Aus der Poliklinik für Kieferorthopädie
der Universitätsmedizin der Johannes Gutenberg-Universität Mainz

Low-Level-Laser-Therapy as an adjuvant therapy for bone regeneration during Rapid Maxillary Expansion and its benefits for the patient
- A systematic review -

Low-Level-Laser Therapie zur Knochenregeneration bei der forcierten Gaumennahterweiterung - eine systematische Übersichtsarbeit -

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Johannes Betschel
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Wissenschaftlicher Vorstand:	Univ.-Prof. Dr. Hansjörg Schild
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2. Gutachter:	XXX
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Abstract:

Background: Over the past years, Low-Level-Laser-Therapy (LLLT) has become a topic of research as an adjuvant therapy to Rapid Maxillary Expansion (RME). The objective of this systematic review is to investigate the benefits of LLLT on bone regeneration of the sutura palatina in patients undergoing RME.

Methods: Systematic literature research was conducted until 08.09.2023. The databases National Library of Medicine (via PubMed®), Cochrane Database (via The Cochrane Library) and Web of Sciences Core Collection (via Web of Sciences™) were used. Additionally, a manual search was conducted. The inclusion criteria were LLLT as adjuvant therapy for RME in clinical studies (CS) or animal studies. The language of the included studies was limited to German or English. No further limitations were applied. A Risk of Bias (RoB) assessment was conducted for the CS. In addition, a GRADE (Grades of Recommendation, Assessment, Development and Evaluation) assessment was performed for the question of the benefits of LLLT in RME on the upregulation of bone regeneration of the sutura palatina.

Results: A total of five CS and twelve animal studies were included. The RoB assessment resulted in the classification for three studies with *some concerns* and two studies with *high*. All CS were included into the GRADE evaluation, either completely or as a subgroup. The result was a *very low* quality of evidence. Both the animal studies and the CS, demonstrated heterogeneity in the laser treatment, laser protocol and evaluation methods used. Regardless, the consensus in the animal studies seems to be that LLLT as an adjuvant therapy for RME shows a positive effect on the bone regeneration of the sutura palatina at the molecular, histological and radiological evaluation. The evaluation methods of the CS were conducted using bone density measurement in cone beam computed tomography (CBCT) or occlusal radiographs, or measurement of the distances of the sutura palatina and qualitative assessment of the shape of the sutura margins in CBCT. The results indicated a tendency of the positive effect on bone regeneration of the sutura palatina in the CS. Since the laser parameters and laser protocol varied among the studies, no conclusion could be drawn about its effective application.

Conclusion: Taking the overall low level of evidence into account, the results suggest that LLLT as an adjuvant therapy for RME might upregulate the bone regeneration of the sutura palatina. It has not yet been clarified which laser parameters and laser protocol are most suitable. No potential benefit for the reduction of relapse or treatment duration can be drawn from these results. Further studies dedicated to these issues, as well as more clinical studies investigating the effect of LLLT on the bone regeneration of the sutura palatina, are needed.

Zusammenfassung:

Hintergrund: In den letzten Jahren ist die Low-Level-Laser-Therapie (LLLT) als adjuvante Therapie zur schnellen Gaumennahterweiterung (RME) zu einem Thema aktueller Forschung geworden. Das Ziel dieses Systematik Review ist es, den Nutzen von LLLT auf die Knochenregeneration der Sutura palatina bei Patienten zu untersuchen, die mit RME behandelt werden.

Methoden: Es wurde eine systematische Literaturrecherche bis zum 08.09.2023 durchgeführt. Die Datenbanken National Library of Medicine (über PubMed®), Cochrane Database (über The Cochrane Library) und Web of Sciences Core Collection (über Web of Sciences™) wurden dafür genutzt. Außerdem wurde eine händische Suche durchgeführt. Die Einschlusskriterien waren LLLT als adjuvante Therapie für RME in klinischen Studien (CS) oder Tierstudien. Die Sprache der eingeschlossenen Studien wurde auf Deutsch oder Englisch beschränkt. Weitere Einschränkungen wurden nicht vorgenommen. Für die CS wurde eine Risk of Bias (RoB) Bewertung durchgeführt. Darüber hinaus wurde eine GRADE-Bewertung (Grades of Recommendation, Assessment, Development and Evaluation) bezogen auf die Frage des Nutzens von LLLT bei RME auf eine verbesserte Knochenregeneration der Sutura palatina durchgeführt.

Ergebnisse: Insgesamt wurden fünf CS und zwölf Tierstudien eingeschlossen. Die RoB-Bewertung führte zur Einstufung von drei Studien mit *einigen Bedenken* und zwei Studien mit *hoch*. Alle CS wurden in die GRADE-Bewertung, entweder vollständig oder als Untergruppe, einbezogen. Das Ergebnis war eine *sehr geringe* Qualität der Evidenz. Sowohl in den Tierstudien als auch in den CS zeigte sich eine große Heterogenität in Bezug auf die verwendete Laserbehandlung, das Laserprotokoll und die Evaluationsmethoden. Ungeachtet dessen scheint der Konsens in den Tierstudien zu sein, dass die LLLT für RME einen positiven Effekt auf die Knochenregeneration der Sutura palatina bei der molekularen, histologischen und radiologischen Bewertung zeigte. Die Bewertungsmethoden der CS wurden anhand der Knochendichtemessung im cone beam computed tomography (CBCT) oder okklusalen Röntgenbildern, oder der Messung der Abstände der Sutura palatina und der qualitativen Bewertung der Form der Sutura-ränder im CBCT durchgeführt. Die Ergebnisse in den CS zeigten eine tendenziell positive Wirkung auf die Knochenregeneration der sutura palatina. Da die Laserparameter und das Laserprotokoll in den Studien unterschiedlich waren, konnte keine Aussage über die effektivste Anwendung des Lasers getroffen werden.

Schlussfolgerung: Unter Berücksichtigung der insgesamt geringen Evidenzlage legen die Ergebnisse nahe, dass LLLT als adjuvante Therapie bei RME einen positiven Effekt auf eine verbesserte Knochenregeneration der Sutura palatina haben könnte. Welche Laserparameter und welches Laserprotokoll am besten geeignet sind, konnte nicht geklärt werden. Eine Schlussfolgerung über einen möglichen Nutzen auf ein geringeres Rezidiv und geringere

Behandlungsdauer, lässt sich aus diesen Ergebnissen nicht ableiten. Weitere Studien, die sich mit diesen Fragen befassen, sowie weitere klinische Studien, die die Wirkung von LLLT auf die Verknöcherung der Sutura palatina untersuchen, sind erforderlich.

Content

List of Abbreviations

CBCT	Cone beam computed tomography
CT	Computerized tomography scan
Ga-Al-As	Gallium-aluminium-arsenide
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
In-Ga-Al-P	Indium-gallium-arsenide-phosphide
LED	Light-emitting diode
LLL	Low-level-laser
LLLT	Low-level-laser-therapy
PICO	Population, intervention, comparison, outcome
RANK	Receptor activator for nuclear factor kappa
RANKL	Receptor activator for nuclear factor kappa ligand
CS	Clinical studies
RME	Rapid maxillary expansion
ROS	Reactive oxygen species
RoB	Risk of bias
SARME	Surgical assisted rapid maxillary expansion

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1 Introduction

1.1 Background

Rapid Maxillary Expansion (RME) is a treatment method that can be performed when there is a transverse maxillary deviancy [1-3]. The indication for RME is determined by malocclusions or medical issues caused by transverse maxillary deviancy [2, 4-11]. Therefore, the Pont's Index may be considered as a reference for measuring the transverse arch dimension [12]. The consequences of transversal maxillary deviancy can result in small intercanine arch width, which may lead to frontal crowding, protrusion of the front-tooth and dental Angle Class II/1 or II/2 [4, 5, 13-15]. Furthermore, a posterior crossbite, which may be unilateral or bilateral, can result from transverse maxillary deviancy. This is caused by a reverse transverse interarch relationship between the maxilla and mandible, due to the narrow transversal arch dimension of the maxilla [16].

Apart from the dental effects, further impacts on the health of the patient are the content of current studies. For example, it appears that posterior crossbite may be a contributing factor in the development of masticatory muscle pain and temporomandibular disorder, which does not seem to be sufficiently proven yet. However, in this topic, the association with disc displacement seems more likely [17, 18]. Posterior crossbite might also be related to obstructive sleep apnoea [19]. In this context, studies have demonstrated an increase in the nasal cavity volume after RME [20, 21]. In addition, patients suffering from posterior crossbite are more likely to show a different chewing pattern and diminished biteforces in the mixed dentition [18, 22]. A possible explanation could be that instead of the musculus masseter, the musculus temporalis it the most active muscle during chewing [18]. However, treatment with RME is associated with relapse and a long retention phase [23, 24]. Some authors suggest, that with increased bone formation in the sutura palatina, relapse and treatment duration of the retention phase after RME might be shortened [25-27]. Therefore, the acceleration of bone formation after RME has been researched for various adjuvant therapies, such as the influence of simvastatin, thymoquinone or curcumin and melatonin [27-29].

Concerning Low-Level-Laser-Therapy (LLLT), current studies analyse the benefit on pain relief, effects on inflammation treatment, tissue and wound regeneration as well as bone regeneration [30-32]. In the field of dentistry, therapy enhancement using LLLT is the topic of various studies, for example in the treatment of periodontitis, xerostomia, neuropathic orofacial pain and tooth extraction [33-37]. In orthodontics, current research is focused on the adjuvant therapy with Low-Level-Laser (LLL) for tooth movement and pain reduction [38-40].

A further approach is the combination of LLLT with RME [41-43]. This review will attempt to analyse LLLT as an adjuvant therapy on bone remodelling for RME. As a primary result of the

treatment, the beneficial effects for the patient are of interest. It aims to provide the most up to date overview of the topic. In order to present the highest possible level of evidence, all clinical and animal studies related to this topic will be included.

1.2 Anatomy

The palate is divided in the anterior hard part, the palatum durum, which is formed by bones and the dorsal soft palate, the palatum molle, which is formed by muscle [44]. The hard palate contains two bilateral fused bones. The anterior two-thirds are formed by the os maxillare, while the posterior one-third is formed by the os palatinum [45].

The maxilla, which forms a considerable part of the upper jaw, is connected to all the other bones of the viscerocranium [45]. It is a bilateral fused bone, which is divided by the sutura palatina [44, 46, 47]. It participates in forming the boundaries for the nasal, orbital and oral cavities. The maxilla consists of several processes, the alveolar, palatinal, frontal and zygomatic process. The alveolar process contains the alveolar socket which serves to anchor the teeth of the upper jaw [45, 48].

The os incisivum is a separate bone conjunct to the os maxillare. It is located on the anterior part of the os maxillare dorsal to the incisivus primus between the sutura palatina mediana. It forms the canalis incisivus, which terminates at the palatially located foramen incisivum [45]. The nervus nasopalatinus (nervus maxillaris (V/2)) traverses the canalis incisivus and leaves at the foramen incisivus [44-47]. The os palatinum forms the dorsal portion of the upper jaw and is conjoined to the os maxillare at the sutura palatina transversa. It also contains a bilateral fused bone divided by the sutura palatina mediana [44, 45, 47]. Furthermore, it is subdivided into two parts, the lamina perpendicularis and lamina horizontalis. The lamina perpendicularis is bordered by the os maxillare and os sphenoidale and takes part in forming the fossa pterygoideus and orbita [45, 48]. The lamina horizontalis forms the dorsal one-third part of the hard palate [44, 47]. On the dorsal lateral region of the lamina horizontalis are the bilateral applied foramen palatinus majus, through which the nervus palatinus major (nervus maxillaris(V/2)) and arteria palatinus major run [45, 47]. The nervi palatini minores (nervus maxillaris(V/2)) and arteriae palatini minores traverse through the bilateral located foramina palatina minora, which are located further dorsal to the foramen palatinus majus [44, 47]. The blood supply for the hard palate is via the arteriae palatinae majores and arteriae palatinae minores. The nerval innervation of the more dorsal part of the palatum durum originates from the nervus maxillaris (V/2), which innervates the mucosa somato-sensitive. [44, 46, 47]. The nervus nasopalatinus innervates the anterior part of the hard palate. The remaining innervation is covered by the nervus palatinus major, which traverses through the foramen palatinum major. They continue to run along the hard palate to rostral and thus undertake the innervation

of the most area of the palatum durum [44, 46, 47]. The nervi palatini minores innervate the dorsal part of the palatum durum [45, 46].
Dorsal to the hard palate is the palatum molle, which is formed by muscles and connective tissue, the aponeurosis palatina. The following muscles are responsible for maintaining the structure of the palatum molle: The musculus uvulae, musculus palatopharyngeus, musculus palatoglossus, musculus tensor veli palatini and musculus levator veli palatinae [44, 47]. The hard and soft palate is covered by oral mucosa. The oral mucosa of the hard palate which is attached to the osseous structures and contains multi-layered keratinised squamous epithelium. In contrast, the soft palate consists of multi-layered non-keratinised squamous epithelium and mucous glands [49].

