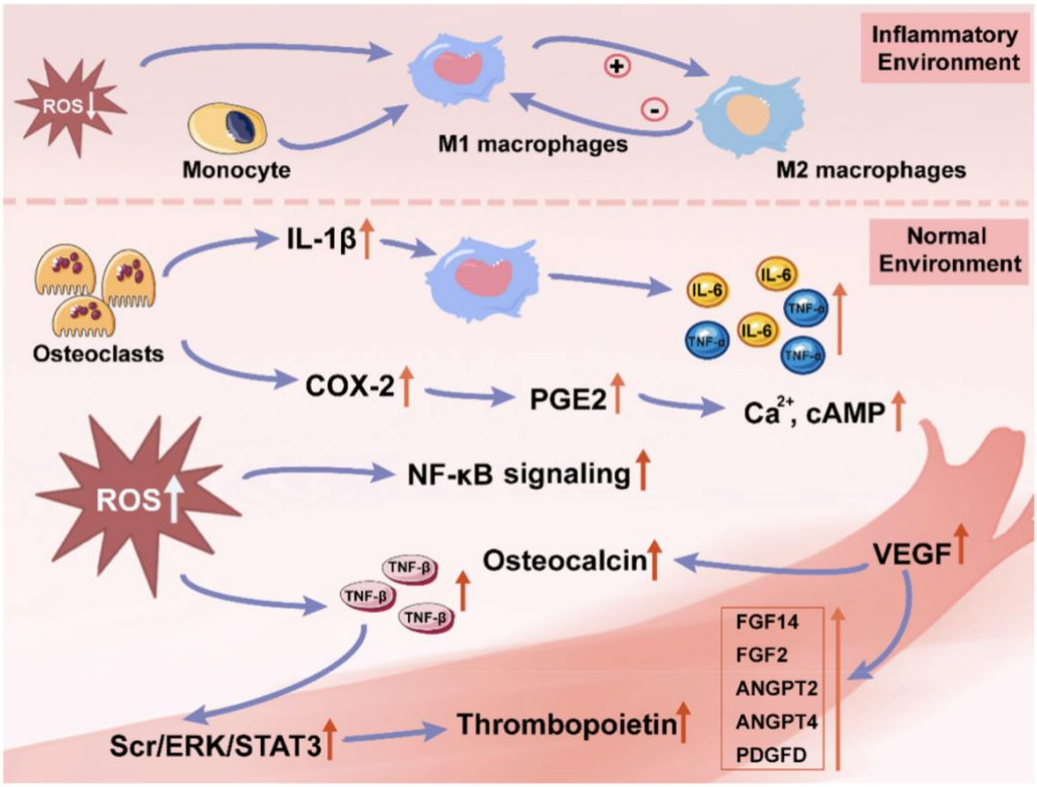

Figure 16 A schematic representation of the effect of photobiomodulation on vasculature: two possible outcomes are shown: one in an inflammatory environment and another in the normal environment [7].

IV. THE DISADVANTAGES AND SIDE EFFECTS OF LLLT

A majority of conducted studies stated no significant side effects with the application of LLLT in orthodontic acceleration [43]. While this is true for the biological aspect it is imperative to acknowledge certain downsides of LLLT.

The primary concern is the financial burden LLLT places on the patients and orthodontists [65]. The specialized laser equipment comes at a high economic cost, though there has been a price decrease, it is still significantly higher than an LED laser application [43,65]. The longer treatment time and frequent orthodontic consultations create an even higher impact to the economic burden [65].

The laser safety concerns should also be considered, specifically the utilization of protective eyewear for the patient and orthodontist through the orthodontic acceleration procedure with low-level laser devices [43].

Moreover, the technique sensitivity emerged as a vital factor in creating a stimulatory effect of LLLT throughout OTM. Beginning with the positioning and angulation of the LLLT handpiece, continued by the correct parameter settings, where too high parameters can create an environment where LLLT does not affect the rate of OTM [43].

The stimulatory effect of LED laser was not as efficient as LLLT, nonetheless the side effects and cost-benefit could make it a much more attractive candidate for accelerated OTM through PBM [30,65]. As well as this the LED equipment is used daily for a couple of minutes, depending on the type of LED device, by the patient himself [66]. While this may be a total of a longer time using the LED device than the LLLT the patient does not need to go to the orthodontic office for in-office treatment, which can be burden for many.

When we compare LLLT to surgical orthodontic acceleration techniques, which have been shown to have a predictable positive outcome in orthodontic acceleration, the physical disadvantages due to their high invasiveness include pain, swelling, and temporary paraesthesia may be a downside which could cause orthodontists and patients to opt for the less invasive LLLT [6]. As well as this the surgical techniques have shown to only accelerate OTM in the first 3 to 4 months, whereas the LLLT would have a constant effect on OTM acceleration [49].

V. CONCLUSION

This literature review has shown that low-level laser therapy exhibits the potential to accelerate orthodontic tooth movement. The positive impact of low-level laser therapy on a cellular and biological level has been shown through its photobiomodulatory effect as well as its impact on bone remodelling and treatment time. When comparing low-level laser therapy to alternative orthodontic acceleration techniques orthodontists and patients could opt for low-level laser therapy due to its low side effects, rather than corticotomies which are currently the most effective technique in increasing orthodontic tooth movement. The fluctuation in results, low evidence and varying parameters used in each study cause skepticism about its effectiveness. To implement low-level laser therapy in daily orthodontic practice, there is a need to establish predictable outcomes through further quantitative and qualitative studies.

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FIGURES

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