1.3 Bone Metabolism and Remodelling of Bone Tissue

Bone tissue consists of about 20 % organic and 80 % inorganic components. Approximately 20% of the bone matrix is water [50]. The organic part contains mainly type I, III and V/XI collagen, proteins and proteoglycans, while the inorganic part contains mainly calcium phosphate which is similar to the hydroxyapatite [50]. Furthermore, there are different cells involved in the metabolism as well as the generation and regeneration of bone tissue. Osteoprogenitor cells are the mesenchymal stem cells from which osteoblast differentiate. In adults, they are predominantly located in the periosteum and endosteum. Osteoblasts are responsible for the generation of the bone matrix. Osteocytes are covered in the bone matrix and are primarily responsible for extracellular regulation of the tissue matrix. Osteoclasts are cells, which are responsible for the resorption of the bone matrix [51].
The activity of the cells is regulated by many factors such as cytokines produced by osteoblasts, interleukin-1 and tumour necrosis factor, while the differentiation is regulated by several factors including calcitriol, interleukin-1 and interleukin-6 and the receptor activator for nuclear factor kappa (RANK), a protein that is localised on the osteoclast surface [50].
To generate the bone matrix, osteoblasts secrete the osteoid, which is not yet mineralized. It contains proteoglycans, glycoproteins and collagen type I. Afterwards, the osteoid will mineralize with hydroxyapatite through precipitation [51]. Furthermore, osteoblasts produce growth factors and secrete the receptor activator for nuclear factor kappa ligand (RANKL), which is able to bind to the RANK receptor of the osteoclast progenitor cell, activating the differentiation of osteoclasts. Additionally, they secrete the macrophage colony-stimulating factor, which also activates osteoclasts differentiation [50, 51]. However, the activation of osteoclasts depends on both factors, macrophage colony-stimulating factor and RANKL, binding to them. While the macrophage colony-stimulating factor is secreted into the blood vessels and thus is available throughout the body, the RANKL is expressed locally on the

cytoplasm membrane of osteoblasts. It is therefore essential that direct contact is established between the osteoblast and the osteoclast progenitor cell [50]. Osteoprotegerin is known to function as an antagonist to the RANKL and therefore inhibits the activation of osteoclast differentiation and activity by binding to the RANK receptor without activating the signalling pathway [50].

The regulatory mechanisms of osteoblasts still require further elucidation. It appears that the oestrogen and androgen hormones have an increasing effect on the differentiation of osteoblasts. They also seem to inhibit osteoclast activity by inhibiting the interleukin-1 and interleukin-6 as well as tumour necrosis factor alpha. Furthermore, oestrogen blocks the RANKL- mediated activation of osteoclasts and therefore increases the apoptosis of those cells. Consequently, the bone degradation is inhibited and bone formation is increased [50].

Glucocorticoids also influence bone remodelling. Osteoblasts contain a receptor for glucocorticoids, which appears to inhibit their differentiation and activation. This also affects osteoclast differentiation, as RANK activation by RANKL of the osteoblasts is reduced [50]. In addition, osteoblast activity is regulated by the parathormone and calcitriol [50, 51]. Prostaglandin, Vitamin-D (calcitriol) and the parathormone increase the expression of RANKL on osteoblasts and thus the activation of osteoclasts. However, the interaction between osteoblasts and osteoclasts is necessary for remodelling as well as the generation of bone tissue [50].

1.4 Rapid Maxillary Expansion

1.4.1 Diagnostic, Indications and Contraindication

The medical indications for rapid maxillary expansion (RME) are the obstruction of the nasal airway and deformity of the septum nasi [2, 6]. The types of malocclusions that may result in orthognathic indications include bilateral or unilateral posterior crossbite and Angle Class III caused by narrow transversal space of the maxilla [2, 4, 7-9]. Furthermore, it is an approach in the treatment of a skeletal and dental Angle Class II [4, 5]. In addition, RME may be indicated for patients suffering from a cleft lip and palate [10, 11].

In addition to the clinical indications, the model analysis by Pont can be considered as a further point of reference. This is performed at two points of the dental arch, in the region of the first premolars and first molars [12, 52]. For the upper jaw, the width of the dental arch is measured from the central fossa [52]. The sum of the mesiodistal diameter of the incisors of the maxilla (SI_M) is taken and multiplicated with the factor 100. The resulting product is then divided by 80 for the premolars and by 64 for the molars [12, 52].

$$premolar\ width = \frac{SI_M\ x\ 100}{80} \qquad molar\ width = \frac{SI_M\ x\ 100}{64}$$

Subsequently, the measured value of the dental arch width is compared with the calculated value. This provides a possible indication of a deficit in transversal width. However, this measurement should only be taken as a reference value for the dimensions of the deficit, as in some cases their results are not fully accurate [12, 52, 53].

Another method for identifying transversal maxillary deviance is the model analysis by Korkhaus. This is conducted by taking the transversal line between the first molars and cutting a perpendicular above the raphe palatina media. With these values, the palatal height index can be determined by dividing the palatal height by the palatal width and then multiplying by a factor of 100 [53, 54].

$$PHI = \frac{palatal\ hight}{palatal\ width} x\ 100$$

The target value for the palatal height index is 42%. A higher index indicates increased palatal height and decreased transversal dimension [53].

Contraindications for RME are a micro mandible and normal occlusions in the permanent dentition [2]. It should be mentioned that RME can cause buccal inclination of the teeth [24, 55]. Furthermore, it might reduce the buccal bone plate thickness as well [56, 57]. These factors might be considered as relative contraindications.

Due to dental tipping during palatal expansion, a slight occlusal bite opening occurs. Thus, a vertical growth pattern could be seen as a relative contraindication [24].

1.4.2 Treatment Methods

One of the first treatment records associated with RME can be traced back to the work of the dentist Emerson Colon Angell. In 1860 he published a case study in which he treated a 14-year-old patient suffering from lateral crossbite using a method of transversal distraction of the maxilla. Since then the treatment methods progressed further [24]. There are different treatment options and orthodontic appliances for gaining maxillary transversal space. They are divided in removeable appliances, tooth anchored appliances and implant anchored appliances. A removeable appliance is used for the early treatment approach in the primary dentition and first phase of the mixed dentition [24, 58]. By activating a screw once a week, which is anchored in the base plate, the required distraction is achieved [24, 55, 59]. One activation distracts by 0.2 mm [24, 59]. The applied force should not exceed 6 - 8 Nm [55, 60]. The literature describes the transversal expansion, that can be achieved with removable appliances, with up to 5 mm [24]. The ratio of skeletal to dental movement is about 1:1 [61]. The duration of treatment is between six to twelve months [55]. An option for a fixed appliance is the transpalatal arch in form of a quad helix. This treatment might be used in the second phase of the transitional dentition or in the second dentition [61, 62]. The requirements for the patient in terms of cooperation and compliance are lower, as activation of the screw is not

necessary. The quad helix is attached to the first molars [61]. It consists of a wire with a diameter of 0.8 - 0.9 mm and contains four loops [59, 62, 63]. The transversal force applied during the therapy is approximately 2 Nm [62]. This enables the achievement of up to 3 - 4 mm of transversal expansion per activation. The clinical gained space is described between 2 and 4 mm [61, 62]. However, this is predominantly a dental effect due to tooth movement [62]. Furthermore, a wide range of discrepancies in applied forces is possible due to different alloys, diameter and construction of the wire [64]. After six to eight weeks, activation can be repeated [62]. After transversal expansion, the quad helix should be left in place for 2-3 months to prevent relapse [61].

If greater transversal space and a higher amount of skeletal expansion is required, a rapid maxillary expansion may be performed [24]. To carry out the treatment, it is necessary that the ossification of the sutura palatina is not yet completed [24, 65]. A study conducted by Knaup et. al. (2004) observed that ossification had not yet occurred in some patients up to the age of 54 years [66]. However, an early treatment approach seems to result in better outcomes [67, 68]. One reason might be the increasing interdigitation of the sutura palatina with progressing age, which could be an explanation for a reduced treatment success due to increasing age [69]. In the primary dentition, an indication for the RME instead of removable appliances is for example the posterior crossbite [59]. Regardless of the patients age, expanders with an incorporated Hyrax screw or Snap-Lock-Expander are appliances which are commonly used for this procedure. They are attached at four points, the first premolar and first molar on both sides. Orthodontic molar bands are used for this purpose. It is necessary to separate the teeth with elastics for approximately a week in advance in order to place the molar bands. Once the expander is in place, several methods for expansion can be performed. They differ in the amount of time required for expansion and the forces applied. In general, a single activation of the screw is a rotation of a quarter, which results in an expansion of 0.2 - 0.25 mm. It thus follows that a complete rotation of the screw will expand 0.8 - 0.9 mm [24].

One possibility for achieving palatinal distraction is the procedure described by Derichsweiler. The screw is activated twice a day. The activation period is about 14 - 20 days. With this method, the applied force is 60 - 90 Nm [24].

A more rapid method is the procedure by Chateau and Chatelier. The initial activation contains two to three quarter turns. After that, one or two activations per hour will be performed for at least five times a day. The activation period proceeds for three days. The effective forces are about 80 to 120 Nm [24].

After the activation the remaining force directed to the suture is about 30 Nm. This might cause a relapse, which is why the expansion has to extend by about 30 % of the required transversal space gain [24]. In total, the application can be extracted up to 12 mm [55]. Liu et al. (2015) found in their systematic review a mean expansion of 2.42 to 4 mm for the anterior part, which

corresponds to 34.6 - 50 % of screw activation [23]. In the dorsal region, the average expansion was about 0.84 to 2.88 mm which corresponds to 12 - 36% of screw activation [23]. However, the possible gain in transversal space can be up to 6 mm [55]. To avoid high relapse, the expander screws should be secured in position to maintain the gained space. After six months the appliance might be replaced with a quad helix or trans-palatal arch for an additional six months [24]. However, Liu et al. (2015) described a retention phase between 3 to 12 months with no significant long-term changes in the opening of the sutura palatina [23].

The gain in space is a consequence of alterations to the skeletal and dental components. The skeletal effect is observed in the opening of the sutura palatina and a buccal inclination of the maxillary bones. The effect of the dental component is a result of a buccal inclination and tooth-movement of the lateral teeth. In addition, the expansion seems to be wider in the anterior region of the maxilla than in the posterior. However, the patients age also seems to have an influence in the relation of dental and skeletal effects by the treatment. The skeletal effect in young patients before the pubertal growing peek is about 25% [55]. A treatment after the pubertal growing peek seems to have a lower effect on the skeletal change. The older the patient becomes, the more likely the effect shifts from the skeletal change to dental components [55, 67]. As a modification of the RME there is the possibility of using micro implants as an anchorage, called mini-implant assisted rapid palatal expansion [70-73]. This is achieved by using one or two screws on each side of the suture to fix the appliance in the maxillary bone. The dimensions of the screws vary from 1.8 x 9 mm to 1.5 x 12 mm. This method is applicable to patients aged 13 and above [70, 72, 73]. Lin et al. (2015) and Celenk-Koca et al. (2018) found in their studies on adolescents that the expansion of the midpalatal suture was greater compared to the non-implant RME [70, 72]. Buccal tipping was also lower in the implant group [70, 72]. However, this does not seem to be sufficiently clarified, as Khosravi et al. (2019) reported in their systematic review that there is no discernible difference between bone-anchored or tooth-anchored expansion devices with respect to these two outcomes [74]. Another topic of discussion is whether the side effect of the loss of buccal alveolar bone thickness by mini-implant assisted rapid palatal expansion might be lower compared to RME. However, the evidence on this topic appears to be limited at present [75].

1.4.3 Ossification of the Sutura Palatina

The ossification of the sutura palatina media begins at the dorsal part and continues to anterior [24]. Also, the ossification is not completed before the age of 40 [24, 66, 76]. Research has been conducted on the obliteration of the sutura palatina in tissue samples of the human palate. Persson et al. (1977) found no significant ossification up to the third decade [76]. In their study, Knaup et al. (2004) reported no obliteration of the sutura palatina above 15% in a group of adults aged between 26 and 63 years [66]. However, the difference to the group up

to the age of 25 years was about 3% and therefore significant [66]. A further study by Korbmacher et al. (2007) examined the osseous structures on tissue samples of the human palatal using micro-computed tomography analysis [77]. They observed no significant difference in the obliteration or interdigitation of the human palate at different ages. However, they found that even though the results varied within the age-dependent groups, obliteration was generally low. Another observation was a significantly higher bone density in the middle-aged group from 25 to 30 years of age. [77] According to these studies, it seems that with increasing age, the obliteration of the sutura palatina might remain low and develop individually independent of age.

Contrary to the findings of Krobmacher et al. (2007), a histological study by Melsen et al. (1975) describes that with increasing age, the shape of the bordering bones at the sutura palatina changes from a Y-shaped broad form, over a sinuous, to an increasing interlocking shape of the bilateral bones [69, 77]. It should be considered that this result might be attributed to the younger intervention group in the age from 0-18 years [69, 77].

When it comes to RME, various studies have investigated the cellular response in the palatal suture in animals [29, 78-81]. Cleall et al. (1965) observed the tissue response of the palatal suture after different time intervals in monkeys [78]. The results show that after two weeks the expanded palatal suture was filled with disorganised connective tissue and irregularly localised bone areas. They also noted elevated cellular activity combined with reparative and osteoclastic activity as well as increased vascularisation [78]. After three months, there was ongoing ossification accompanied by increased osteoblast activity. By six months, the histological osseous structures seemed similar to those in the control group without palatal expansion [78]. Murray et al. (1971) also observed the ossification of the palatal suture in monkeys after palatal expansion by histological methods [79]. After four days, they also found increased vascularisation and cellularity. Also, a higher number of osteoclasts was observed. After 14 days, the connective tissue appeared disorganised with increased cell numbers and bone disposition combined with the occurrence of osteoblasts [79]. However, due to the study design with a small intervention group, these results should be interpreted with caution [78, 79].

Furthermore, some animal studies examined bone formation after RME in rats. Altan et al. (2013) and Kara et al. (2012) both found an upregulated bone formation in the group treated with palatal expansion compared to the no-treatment control group [29, 80]. They observed increased numbers of osteoblasts, osteoclasts, higher vascularisation, and upregulated inflammatory activity in the group treated with RME [29, 80]. In addition Arnez et al. (2017) found that RANK, RANKL and osteoprotegerin appears to be upregulated [81].

As these results are derived from animal studies only, further investigations were undertaken to examine bone formation in human subjects. Fastuca et al. (2020) observed the bone density

of patients treated with RME using low-dose computed tomography [82]. Their results showed that there was no difference in the bone density of the patients before palatal expansion and six months later [82]. These results corresponds to the study by Franchi et al. (2010), in which they examined bone density using low- dose computed tomography after palatal expansion as well [83]. They also observed the same bone density before treatment and after six months of retention. However, the bone density in the palatal suture was lower than in the maxillary bone [83]. The age of the patients in both studies was before the pubertal growth peak at an average of 10.2 (Fastuca et al. 2020) and 11.2 (Franchie et al. 2010) years [82, 83]. Schauseil et al. (2014) observed the bone density of the patients at an average age of 15.8 years [25]. Contrary to the previously mentioned studies, they found lower bone density after six months of retention compared to pre-palatal expansion. This discrepancy may be attributed to the post-pubertal age of the patients [25].

Some authors state, that the prevention and amount of relapse after RME is related to the new bone formation in the sutura palatina. They concluded that the formation of new bone tissue in the expanded suture is one of the determining factors for the duration of the retention phase after RME. Thus, the duration of the retention phase would be related to the time needed for the reorganisation of the tissue in the sutura palatina [25-27]. However, there seems to be no evidence on whether relapse after treatment with RME is positively influenced by the bone regeneration of the sutura palatina, as no other specific studies on this topic could be identified.

1.5 Low- Level- Laser- Therapy

1.5.1 The Generation of Laser

The term laser is an acronym formed by the words *light amplification by the stimulated emission of radiation* [84]. Laser is a form of light, that is part of the electromagnetic spectrum as we know it [84, 85]. Thus, light is described as a mixture of waves and particles called photons [84].

The generation of laser is based on the principle of spontaneous emission of radiation [84, 86]. This was first described by Albert Einstein in 1917 [87]. This is based on Bohr's atomic model, which postulates that an atom contains a positively charged nucleus and an orbit with negatively charged electrons. The electrons are arranged in a stable resting state of the lowest energy, which is the closest possible orbit to the nucleus. The force that stabilises the atom in this stable state is the electrical attraction between the positively charged protons and the negatively charged electrons [84]. When an electron is hit by energy, such as a photon of light, it might transduce the energy by moving to a higher orbit [84, 86]. The electron is now in an excited state [86]. Since the atom tends to seek a more stable state closer to the nucleus, the excited electron returns to its former orbit after a short period of time [84]. In doing so it emits

the energy in form of photons [84, 88]. This process is known as spontaneous emission [84, 88, 89].

If an electron that is already in an excited state is hit by a photon, it will return back to its resting state without absorbing that photon [84, 89]. In this process, the electron will emit another additional photon. These two photons are now of the same energy, wavelength, and direction [84, 86, 89]. This process is called stimulated emission [88, 89]. These photons are now able to stimulate the further emission of other photons [84].

In order to achieve this effect, population emission is required [89]. This means that the atoms, which serve as the medium for the generation of the laser beams, must be put into an excited state [88, 89]. This is achieved by adding energy to the medium, such as light or electricity [89]. Once this is accomplished, spontaneous emission and stimulated emission can occur in the medium. Furthermore, a cumulative effect of the stimulated emission is required to generate a laser beam. Therefore, an amplification of the produced photons is needed [88, 89]. For this purpose, the medium is positioned between mirrors [86, 88, 89]. The generated photons are then reflected and will hit the medium with excited photons again, which causes a chain of reaction in the generation of further photons. This effect raises the number of emitted photons, which now can leave the device as a single laser beam [88, 89].

1.5.2 The Characteristics of Laser

As previously stated, laser is a form of light, which is part of the electromagnetic spectrum [84, 85]. Therefore, laser has the same characteristics as light. Electromagnetic waves are on their part a form of energy which traverse through space [84]. However, they not only consist of waves but also of particles. The wavelength, among other factors, influences which of the two is more predominant [85]. The known spectrum of electromagnetic waves ranges from a wavelength of 10^{-14}m, which is known as γ- irradiation, to microwaves and radio waves with a wavelength of 10^{4}m. The visible spectrum is between 400-760nm [84]. The wavelength is related to the energy of the light. While long waves contain low energy, short waves contain high energy [90].

Apart from these general characteristics of light, laser has some characteristics of its own. One of these is that laser is monochromatic, which describes that it contains a single specific wavelength. Another defining characteristic is coherence, which refers to the phase alignment of the waves. Considering that light moves a distance over time, the sine rhythm of each wave is in the same phase [84, 86]. Consequently, the waves do not interfere with one another, resulting in a constant level of energy over the distance [86]. A third characteristic is collimation. This describes that the emitted waves are considered parallel in their direction. This results in no or very small divergence of the waves. Thus, the size of the beam diameter remains constant at varying distances from the source [84, 86]. These three characteristics of laser

lead to the possibility to create light of a constant and defined amount of energy level and area. Additionally, there is no loss of energy due to the distance to the source [84].
A difference among the lasers is the continuous wave and the pulsed laser beam. While there are laser devices, that are capable of generating a continuous beam of light, some generate a beam with an intermittent frequency [88, 89]. This is due to the construction of the device. Depending on the type of laser the active media is able to generate and whether there are component parts which are capable to transform continuous waves into pulsed [88]. Pulsed lasers are divided into long pulsed (40 - 450 ms duration) or very short pulsed (5 - 100 ns duration). The number of pulses generated per seconds is called pulse repetition rate [89]. However, this difference does not affect the energy output of the laser beam [88].

1.5.3 The Tissue Interaction of Laser

When laser interacts with a biological tissue, four interactions occur: It is reflected, transmitted, scattered and absorbed [84, 89, 90]. The amount of reflected light affects extent to which the laser beam penetrates the tissue and thus the laser will be able to interact with the tissue [84, 89]. The amount reflected from the skin is about 4-6% [84]. However, dry surfaces and the angle of the light hitting the surface result in a higher amount of reflection. A perpendicular angle to the surface will decrease the amount of laser reflected [84, 89].
Transmission refers to the phenomenon, that light which has not yet interacted with the tissue by reflection, absorption or scattering, will continue to transmit into deeper areas. The transmission of the tissue is related to the wavelength of the laser. Shorter wavelength, such as 300 nm, will not penetrate the tissue to the same depth as a longer wavelength, for example 750 nm. The transmission is directly related to the absorption of the medium. Absorption by water, for instance, starts at a wavelength of about 900 nm and reaches its peak at 2940 nm. This limits the transition of light at this wavelength into deeper structures [84]. Furthermore, haemoglobin has an absorption peak at a wavelength of 400-600 nm and oxyhaemoglobin reaches its maximum peak at 418 nm [84]. In conclusion, the chosen wavelength will influence the depth of tissue penetration by the laser beam [84, 89]. Therefore, the wavelength might be chosen in relation to the depth of the tissue layer it is intended to affect [84].
Furthermore, the laser is scattered by tissue [84, 89]. When light interacts with a molecule, the direction of the light beam may change. This results in scattering of the light beam [89]. This occurs without any biological effect of the light on the tissue and at the same time, the amount of energy in the target area is reduced [85]. This effect can be reduced with a larger diameter of the laser beam. This does not reduce the amount of scattered light, but by directing more light to the target area through scattering, the amount of laser beams interacting with the tissue in the target area increases. Thus, the amount of energy in the target area is increased [89].

Additionally, this effect is also related to the wavelength of the laser. Shorter wavelengths are more likely to be scattered than longer wavelengths [84].
Furthermore, the energy profile of the laser beam seems to be of interest. The beam profile of the laser spot is of Gaussian shape. This implies that the laser intensity is at its maximum in the centre and decreases with distance to it [84, 86]. This phenomenon occurs with a factor of 0.135 to the distance of the beam centre [86]. The result is that the power density of the laser is diminished at the border area of the spot, which might result in an ineffective dose application in this area. To avoid a lower dose application in these areas, the overlapping of the laser beam spots is necessary in order to cover the entire tissue area with the required energy dose [84]. As a consequence to this phenomenon, some lasers have a beam profile which is formed in a doughnut-like shape [84, 86]. This results in a higher power density in the border area and enables a more constant application dose in the targeted tissue area. An overlapping of the laser spots is therefore no longer necessary [84].
The biological effect of laser is given by absorption. The light-absorbing molecules in the tissue are known as chromophores. The amount of absorbed laser light depends on the chromophores that are present in the tissue and the wavelength [84, 89]. While infrared light is highly absorbed by water, melanin and haemoglobin primarily absorb ultra violet light and the visible spectrum [89].

1.5.4 The Effect of Absorbed Laser on Tissue

When a laser is absorbed by biological tissue, three possible reactions may occur: A photothermal, a photomechanical and a photochemical reaction [86, 89].
In the event of a photothermal reaction, the tissue chromophore that absorbs the laser beam transforms the energy into heat [84, 86]. This effect on the tissue depends on the energy of the laser as well as and the duration of exposure. These two parameters influence the degree of temperature change in the target tissue [86, 89]. Depending on the amount of the temperature rise, this can lead to tissue necrosis, denaturation of proteins, increased membrane permeability or vaporisation of the tissue [84, 86, 89]. For these effects to occur, the tissue temperature must rise above at least 60 °C [84, 89]. However, a temperature rise of 5 °C might already provokes tissue damage resulting in an inflammatory and repair process of the tissue [84]. With regard to LLL, this effect is unlikely to have any impact and may therefore be neglected [86].
The phenomenon of photomechanical interaction appears when a high level of energy is absorbed over a comparatively brief time interval. This results in significant heat dissipation due to a faster accumulation of heat than the thermal diffusion of the tissue [86, 89]. This results in an explosive vaporisation of the tissue [89]. However, since this effect also requires a thermal increase of the target tissue, it is of negligible consequence in the context of LLLT.

In addition, there is the photochemical reaction, which describes the chemical and biochemical reactions that occur when chromophores absorb light [84, 89]. For example, this effect is used to treat tumours with photodynamic therapy. Also, bio-stimulation of tissue by lasers is part of the photochemical reaction which can occur due to LLL exposure [89].

1.5.5 The Parameters and Biochemical Effects of Low- Level- Laser

As previously stated in section 1.5.2, lasers vary in wavelength. In the case of Low-Level-Laser, some authors mention a wavelength between 600-1070 nm [30, 32]. However, there seems to be a consensus on the different effect on the tissue depending on the wavelength [30]. This could be attributed to the different specific absorption ranges of tissue chromophores in relation to the wavelength [30, 88, 89]. For example, haemoglobin is known to have an absorption peak below 600 nm [30, 88]. The same appears to be the case for melanin, which is one of the most absorbent chromophores in the tissue [30]. There is also a diminished biochemical activity response of the tissue in the range of 700-770 nm [30, 32]. Furthermore, a longer wavelength of 780-950 nm penetrates deeper into the tissue before being absorbed compared to waves in the range of 700-770 nm [30].

The parameter of dosimetry seems to be of further interest. Considering, that the laser beam can have different diameters, it is possible to measure the power in watt per area ($\frac{W}{cm^2}$), also known as the irradiance [30, 89]. Another method to describe the dosimetry of the laser is by the energy in joule per area $\left(\frac{J}{cm^2}\right)$, which is called the energy density [30, 32, 89]. In an in vitro study, Migliarino et al. (2014) examined the proliferation of pre-osteoblast cells with different amounts of applied energy [91]. They observed the range of 1-50 Joules, which were related to 1.57, 7.87, 15.74, 39.37 and 78.75 $\frac{J}{cm^2}$ at different irradiation time. The wavelength of the laser was 980 nm. The results demonstrated that cell proliferation increased in the range up to 39.37 $\frac{J}{cm^2}$ with a peak at 15.74 $\frac{J}{cm^2}$ and decreased at 78.75 $\frac{J}{cm^2}$. This could lead to the conclusion that there is an upper threshold for a dose at which cell proliferation decreases [91]. Contrary to this, de Souza et al. (2012) published an animal study, in which they exposed a bone defect to an energy density of 60 and 80 $\frac{J}{cm^2}$ and found an increased bone remodelling in both groups [92]. Additionally, Atasoy et al. (2017) found no different outcomes on bone regeneration in their animal study using energy densities of 5, 10 and 20 $\frac{J}{cm^2}$ and the same wavelength of 980 nm [93]. Furthermore, according to Chung et al. (2012) there also seems to be a defined range of energy and exposure time, in which an adequate tissue response to LLLT occurs [30]. It appears that either an exposure time too long or too short has a negative effect on the tissue response [30]. Aleksic et al. (2010) investigated increased cell proliferation in a cell population exposed to 30-60 seconds of LLL, compared to 90-120 seconds in an in

vitro-study [94]. As demonstrated, discrepancies have been noted in published study results regarding the most effective absorbed dose. However, it seems likely that an energy density of 1-5 $\frac{J}{cm^2}$ can already achieve an adequate tissue response [31, 32]. Furthermore, a study on rats indicated, that there might be a difference between the chosen wavelength in terms of bone regeneration. The wavelengths of 660-690 nm and 790-830 nm were compared. The result was increased ossification in the group with the wavelength of 790-830 nm compared to the other [95]. These cases demonstrate that different parameters in the laser settings such as energy, irradiation time and wavelength could lead to different results [31, 32].

With regard to bone regeneration and ossification, LLLT appears to increase the expression of osteogenic genes such as alkaline phosphatase, bone morphogenetic protein 4 and runt-related transcription factor 2 [31, 96]. In addition, Migliario et al. (2014) observed higher levels of reactive oxygen species (ROS) combined with higher cell proliferation of pre-osteoblasts in a cell culture exposed to LLL [91]. Several studies examined the expression of the pro-osteoblastic factor osteocalcin and found an increased amount in the LLLT-treated group, compared to the non-laser group. There also seems to be a higher amount of osteocalcin and collagen type I in the LLL-treated tissue due to LLLT [31]. In an animal study, an increased amount of chondroitin sulphate, hyaluronic acid, small leucine rich proteoglycans, Small Integrin-Binding Ligand N-linked Glycoprotein, osteonectin and osteocalcin were observed in the bone matrix after LLLT. Thus, it could be concluded, that LLLT also has an altering effect on the extracellular bone matrix [92]. In an in vitro study, Aihara et al. (2006) investigated increased osteoclast and RANK expression for preosteoclast cells [97]. LLLT also seems to increase the mitogen-activated protein kinase 5-30 minutes after the exposure [94].

Concerning internal cell regulation, there seems to be an upregulation of adenosine triphosphate and reactive oxygen species (ROS) production in the cell, suggesting that LLLT may have an impact on the mitochondrial respiratory chain [30, 98]. This results in increasesed cell proliferation and protein synthesis [98]. Though so far, the mechanism does not seem to be fully understood. One potential explanation could be that cytochrome c oxidase absorbs light at a wavelength of 810 nm and thus increases the mitochondrial activity for adenosine triphosphate production. The increase of the ROS and therefore the increased cell proliferation might be due to light-sensitive ion channels, which enhance Ca+ concentration in the cytoplasm. This leads to increased interactions with ROS, nitric oxide and cyclic adenosine monophosphate, resulting in upregulated activation of transcription factors and thus cell proliferation [32].

In contrast, Chung et al. (2012) explain the result of increased ROS by a different mechanism by the upregulated respiratory chain reaction [30]. Oxygen, as a product of the electron transport chain, produces ROS as a by-product. ROS production could therefore be increased

as a product of the enhanced respiratory chain reaction and also result in the upregulation of transcriptions factors [30].
The known side effects of LLLT may be related to the skin irritation that can lead to redness and itching [32]. However, the temperature of the tissue seems not to be affected [32, 86].

1.6 Aim of the Study

This study aims to investigate LLLT as an adjuvant therapy for RME in terms of bone regeneration and its benefits for the patient. It is also assumed, that one of the benefits for the patient is reduced treatment duration and reduced relapse.
In conclusion the following hypothesis will be investigated: Patients treated with LLLT as an adjuvant therapy for RME have increased bone regeneration of the sutura palatina, compared to patients treated only with RME.
In addition, the question of whether LLLT enables a reduction in the duration of treatment, or a reduction of the relapse for patients will be addressed.
In this regard, all clinical and non-clinical studies available to the authors will be analysed. The differences and similarities of the study methods, such as laser parameters, treatment duration of LLLT and evaluation criteria, will be discussed to provide guidance for further research.

2 Materials and Methods

2.1 Used Materials

The materials used were exclusively computer software or digital databases.
Microsoft® Excel (version 16.74) was used for the preparation of tables and figures.
The databases National Library of Medicine (via PubMed®), Cochrane Database (via The Cochrane Library) and Web of Sciences Core Collection (via Web of Sciences™) were used for literature research.
The computer program EndNote™ (version X9.3.3) was used for literature management.
The plagiarism scan was conducted using the Turnitin™ software, accessed via the Scribbr website.

2.2 Literature Research

2.2.1 Initial Literature Research

An initial literature research was conducted using the National Library of Medicine (via PubMed) database. The search terms used were Rapid-Maxillary-Expansion and Low-Level-Laser-Therapy. They were combined with the Boolean operator AND. The aim was to obtain an initial overview of the studies on the topic, as well as identify search terms and synonyms for systematic research.

2.2.2 Systematic Literature Research

In order to conduct the systematic literature research, the databases National Library of Medicine (via PubMed®), Cochrane Database (via The Cochrane Library) and Web of Sciences Core Collection (via Web of Sciences™) were chosen, due to their focus on medical topics. Various terms and synonyms for Rapid Maxillary Expansion were combined using the Boolean operator OR. The same was applied for synonyms and terms related to Low-Level-Laser-Therapy. Medical subject headings were also included in the National Library of Medicine (via PubMed®) and the Cochrane Database (via The Cochrane Library). For terms where it seemed appropriate, truncation was used. The resulting search terms that related to RME and LLLT were combined with the Boolean operator AND.

However, the exact search algorithm varied between databases. This was due to differences in the possibilities of utilising the truncation operator or the availability of medical subject headings. For databases that could not use truncation or medical subject headings, additional terms were added to cover the possible variations. As the databases publish the publications predominantly in English, search terms were constructed in English language.

Additional hand search was conducted. Dental journals were used as primary media.

With regard to the search strategy, no limitations were applied in terms of publication date or language. No other limitations related to study design or type of publication were set. This approach was applied consistently across all databases.

2.2.3 Inclusion and Exclusion Criteria

The inclusion criteria were defined as follows: English or German language. Publications translated from another language into English were accepted as well. Clinical studies or animal studies. The defined intervention group was the treatment of RME combined with LLLT as a benefit on bone regeneration of the sutura palatina.

Studies that did not aim on the specific intervention or population as the main topic or subgroup were excluded. Meta-analyses, systematic reviews and case studies were excluded as well.

No limitation on publication date was applied. Furthermore, no restrictions were set concerning the population included or the animals used. There were also no limitations with regard to size, treatment or intervention protocol and the chosen method of outcome measurement. Studies that met the inclusion criteria for a subgroup were included.

2.2.4 Screening and Evaluation of Eligibility

The steps of the literature search were visualised in a flow chart. First, the total number of all researched studies was imported into EndNote™ (version X9.3.3) for further processing. Following this, any duplicates were excluded, and the relevance of each study was assessed by screening of the title and abstract. The remaining titles were then screened for eligibility to the topic of this review based on the full text. This step was performed by two independent researchers. Any disagreements regarding inclusion or exclusion were discussed by the researchers until a consensus was reached.

2.3 Data Collection of Researched Studies

2.3.1 Data Collection Process

Once the literature research was completed, the data collection was carried out. For this purpose, Microsoft® Excel (version 16.74) was used to create a table with the relevant study content. This was carried out by a single researcher. The data collection was reviewed by the same researcher twice, with an interval of one month between the two reviews. As all studies were written in English or German, no translation was required. No automation tools were used for data extraction. Each result found in a study on the corresponding domain was collected. No limitations were placed on the results for any domain.
This review collected data from animal studies and CS. The data extracted from these different study designs were not combined in the same table, but were listed in separate tables.

2.3.2 Description of Collected Data

The data collected included the following domains:

- Author
- Year published
- Laser parameters: Type of laser, wavelength, dosage parameters, application frequency
- Expansion device and protocol
- Total of participants (including group sizes)
- Evaluation method

- Results
- Inclusion of a control group
- Only for CS: Signalling question
- Only for animal studies: Timepoint of evaluation starting from first laser application.

With regard to the laser dose parameters, all ot hte physical parameters reported in the study were collected. These included parameters such as spot size or diameter, power, energy, energy- or power-density as well as irradiation time. The units of measurement chosen were the same as those reported in the study.

When it was part of the study design, divided groups and group sizes were mentioned in the *total of participants* section. Additional information about the sample group, for example the age of the participants, was also reported in this domain.

Unknown data were not explicitly stated as such.

For all domains, data were collected as free text and no pre-set answers were used, except for the domain *control group*. In this domain, responses were limited to *yes*, *no,* or *unknown*.

2.4 Risk of Bias Assessment

To provide higher evidence for this review, a risk of bias assessment was conducted on all CS. An assessment of risk of bias in animal studies was not performed.

To carry this out, the Cochrane RoB 2 tool by Sterne et al. (2019) was used [99].

Risk of bias assessment was conducted using the “Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)” by Higgins et al. (2019) and “Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) SHORT VERSION (CRIBSHEET)” by Higgins et al. (2019) as a guideline [100, 101].

The RoB 2 tool is divided into seven domains. Each domain is designed to identify and address a specific cause of bias. This includes a domain targeting on randomization process, deviation from intended intervention, missing outcome data, measurement of the outcome, selection of the reported outcome and an overall risk of bias [99-101].

Several signalling questions were used for each domain. The questions were answered with the terms *yes*, *probably yes*, *no*, *probably no* or *no information*. Some questions only became relevant through a specific answer to a guiding question which had been answered previously. In the event that these questions were not relevant due to the answer to the guiding question, they were indicated as *not applicable*.

Once the questions for the domain had been answered, an individual rating of the bias risk was carried out. This resulted in a risk of bias rating of either *high*, *low* or *some concerns*. Additionally, each domain contained an optional module, that enabled the prediction of the

direction of the assessed bias. This was divided into *favours experimental*, *favours comparator*, *towards null*, *away from null,* or *unpredictable* [100, 101].
An additional text field enables the explanation of the selected evaluation.
After the risk of bias assessment was carried out for each domain, an overall assessment of the risk of bias was finally made. This was divided in *low* risk of bias, *some concerns* and *high* risk of bias and strictly based on the results of the domains. In case all domains resulted in *low* risk of bias, the overall risk of bias assessment would likewise be low. *Some concerns* might be the result if a domain resulted in *some concerns*, but none had a *high* risk of bias. The overall risk of bias was considered *high* if at least one domain had a *high* risk of bias or several domains were reported with *some concerns* [100, 101].
In order to improve the efficiency of the workflow and obtain an overview of the results, a table was created for the data collection in Microsoft® Excel (version 16.74).
The assessment was performed by two independent researchers. Each one evaluated the risk of bias without knowledge of the results obtained by the other researcher. The results were afterwards compared with each other. Discrepancies in outcomes were discussed in order to obtain consistent final results. In the event that no agreement was reached, a third person was consulted for the evaluation.
Concerning the assessment of risk of bias, a summary diagram for the different outcomes of the risk of bias assessment was created. For each domain, an overview of the assessed risk of bias was presented in a table with the results of the individual studies.
The assessment of reporting bias was part of the domain that aims to address the risk of bias in the selection of reported results. This also aimed on the evaluation of publication bias of the included study. Since studies with a negative outcome were less likely to be published, an attempt was made to evaluate whether there were indications of distortions in the results. To achieve this, signalling questions were directed on evaluating the accordance of the published report of the outcome to pre-specified intentions, planned outcome measurements and analyses. A comparison of the reported trial protocols and reported outcome protocols did not take place. This was due to lack of access to trial protocols. Lack of presentation of collected data was also included as an evaluation criterion in this domain. However, this only referred to the individual study itself and not on the publication bias to the studies as a whole.

2.5 Synthesis Method

In order to understand the differences in study design and its impact on the outcome of the study, two different parameters were compared across the studies. The frequency and duration of laser application as well as the laser parameters in relation to the outcome seemed to be of interest. In addition, the time at which the results were assessed also seemed to be a relevant

parameter. Parameters such as age or gender of the participants and their effect on the outcome were not considered in this study.
When investigating the intervention, this review primarily refers to a potential statement for patient treatment. Consequently, the results of CS were considered of greater interest than those of animal studies. In order to provide as comprehensive an overview as possible of the current state of knowledge, the animal studies were also included. No further limitations on the study selection for each table was made.

2.6 Certainty Assessment of the Outcome

To provide higher level of evidence for this review, the certainty of evidence for the included CS was assessed. This was not carried out for the animal studies. The GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach to assess the certainty of evidence was carried out for this purpose. The assessment was conducted using the GRADE manual by Schünemann et al. (2013) as a guideline [102]. The assessment was carried out by two researchers. This was performed separately and afterwards compared.
GRADE assesses the quality of evidence for the outcome, which is defined in the addressing question. This was not performed for each study individually but was applied as a single assessment of the entirety of the studies. The question was defined by specifying the population, intervention, control group and outcome (PICO). In order to refer sufficiently to the signalling question, subgroups of individual studies were included where appropriate [103].
The result of the GRADE evaluation results in a score from *high* to *very low*. This is assessed on a scale where *high* is rated with four points and *low* with one point [104].
Initially, a rating was set depending on the study design. For CS it was set *high*, for non-randomised controlled trials *low*. Subsequently, an adjustment was made on the basis of five evaluation criteria. This resulted in a downgrading of the rating by one or two points for each criterion, if required. The criteria were addressing risk of bias, inconsistency, indirectness, imprecision, and publication bias [104].
No narrowly defined criteria for the evaluations were given by a list of questions or predetermined facts against which the studies were judged. The judgement was based on the researcher's evaluation, which was guided by certain criteria. However, all reasons for upgrading or downgrading were stated, and if there were no changes in the assessment despite concerns, reasons were also explained. Possible criteria for the assessment are briefly outlined in the following section.
The reasons to downgrade due to risk of bias were evaluated by the results of the assessment of risk of bias with the RoB2 tool.

Inconsistency aimed to provide an information on the similarity of the included studies. In a meta-analysis the *p*-value, I^2- value or confidence interval may be used for the evaluation. This was not possible in this review as these values were not calculated. However, signalling questions on the similarity of the studies regarding intervention, definition of outcome and quality of conduct, as well as subgroups of patients with different effects between the studies were addressed [104].

Indirectness focused on whether the included studies addressed the question used for the GRADE assessment [104].

Imprecision may be evaluated using the confidence interval in a meta-analysis. This value was not calculated in this study. However, an indication of imprecision could be the summed size of the total population of all included studies. A total population of 400 and above was considered of sufficient for continuous outcomes, which applied to the included studies in this review [104].

GRADE also evaluates the potential for publication bias. In contrast to the evaluation in the risk of bias analysis, the entirety of published studies was considered. This included another aspect of publication bias, which does not refer to the results of a single study, as in the case of the risk of bias assessment. There are different possibilities to evaluate publication bias. In meta-analysis an asymmetrical distribution in the funnel-plot might be an indication on publication bias. To create a funnel-plot at least five studies should be included in the analysis. Smaller studies with smaller population sizes and the absence of larger studies can also be an indication of publication bias. This is due to the consideration that smaller studies with no positive outcome were less likely to be published. However, publication bias may be undetected or highly suspected, which leads to a downgrade by one point. For this criterion, the maximum downgrade is one point [104].

Three additional assessment criteria can be used to upgrade the quality of evidence. This usually is conducted for non-randomised controlled trials. The three criteria assess the domains of large magnitude of effect, dose response and effect of all plausible confounding factors. These may lead to an upgrade of the quality of evidence by one or two points[104]. However, applying these to CS is uncommon and was not performed for this review.

A table was designed to evaluate each criterion. For each criterion there was an additional field for comments and reasons that led to the decision.

According to PICO, the signalling question for the GRADE evaluation was defined as follows: Patients treated with LLLT as an adjuvant therapy for RME have increased bone regeneration of the sutura palatina, compared to patients treated only with RME.

3 Results

3.1 Literature Research and Study Selection

The first systematic literature research was conducted up to the date of 14.03.2021.
The databases used were the National Library of Medicine (via PubMed®), the Cochrane Database (via The Cochrane Library) and the Web of Sciences Core Collection (via Web of Sciences™). A detailed search history of the search terms and combinations of Boolean operators used is presented in Table 1 for the National Library of Medicine (via PubMed®), Table 2 for the Cochrane Database (via The Cochrane Library) and Table 3 for the Web of Sciences Core Collection (via Web of Sciences™).
Manual search was conducted until 14.03.2021 as well.

The following steps are shown in the flowchart in
Figure 1.
A total of 215 studies were identified and imported into EndNote™ (version X9.3.3). After excluding duplicates 187 studies remained for screening by title and abstract. At this stage, 153 studies were excluded. The resulting 34 titles were screened for eligibility using the full text. As a result, a total of 17 studies were included. They contained twelve animal studies and five clinical studies. Three studies were excluded due to unavailability of the full text, nine due to the study design, four due to intervention therapy and one due to insufficient report.
A study protocol published by da Fonseca et. al. (2019) indicated an ongoing study that seemed eligible for this review. However, no published results were found at the time of the literature search. It was therefore not included in this study [105].

In order to provide an overview of the current state of studies, a second literature search was conducted. The same databases were searched using the identical search terms and links to the terms. The search was limited to literature published between 14.03.2021 to 09.08.2023. If no exact day specifications were possible for the limitation, the period from March 2021 to August 2023 was specified.
The detailed search history for the second literature research is presented in Table 4 for the National Library of Medicine (via PubMed®), Table 5 for the Cochrane Database (via The Cochrane Library) and Table 6 for the Web of Sciences Core Collection (via Web of Sciences™).
Manual search was conducted from 14.03.2021 to 09.08.2023 as well.

The following steps are illustrated in the flowchart presented in

Figure 2
A total of 52 studies were identified and imported into EndNote™ (version X9.3.3). After excluding duplicates, 50 studies were left for screening by title and abstract. Forty-five studies were excluded. The remaining 5 titles were screened for eligibility using the full text. None of the studies met the inclusion criteria. Four studies were excluded because of the study design, and one study was excluded because it was a duplicate from the previous search.

Finally, a total of 17 studies were included in this systematic review. They included five CS and twelve animal studies.

3.2 Description of the Included Studies

3.2.1 Clinical Studies

Five randomised controlled clinical trials were assessed in this review. In order to provide an overview of the data collected, two tables were prepared. Table 7 reports the study design and Table 8 provides an overview of the laser parameters used and the outcomes.
Of the studies included, Angeletti et al. (2010) were the only researchers to use surgically assisted rapid maxillary expansion (SARME) [106]. This was conducted by a surgical technique using the LeFort-1 osteotomy. Afterwards, palatal expansion was performed with a dental fixed appliance with a Hyrax screw. A total of 13 patients in the age between 18-33 years were included. They were divided into two groups, with six patients in the control group and seven in the laser group [106].
Each patient underwent a total of eight laser treatment sessions. The first 24 hours after surgery and each subsequent treatment with an interval of 48 hours. This resulted in laser treatment on the first, third, fifth, seventh, ninth, eleventh, thirteenth and fifteenth days. Each treatment involved three laser applications at three different points with an energy density of 140 J/cm^2 and an irradiation time of 84 seconds per point. To achieve this, a gallium-aluminium-arsenide (Ga-Al-As) diode laser with a wavelength of 830 nm was used [106].
Evaluation of the bone regeneration of the sutura palatina was performed using digital radiographs. The first was taken preoperatively, followed by postoperative radiographs on days 30, 60, 90, 120 and 210. In order to draw conclusions about the bone regeneration that had taken place, the optical density was evaluated based on the total number of pixels within a defined area. A trapezoidal area was constructed for each radiograph using a standardised technique. The computer program Adobe Photoshop CS 8.0 software was used for this purpose. Evaluation of the total number of pixels in this area was performed using the program Histogram. This was performed three times for each radiograph image until there was no

statistically significant difference between the measurements for one radiograph image. The mean value of the evaluated data was then used [106].
In the study report, no results comparing the direct bone density values of the groups at the measurement time points were presented. However, the results of the measurements were presented in a table. As an evaluation method, the results within the group were related to each other on a percentage basis. In order to perform this, the radiograph image before the palatal expansion was taken as the reference value for the respective group [106].
After one month, the difference in the measured ratio between the control group and the LLL group was 10.6%. After 7 months, this value increased constantly to 26.3 % [106].
As a result, a significantly higher bone density was found for the laser group compared to the control group at each time point. The *p*-value in the Mann-Whitney test was 0.022 after one month (F1), 0.007 after two months (F2), 0.004 after three months (F3), 0.003 after four months (F4) and 0.003 after seven months (F5). Furthermore, the researchers evaluated that total ossification of the sutura palatina had not yet occurred after seven months. Also, the evaluated optical density data showed individual variability in both groups [106].

Cepera et al. (2012) investigated the effect of LLLT on bone regeneration in the sutura palatina after RME with a dental fixed expander using a Hyrax screw [107]. The LLL-Group contained 14 patients and the control group 13 patients. The age of the patients ranged from 8.2 to 12.1 years. The individual desired expansion was achieved after approximately eight days. LLLT was conducted using a diode laser with a wavelength of 780 nm. The energy density was reported to be 10 J/cm^2 per point with an irradiation time of 10 seconds per point. Each application contained 10 irradiation points. The LLLT was performed for five days from the start of screw activation (stage 1), for a further three days after the end of expansion (stage 2) and on days 7, 14 and 21 after stage 2 [107].
Occlusal radiographs were taken at different timepoints. An initial radiograph after expansion was achieved and at 3 - 5, 33 - 35, 93 - 95 days thereafter. Each radiograph contained an aluminium step wedge to provide a reference for the radiographic density. The radiographs were digitalised using a scanner, and a standardised area was defined by drawing two perpendicular lines orientated to fixed points of the palatal expander. The defined area was then analysed using optical density software (Image Tool). This software generated a histogram which was equivalent to the grey scale. The ANCOVA test was used to compare the optical density at different timepoints, while the students-t test was used for comparison between the optical density of the groups over a period of time [107].
No statistically significant difference in optical density was observed between the two groups prior to RME (p = 0.757). After expansion (T2), the group treated with LLLT had statistically significant lower bone density (p = 0.016) compared to the control group. A comparison of the

density values from T2 - T1, representing the time of screw activation, was statistically significant (p = 0.049). Thus, Cepera et al. (2012) conclude a higher opening of the sutura palatina in the group treated with LLLT. Statistically significant differences were demonstrated for the time points of T2 - T4 with lower optical density for the LLLT group. This represents the timeframe from immediately after expansion to 33 - 35 days after expansion. A comparison of the extent of density changes over this time period revealed no statistically significant differences between the groups. On days 93 - 95 (T5), there was no statistically significant difference for the optical density for the LLL group compared to control (p = 0.184). Comparing the difference of density for each group over the period from immediately after expansion (T2) to day 93 - 95 (T5), there was a statistically significant difference (p = 0.017) favouring the experimental group. This also applies to the time span from day 33 - 35 to 93 - 95 (T4 - T5) (p = 0.001). Thus, Cepera et al. (2012) concluded that LLLT accelerates bone regeneration and has a positive effect on the suture opening as well [107].

Garcia et al. (2016) investigated the impact of LLLT on RME at 39 patients divided into two groups. An LLL-treated group with 20 patients and a placebo group with 19 patients [108]. The age ranged from 6.2 to 12.4 years with a mean age of 8.45 years. RME was conducted using an acrylic splint in which a Hyrax screw was incorporated. After the desired expansion was achieved, the acrylic splint was used as a retention for six months [108].
The LLLT was performed with an indium gallium aluminium phosphide (In-Ga-Al-P) laser with a wavelength of 660 nm. Each session contained six application points. Four application points with an energy density of 23 J/cm^2 along the midpalatal suture (A) and two with an energy density of 12 J/cm^2 at the side of the suture (B). The irradiation time was set at 60 seconds (A) and 30 seconds (B). A total of seven treatment sessions were performed at 1, 7, 14, 28, 42, 56 and 70 days after RME. The control group underwent the same laser protocol in placebo mode. A cone beam computed tomography (CBCT) was conducted on the first day of LLLT and on day 75 [108].
Two evaluation methods took place. For qualitative evaluation, two independent researchers assessed the ossification of the suture palatina into four possible stages: Separate, well-defined margins, separate poorly defined margins, diffuse scalloped margins and near margins. In addition, a classification was carried out depending on the approximation of the sutura with regard to individual sections. Depending on whether there was partial approximation or complete approximation throughout the sutura, five classifications were possible. Separate, minimal, moderate, significant, or complete approximation [108].
For quantitative analysis, the distance of the suture was measured at four points. The maximum possible distance, the distances at the anterior inferior suture, posterior superior sutura and anterior nasal spine were evaluated. No results were presented for the comparison

of the first and second CBCT scans within each group. Comparing the LLLT group with the control group in the first CBCT scan, no significant differences were found at each measurement point. In the second CBCT scan the only significant difference between the groups were found for the posterior superior distance (p = 0.04). No statistically significant difference was identified for the remaining three measurement points. The median distances for the LLLT group in the second CBCT scan was 0 mm for each measured distance. The maximum distance measured ranged from 0 mm to 23.5 mm. The control group also had a median of 0 mm for the inferior and anterior nasal spine distances. The maximum measured distances varied from 0 mm to 27 mm [108].
However, a statistically significant difference between the measurements of the intrasutural distances was reported in favour of the LLLT group. The evaluation of the qualitative analysis resulted in a statistically significant difference favouring the LLLT group in both outcome measurements [108].

Ferreira et al. (2016) investigated the effect of LLLT on bone regeneration of the sutura palatina after RME in 14 patients [109]. The age of the subjects varied between 8 to 14 years with a mean age of 11 years. The patients were divided into two groups, 10 patients treated with LLLT and 4 patients without LLLT as a control group. In a flowchart, the authors stated that the control group initially included eight participants, of whom four were lost to follow-up due to the use of corticosteroid or anti-inflammatory medications or technical issues with the computed tomography scanner. However, a sample size calculation was performed for two groups with an alpha type error of 0.5 and a power test of 0.91, resulting in a minimum sample size of four for the control group and 10 for the experimental group. A dental fixed appliance with a Hyrax screw was used for RME. The desired expansion was achieved after approximately 14 days [109].
The LLLT was conducted using a gallium-aluminium-arsenide (Ga-AI-As) infrared semiconductor diode laser with a wavelength of 780 nm and an energy density per point of 35 J/cm^2. The irradiation time per point was 20 seconds. The laser application consisted of two weekly treatments in the first month and one weekly treatment in the second month after expansion was achieved. This resulted in a total of 12 applications. Each treatment contained of four application points. For evaluation, two cone beam computed tomographs (CBCT) were taken from each patient. The first was taken immediately after the expansion and a second one four months later. In order to evaluate bone density, a standardised procedure was used to determine three points at which the optical density was measured. The InVivoDental 5.0 software was used for this purpose. The procedure was repeated after 30 days by the same operator. The method used by the program to evaluate the optical density was not mentioned

in the report itself. However, in the description of the figures it was mentioned that it measured the optical density values in pixels [109].
Ferreira et al. (2016) stated that they found significant difference in bone regeneration in favour of the LLLT treated group. A *p*-value of $p = 0.0$ was reported for optical density in the LLLT group at the time points T0 and T1. In the control group, the increase in optical density was not statistically significant ($p = 0.2$). When comparing the LLLT and control groups at time point T1, a statistically significant difference ($p = 0.05$) was identified using the Students *t*-test. Furthermore, the authors stated, that in both groups, complete ossification of the palatal suture was observed after four months [109].
However, additional values, such as the optical density for each patient or mean values, were not published in the article. No mean values for the groups were reported either. Only two graphs provide a rough impression of the different values determined [109]. The attempt to obtain the data by contacting the authors was not successful.

Matos et al. (2020) examined LLLT as an adjuvant treatment for RME in 34 patients [43]. The experimental group contained 18 patients and the control group 16 patients. An age range of 6 to 12 years was specified in the inclusion criteria. The highest and lowest value is not mentioned in the study. The mean age of the experimental group was 9.2 years and for the control group 8.2 years. Initially, 40 patients were selected for the study, who were evenly distributed between the groups. Due to the loss of follow-up and the exclusion of two patients who did not receive the treatment, the sample size became smaller. The flow chart presented in the publication was consistent with the resulting group sizes, but the numbers of excluded patients mentioned in the text were different. In the flow chart, a total of six patients were excluded, while the text mentioned a total of seven excluded patients [43].
For the treatment of RME, a dental fixed expander with a Hyrax screw was used, and the desired expansion was mostly achieved after 15 to 21 days of activation [43].
LLLT was conducted using a diode laser with a wavelength of 980 nm. The energy density was stated to be 238.85 J/cm^2 with an energy of 3 J. The diameter of the laser beam was specified as 0.4 mm, while the spot size was reported as 1.26E3 cm^2. The power density was stated to be 238.85E3 mW/cm^2 with a power of 300 mW. The irradiation time was 10 seconds per point [43].
The application was performed 12 times, during the activation phase on day 1, 5, 10 and 15 and afterwards once per week after expansion for eight weeks. Each session included six points of laser irradiation. In order to perform a placebo treatment, the control group was treated with the laser device in standby mode [43].
The results of bone regeneration of the sutura palatina were assessed by analysing occlusal radiographs. These were taken after screw fixation and at a follow-up examination after one,

two, three, and six months. A penetrometer was incorporated into the radiographs to provide a comparison module. A standardised area was defined using the palatal expander and the radiolucent area bordered by the suture margins. With the help of software, the pixel value of the selected area was compared with the value in the centre of the penetrometer and thus a statement was made about the ossification that had taken place [43].

The comparison of optical density over the period of time evaluated was statistically significant when the groups were evaluated individually ($p = 0.001$). However, no statistical differences occurred between the groups. When comparing the LLLT group and control group, they reported a *p*-value of $p = 0.2273$, resulting in no statistical difference in bone regeneration. A comparison of optical density at thee and six months also demonstrated a statistically significant difference with a *p*-value of $p = 0.001$ for the LLL group and $p = 0.0249$ for the control group. From this, Matos et al. (2020) concluded that ossification was not yet complete after three months. Furthermore, they evaluated pain sensation by recording pain intensity daily using a visual analogue scale. They found no significant difference between the two groups [43].

3.2.2 Animal Studies

Twelve animal studies were included in this review. An overview of the studies is provided in Table 9 and Table 10.

A single study by Santiago et al. (2012) was conducted using 11 dogs [110]. RME was performed over a period of seven days. Afterwards the success of RME was controlled by occlusal radiographs. Laser application was carried out from the start of palatal expansion. A photon laser device with a wavelength of 790 - 940 nm and an energy density of 90 - 120 J/cm^2 was used. Further parameters were not stated. The LLLT was conducted for 39 days with an interval of two days, resulting in 20 applications. For evaluation, histological examination was performed 40 days after the first laser application, which was approximately one month after achieved palatal expansion. It involved the examination of the connective tissue, blood vessels, cells, palatal bone tissues at edges of the suture via score and number of osteoblasts. Significant differences favouring the LLLT for connective tissue of the suture, blood vessels and bone tissue were reported. No statistically significant difference was found for osteoblast counts or relation to the width between the edges of the suture and the width of the area of newly formed bone [110].

A total of eleven studies investigated the effect of LLLT on bone regeneration after RME in rats.

The first study was conducted by Saito and Shimizu in 1997 [111]. They observed the effect of LLLT on new bone formation in 56 rats in the histomorphometric and 20 rats in the

histological examination. The rats were divided into seven groups containing eight rats in each group: one untreated, one group only treated with palatal expansion and five groups with different irradiation protocols [111].
The laser device used was a gallium-aluminium-arsenide (Ga-Al-As) diode laser with a wavelength of 830 nm. The diameter of the optical fibre was 0.6 mm. The used power was 100 mW with a power density of 35.3 J/second/cm^2. Depending on the group, the total dosage of energy was 126 J or 420 J. Depending on the allocated group, laser application took place over seven days, divided in 3 min or 10 min of irradiation time, or three days from day 0 - 2 or day 4 - 6 for 7 min or a single irradiation on day 0 for 21 min [111].
The histomorphometric examination for the seven days irradiated groups showed significantly higher newly formed bone area on the third and seventh day in favour of LLLT. Mineral apposition was also increased. The results for the 10 min irradiation group where higher than those for the 3 min irradiation group. Additionally, a statistically significant higher amount of newly formed mineralised bone area and a higher mineral apposition rate was reported on day 0-2 [111].
No significant difference was observed for the group irradiated at day 3 to 6 or the single irradiation group [111].
In the histological examination, extension of the transverse fibres and enlargement of vessels were observed in each group. No pathological tissue changes, such as sclerosis or excessive inflammation, were observed [111].

Da Silva et al. (2012) investigated the effect of LLLT on the osteoblastic cell activity in the midpalatal suture of rats after palatal expansion [112]. For this purpose, they divided 30 rats into a control and a treatment group. In each group, five rats were euthanised and examined after 24h, 48h and seven days [112].
The laser parameters described was a Ga-Al-As diode laser with a wavelength of 830 nm. The spot size was 0.00785 cm^2 with a diameter of 1 mm. The irradiation time was 0.42 sec at a power of 30 mW resulting in an energy density of 160 J/cm^2. Laser irradiation was performed once, immediately after expansion [112].
The results were evaluated using cell cultures harvested from palatal bone fragments. They showed that the doubling time between day 3 and 7 decreased in cells harvested 24 and 48 hours after LLLT, indicating an increased cell proliferation rate. In contrast, an increased doubling time was observed in cells harvested 7 days after LLLT, indicating a decreased cell proliferation [112].
Alkaline phosphatase activity was increased in all LLLT-treated groups. Furthermore, increased messenger ribonucleic acid expression of osteoblast markers (alkaline

phosphatase, runt-related transcription factor 2, osteocalcin, type I collagen, and bone sialoprotein) was detected for each evaluated LLLT group [112].
Increased mineralisation was also noted for each group exposed to LLLT. The highest level was observed in the cells harvested 48 hours after RME [112].

Rosa et al. (2014) investigated different laser parameters and their impact on bone formation in the midpalatal suture in rats. 20 rats were divided into four groups, one group without treatment, one group with expansion only and two groups with expansion and laser irradiation [113].
Two different devices were used for the irradiation therapy. A diode laser with a wavelength of 780 nm. The irradiation time was 257 seconds and the used energy was 18 J with an energy density of 18 J/cm^2. The spot size was reported to be 0.04 cm^2. The other device was a light-emitting diode (LED) laser with a wavelength of 850 nm. The irradiation time was 120 seconds and the used energy was 18 J with an energy density of 18 J/cm^2. The spot size was reported to be 0.4 cm^2. Additionally, they stated for both devices a size of 1 cm^2 for the illuminated area. The discrepancy between the reported spot size and the actual irradiated area was explained by the light scattering and Gaussian distribution of the laser beam. The laser application was performed three times at 48-hour intervals, that is one, three and five days after expansion [113].
For evaluation, Raman spectroscopy was performed after eight days. They reported a statistically significant difference in favour of LLLT for hydroxyapatite mineralisation in the midpalatal suture. This was observed for both types of laser irradiation. No difference in collagen disposition in the midpalatal suture was observed. No statistically significant difference was observed with regard to collagen disposition or hydroxyapatite mineralisation in the cortical bone [113].

Rosa et al. (2017) conducted a second study to investigate the effect irradiation therapy on bone formation after palatal expansion in rats [114]. A total of 45 rats were divided into nine groups. Four groups were observed after 7 days. These consisted of a control group that received no treatment, an expansion only group, an LLLT group and an LED treatment group. The remaining five groups were used for the assessment after 14 days. They consisted of an expansion-only group, two groups treated with either LED or LLLT during the first week, and two groups treated with either LED or LLLT during a two-week period [114].
The LED and LLL parameters used were identical to the aforementioned study. However, the application protocol varied. Irradiation was performed at two-day intervals on day 1, 3, 5 and, depending on the assigned group, additionally on day 8, 10 and 12 after expansion [114].
Similar to the study conducted in 2014, Raman spectroscopy was performed as well [114].

The following results are referred to the evaluation of the tissue of the midpalatal suture.
No difference in collagen presence was observed in the evaluation after seven days. Concerning the concentration of hydroxyapatite, LLLT and LED showed a statistically significant difference compared to the expansion-only group. Also, the LED demonstrated a statistically significant higher value compared to the LLLT. No statistically significant difference for hydroxyapatite concentration in the cortical bone was observed after seven days [114].
The results evaluated after 14 days showed a statistically significant difference in the occurrence of lower collagen peaks in the one-week LED treated group compared to expansion only. No statistically significant difference was identified for the remaining LED or LLL irradiated groups after 14 days [114].
With regard to hydroxyapatite concentration, both the two-week LLLT and LED irradiation demonstrated a statistically significant increase compared to expansion alone. Between the two-week irradiated groups, LLLT had statistically significantly higher values than LED irradiation [114].
The results for the cortical bone were as follows.
When evaluated after seven days, no difference was observed in the collagen peaks or hydroxyapatite. When evaluated after 14 days, the group with LLLT and LED irradiated for one week demonstrated a statistically significant difference with lower values for collagen peaks compared to the group with expansion only. No statistically significant difference was found for LLL or LED therapy for two weeks compared to expansion only after 14 days. No statistically significant difference was identified for the hydroxyapatite peaks [114].
With regard to the histological analysis, Rosa et al. (2017) observed inflammation for all groups except the untreated control group [114]. Comparing all LED and LLL therapy groups with the expansion only groups, collagen disposition was statistically significant increased. They also reported greater osteoblast activity and diminished osteoclast activity in the irradiated groups [114].

Altan et al. (2015) investigated the impact of different doses of LLLT on bone regeneration at the sutura palatina in rats [115]. For this purpose, a total of 28 rats were divided into four groups. One group received only expansion treatment and three groups were treated with different doses of LLLT [115].
A Ga-Al-As diode laser with a wavelength of 820 nm was used for LLLT. The fibre diameter was reported to be 2 mm. The low-dose application was conducted with an irradiation time of three seconds and an energy density of 5 J/cm^2. The energy dose used was 0.15 J. The medium dose application contained an irradiation time of 13 seconds and an energy density of 20 J/cm^2. The energy dose used was 0.65 J. The high dose application was reported with an irradiation time of 1,930 seconds and an energy density of 6,300 J/cm^2. The energy dose

used was 198 J. For each group an irradiance of 1.6 W/cm^2 was reported. A total of four LLLT treatment sessions were stated [115].
A histological examination of osteoblasts, osteoclasts, fibroblasts, vessels and transforming growth factor beta was performed for evaluation. For each parameter a statistically significant difference was found in favour of LLLT. There was an upregulation for all outcomes, except for osteoclasts, which were at a lower level than in the expansion-only group. In the low-dose LLLT group, the increase in vessels, transforming growth factor beta and new bone formation were the highest. They were lowest in the mid-dose LLLT group. However, the number of osteoblasts and fibroblasts were highest in the mid-dose LLLT group. New bone formation was only statistically significant in the low- and high-dose groups [115].

Amini et al. (2015) examined the effect of LLLT on bone regeneration after palatal expansion in rats. For this purpose, 78 rats were divided into seven groups [116]. The groups contained a control group and six pairs of groups in which expansion was performed alone or in combination with LLLT. An evaluation was conducted for each pair of groups after 7, 14 and 30 days. This resulted in a group size of 12 rats each [116].
For the LLLT, a Ga-Al-As laser with a wavelength of 810 nm was used. An energy density of 4 J/cm^2 was chosen. Irradiation was performed on days 0, 2, 4, 6, 8, 10, 12 and 14 after expansion, resulting in a maximum of eight treatment sessions. Four application points were irradiated per session. No further parameters were reported [116].
The metric measurement of bone regeneration in the histological sample was investigated as the evaluation method. No significant difference was observed between the evaluated groups after seven days. A statistically significant difference in favour of LLLT was reported in the evaluated groups at 14 and 30 days. However, the highest extent of bone regeneration was observed after seven days, but the benefit of LLLT was noted after 14 and 30 days. This indicated a late effect of LLLT [116].

Aras et al. (2015 and 2015) conducted two studies in 2015 [117, 118]. Both investigated the influence of LLLT on bone formation in rats after palatal expansion. The studies were similar in the following aspects of the study design [117, 118].
A total of 32 rats were divided into a LLLT and control group of 16 rats each. The groups were divided in half for examination after seven and 17 days, resulting in a group size of eight animals per group [117, 118].
The laser used was a Ga-Al-As diode laser with a wavelength of 808 nm. An area of 1 cm^2 was irradiated for a period of 20 seconds. The energy used was 5 J with an energy density of 5 J/cm^2. Irradiation was conducted four days after expansion, with a daily treatment for four days. This resulted in four treatment sessions [117, 118].

Results

For evaluation, both studies used histological examination. The number of osteoclasts, osteoblasts, capillaries, and inflammatory cells were evaluated. Additionally, the extent of new bone formation was analysed [117, 118].

The study by Aras and Erkilic et al. (2015) revealed no statistically significant difference in the number of osteoblasts [118]. In the case of osteoclasts, the LLL-treated group examined after seven days demonstrated a significantly higher amount. No osteoblasts were found in the corresponding control group. In the groups observed after 17 days, no significant difference was found for osteoblasts. With regard to the capillaries, no statistically significant difference between the groups was observed. Concerning the inflammation, the LLLT treated group observed after seven days showed less signs of inflammation compared to control group. Additionally, the trabecular bone extent was larger. The evaluation conducted after 17 days revealed an increased ossification for the group treated with LLLT [118].

In contrast to the aforementioned results, Aras and Bozdag et al. (2015) observed a greater amount of osteoblasts in the LLLT group after seven days [117]. No significant difference was revealed after 17 days. The number of osteoclasts were higher in both control groups than in the LLLT group [117].

Similar to the aforementioned study, no significant difference was observed in the quantity of capillaries between the groups. When assessed after seven days, the precence of trabecular bone was observed in the LLLT group, while none was found in the control group. After 17 days, the LLLT group revealed greater bone regeneration compared to the control group. At both time points of assessment, inflammation was lower in the LLLT-treated groups [117, 118].

Tas Deynek and Ramoglu (2019) investigated the effect of varying laser parameters on the bone regeneration after palatal expansion in rats [119]. A total of 80 rats were divided into four groups. They contained a control group, and a high, mid, and low LLL-dose group. Each group was subdivided for evaluation at 7 and 21 days. This resulted in a sample size of ten rats per group [119].

An indium-gallium-arsenide-phosphide (In-Ga-As-P) laser device with a wavelength of 940 nm was used. The irradiated area was 1 cm^2. The irradiation time was 180 seconds. The low-dose application included an energy density of 18 J/cm^2, the medium-dose 42 J/cm^2 and the high-dose 60 J/cm^2. Irradiation was performed two times in the first week after palatal expansion [119].

The evaluation was conducted based on a histological examination. When assessed after seven days, the number of osteoblasts were higher in the low-dose group compared to all other groups. The same outcome was observed with regard to osteocytes. The quantity of connective tissue was diminished in the low-dose group compared to all other groups. The newly formed bone area and the ratio of newly formed bone area to total bone area were

observed to be greater in the low-dose group than in all other groups. No statistically significant difference was reported in the number of vessels and with regard to inflammation. Furthermore, no significant difference was observed for the medium- or high-dose groups [119].
In the evaluation after 21 days, the number of osteoblasts was higher in the low-dose irradiated group than in all other groups. Furthermore, the number of osteocytes was higher in the low-dose group than in the control group. The quantity of connective tissue was smaller in the low-dose group compared to all other groups. No statistically significant difference was observed for connective tissue or the number of osteoblasts between the medium- and high-dose groups and the control group. With regard to the number of vessels, a statistically significant difference was only observed in the low-dose group. The evaluated results for the newly formed bone area and the ratio of newly formed bone area to total bone area were the highest in the low-dose group compared to all other groups. An increased level of inflammation was observed in the high-dose group [119].

Eslamian et al. (2020) compared the effect of LLLT on bone regeneration and bone density after palatal expansion in rats [120]. A total of 40 rats were divided into four groups. They contained of a group sacrificed immediately after palatal expansion to obtain a reference value, a control group, a single irradiation group and a multiple irradiation group. Each group contained 10 rats [120].
A diode laser with a wavelength of 808 nm was used. A power density of 100 J/cm^2 and an irradiation time of 0.1 msec were used. No additional parameters were reported. Irradiation was performed once for group A after a retention period of seven days. Group B was irradiated on days 7, 9, 11, 13 and 15 after palatal expansion [120].
Bone density was assessed via occlusal radiographs. The results demonstrated a significantly higher bone density in the multiple irradiation group compared to all other groups. The single irradiation group demonstrated no statistically significant difference when compared to the control group [120].
Additionally, the bone density was evaluated through micro-computed tomography. A statistically significant difference was only demonstrated for the multiple irradiation group. The results were in accordance with those of the occlusal radiographs [120].
In addition, the histological examination of the suture palatina width was conducted. Compared to the control group, a statistically significant smaller suture width in the multiple irradiation group was reported. The evaluation of this parameter revealed no statistically significant difference between the single irradiation group and the control group [120].

Mohaghegh et al. (2020) investigated the impact of LLLT and bone marrow-derived stem cell injection on the bone formation in rats [121]. A total of 60 rats were divided into four groups: a control group, an LLLT group, a stem cell therapy group and an LLLT with stem cell therapy group [121].
A Ga-Al-As diode laser with a wavelength of 810-830 nm was used. The power was 250-300 mW with an energy density of 4-6 J/cm^2. No further parameters were reported. Irradiation was performed twice on the day of retainer placement and once more seven days later [121].
An evaluation was performed after 28 days. For this purpose, bone density was measured in the occlusal radiographs. Only the group that received LLLT and stem cell therapy showed a statistically significant increased bone density compared to the control group. No statistically significant result was observed for only LLLT or stem cell mono-therapy. Furthermore, bone density was assessed using a micro- computerized tomography (CT) scan. The results were consistent with the analysis of occlusal radiographs [121].
In addition, a histological examination was performed. With regard to the number of osteoblasts, only the LLLT group without stem cell therapy demonstrated statistically significant greater results. The assessment of vascularisation was only in the stem cell group significantly significant. The results for connective tissue quality were statistically significantly in favour of the groups with stem cell therapy with and without LLLT. The group treated with LLLT only showed no statistically significant difference for this outcome. No statistically significant difference was observed for new bone in any of the experimental groups. The assessed sutural width showed no statistically significant difference for all groups [121].

3.3 Results for Clinical Studies

3.3.1 Results for Risk of Bias Assessment

As this review implements non-clinical studies in an exploratory approach, no risk of bias was assessed for animal studies. Risk of bias assessment was conducted for clinical studies.
The Cochrane RoB 2 tool by Sterne et al. (2019) was used for this purpose [99].
As described in 2.4, the risk of bias assessment was conducted by two independent researchers. A consensus was reached on all domains, therefore no third researcher was requiered. In the following section, the results are presented.

Table 17 provides an overview of the results obtained in each domain. For improved visual presentation, the percentage risk of bias distribution for each domain was also provided in Figure 3. The detailed evaluation of each domain is presented in Table 11 to Table 16.
Overall, two studies were rated with a *high* risk of bias, while three were rated with *some concerns*. No study was rated with a *low* risk of bias.

Concerning risk of bias arising from the randomization process, Cepera et al. (2012) and Angeletti et al. (2010) were rated as *some concerns*, while the other studies were rated as *low* [43, 106-109].
In the domain risk of bias due to deviations from the intended interventions - effect of assignment to intervention, Cepera et al. (2012) and Angeletti et al. (2010) were rated as *high* [106, 107]. Garcia et al. (2016) and Matos et al. (2020) were rated as *some concerns*, while only Ferreira et al. (2016) was rated as *low* [43, 108, 109].
The risk of bias due to deviations from the intended interventions - effect of adhering intervention was found to be *high* for Cepera et al. (2012) and Angeletti et al. (2010) [106, 107]. The remaining studies were rated as *low* [43, 108, 109].
With regard to the domain assessing the risk of bias due to missing outcome data, all studies were rated as *low* [43, 106-109].
The risk of bias in measurement of the outcome was rated as *some concerns* for the studies by Cepera et al. (2012) and Matos et al. (2012) [43, 107]. The remaining studies were rated as *low* [106, 108, 109].
The risk of bias in selection of the reported result only the study by Matos et al. (2020) was rated as *low*, while all other studies were rated as *some concerns* [43, 106-109].
Based on these findings, the overall risk of bias was evaluated.
As previously stated, the overall risk of bias was rated as *high* for Cepera et al. (2012) and Angeletti et al. (2010) [106, 107]. *Some concerns* were assessed in the studies by Garcia et al. (2016), Ferreira et al. (2016) and Matos et al. (2020) [43, 108, 109]. No study was rated as *low* risk of bias.

Figure 3 presents the percentage distribution of the risk of bias evaluation for the individual domains. Without the consideration of the overall risk of bias, the graph seems to show that for two domains in particular, only 20% risk of bias was evaluated as *low*. With regard to the domain risk of bias due to deviations from the intended intervention - effect of assignment to intervention the evaluation revealed 40% with *high* risk, 40% with *some concerns* and only 20% with low risk of bias. In the domain risk of bias due to the selection in the reported result, 80% of the studies were rated with *some concerns* and only 20% with *low* risk. In the remaining domains, 60% was rated as *low* risk of bias, as well as for the domain risk of bias due to missing outcome data 100% were rated as *low* risk of bias. Altogether, the overall risk of bias was rated as 40% *high* and 60% *some concerns*.

3.3.2 Results for Certainty Assessment of the Outcome

In order to provide a higher level of evidence for this study, the GRADE approach to assess the certainty of evidence was carried out [102]. This was conducted by two independent

researchers. A single assessment was performed on a PICO (population, intervention, comparison, outcome) -generated question.
The addressing question, to which GRADE was applied, was the initial question presented in the section 1.6. According to the PICO scheme, the following question was formulated: Patients treated with LLLT as an adjuvant therapy for RME have increased bone regeneration of the sutura palatina, compared to patients treated with RME only.

The results of the GRADE evaluation are presented in an overview in Table 18.
In the case of two studies, the GRADE analysis was conducted on a subgroup only. This was the case for Garcia et al. (2016) [108]. In the study, qualitative and quantitative data were collected. In the qualitative data collection, the shape of the margins of the sutura palatina was assessed by two researchers using a scale. The quantitative data collection included the measurement between the distances of the bone margins along the sutura palatina [108]. For the purposes of the GRADE analysis conducted for this review, only the results of the quantitative analysis have been included.
Matos et al. (2020) assessed bone regeneration and pain sensation in their study [43]. Only the results related to bone regeneration were included in the GRADE assessment [43]. The studies by Ferreira et al. (2016), Angeletti et al. (2010) and Cepera et al. (2012) were fully included into GRADE evaluation without limiting them to a subgroup [106, 107, 109]. Consequently, a total of five studies were included in the GRADE evaluation [43, 106-109].
Overall, the rating of the certainty of evidence by GRADE resulted in *very low*. The reasons for the downgrading are explained in the following section.
The study design of the included studies was randomised controlled trials only. Therefore, the assessment began with a rating of *high*.
Concerning the risk of bias, the overall assessment resulted in a *high* risk for the studies by Angeletti et al. (2010) and Cepera et al. (2012) [106, 107]. Furthermore, the overall assessment resulted in *some concerns* for Matos et al. (2020), Ferreira et al. (2016) and Garcia et al. (2016) [43, 108, 109]. However, an examination of the individual evaluations of the domains revealed that many were rated as *low* or *some concerns*. Only in two studies were two domains each rated as *high*. However, these domains were considered less of a risk by the authors due to the study design. Therefore, a downgrading of one point for the risk of bias was made.
With regard to inconsistency, the study was downgraded by one point. As no meta-analysis was conducted, no *p*-values, I^2, or confidence intervals were available for evaluation. The evaluation was conducted by comparing the studies, whether there were differences in the patients or different subgroups of patients, similarity of the intervention, the definition of the outcome and the quality of the study.

While the majority of the included studies the age of the patients was between six and fourteen years, the age of the patients in the study by Angeletti et al. (2010) was between 18 and 33 years [43, 106-109]. However, as described in the section 1.4.3 ossification is not complete at an advanced age. This led the authors to conclude that the effect of older age as a subgroup was not of great relevance.

Additionally, Angeletti et al. (2010) investigated their research on patients with SARME [106]. They reported that a subtotal LeFort I osteotomy and palatal expansion were performed using dental fixed appliance with a Hyrax screw [106]. The surgical procedure of the LeFort I osteotomy usually implies that the sutura palatina is not part of the surgical intervention [122]. As in this case, a non-invasive expansion of the sutura palatina was performed using an orthodontic appliance [106]. With respect to the research question, the intervention of RME and SARME was thus considered equivalent in terms of its impact on the sutura palatina. However, concerning inconsistency between the studies it seems noteworthy that, the laser parameters and protocol varied between the studies. In addition, the time point of evaluation did differ between the studies. Overall, these arguments resulted in a downgrade of one point for inconsistency [43, 106-109, 122].

All studies addressed LLLT as an adjuvant therapy for RME or SARME and its benefit on bone regeneration in the sutura palatina [43, 106-109]. As previously stated, SARME appears to be comparable to RME concerning its effect on the sutura palatina.

Each study investigated the direct effect of LLLT on bone regeneration of the sutura palatina as a leading question [43, 106-109]. Furthermore, the methods of assessing bone density using occlusal radiographs or computed tomographic scans were considered valid. As mentioned above, differences in time point of the evaluation or the laser parameters as well as laser protocol were taken into account as an effect of inconsistency between the studies. Therefore, no downgrading for indirectness was performed.

In terms of imprecision, a downgrade of one point was applied. As the confidence interval could not be evaluated as a parameter in this section, the sample size was used as a guide for the assessment. For continuous outcomes, as in this review, a sample size of all included studies exceeding 400 is recommended [104]. This criterion was not met by the included studies, resulting in a downgrade of one point.

Publication bias was not detected. It seems worth mentioning that the absence of larger studies with a larger number of subjects makes it difficult to assess this issue. Overall, most studies declared that there was no conflict of interest associated their research. The only sources of sponsorship mentioned were from independent academic or university institutions.

No reasons for upgrading due to large magnitude of effect, dose response or effect of all plausible confounding factors were identified.

Considering the aforementioned assessment, the overall quality of evidence assessment rating for this review was downgraded by three points.
This resulted in the quality of the evidence being rated as *very low*.

3.3.3 Results in Relation to Laser Parameters and Application Frequency

As presented in Table 8, the laser parameters used varied between the studies [43, 106-109]. Summarising Table 8, the following results can be revealed for the laser parameters.
Results in favour of LLLT were reported by Ferreira et al. (2016), using a spot size of 0.04 cm^2, an energy density of 35 J/cm^2 and an irradiation time of 20 seconds per point [109]. The wavelength was 780 nm [109].
Cepera et al. (2012) stated positive results favouring LLLT by using a spot size of 0.04 cm^2 and a wavelength of 780 nm as well [107]. However, the energy density was reported as 10 J/cm^2 and the irradiation time was stated to be 10 seconds [107].
Angeletti et al. (2010) found positive results in favour of LLLT with a spot size of 0.06 cm^2, an energy density of 140 J/cm^2, an irradiation time of 84 seconds and a wavelength of 830 nm [106].
Garcia et al. (2016) stated positive results favouring LLLT [108]. As mentioned in section 3.2.1, the quantitative analysis revealed a significant result at only one out of the four measuring points. A positive outcome was reported by the qualitative analysis. The result of the qualitative analysis was not incorporated into the GRADE assessment.
However, the laser parameters used were a wavelength of 660 nm and a spot size of 0.26 cm^2. They were the only authors who used two different parameters for the irradiated points along the midpalatal suture (A) and side of the suture (B). For A, the irradiation time was 60 seconds with an energy density of 23 J/cm^2. With regard to B, the irradiation time was 30 seconds, with an energy density of 12 J/cm^2 [108].
Matos et al. (2020) stated results that were not favour of LLLT [43]. The laser parameters used were reported with a wavelength of 980nm, an irradiation time of 10 seconds, a spot size of 1.26E3 cm^2 and a power density of 238.85 J/cm^2 [43].
The following results apply to all studies except Garcia et al. (2016).
The number of application points per treatment ranged from three to twelve. The time interval of LLLT started with the retention phase of RME and extended up to eight weeks. The total number of treatment sessions ranged from eight to twelve [43, 106, 107, 109]. In addition, Cepera et al. (2012) and Matos et al. (2020) performed LLLT from the onset of screw activation of RME [43, 107].
Garcia et al. (2016) conducted a total of seven applications over a time interval of 70 days [108].

3.3.4 Results in Relation to Timepoint of Evaluation

In the context of clinical studies, different assessment methods were applied regarding the time point of evaluation. One method involved a comparison of the bone density of the groups at a specific time point. This was performed by Angeletti et al. (2010), Garcia et al. (2016) and Cepera et al. (2012) [106-108]. However, Cepera et al. (2012) used an additional method, which was to compare the change in bone density over a period of time [107]. This approach was also performed by Ferreira et al. (2016) and Matos et al. (2020) [43, 109].

In the case of the comparison of bone density at a specific time point, the following results can be presented.

Angeletti et al. (2010) reported results in favour of LLLT after one (p = 0.022), two (p = 0.007), three (p = 0.004), four (p = 0.003) and seven months (p = 0.003). No results were reported that were not in favour of LLLT [106].

Garcia et al. (2016) presented a result favouring the LLLT after approximately two and a half months (75 days) (p = 0.04) [108]. However, this finding was limited to the upper posterior distance of the sutura palatina. The results of the same CBCT scan at the anterior nasal spine, inferior distance and maximum distance measured were not statistically significant. Additionally, at the same time point, a significant result was reported in the qualitative assessment of the sutura palatina in favour of LLLT [108].

The following results can be extracted for the comparison of the change in bone density over a specific period of time.

Cepera et al. (2012) reported the results of a comparison between LLLT and the control group in their study [107]. The results were in favour of LLLT when the period from immediately after expansion to three months later was compared (p = 0.017). The results for the period between one and three months were also in favour of LLLT (p = 0.001). No statistically significant difference was observed between the groups immediately after expansion and 3-5 days later, and between 3-5 days after expansion and one month later [107].

Ferreira et al. (2016) reported statistically significant results in favour of LLLT when comparing bone density immediately after RME and after four months (p = 0.00) [109]. The results measured in the control group were not statistically significant for the same period (p = 0.2). A direct comparison between the groups was not reported. No further results were evaluated [109].

Matos et al. (2020) reported results of changes in bone density over a period of six months after RME [43]. A comparison of the groups revealed no statistically significant difference (p = 0.2273) [43]. The exact time interval to which this value refers was not stated.

Furthermore, a statistically significant change in bone density between month three and month six in the LLLT and control groups was stated, suggesting that bone formation was not complete at three months. However, no statistically significant difference in bone formation between the groups was observed [43].

Summarizing the results for the change in bone density over a specific period of time, the following was reported.
One study reported results in favour of LLLT for the time interval between one and three months, immediately after RME and after three months. No significant differences were observed in the time interval between immediately following RME and 3-5 days later, as well as between 3-5 days after RME and one month [107]. One study reported outcomes in favour of LLLT comparing the time interval immediately after RME to four months [109].
As previously stated, one study reported results that showed no significant difference between the LLLT and control groups. The exact time interval to which this value refers was not stated [43].

3.3.5 Results in Relation to Evaluation Method

Table 8 provides information on the evaluation method. Three studies used optical density measurements in occlusal radiographs. For example, Cepera et al. (2012) used a histogram equivalent to the grey scale, while Angeletti et al. (2010) and Matos et al. (2020) used the measurement of pixels to draw conclusions about bone density [43, 106, 107]. The use of occlusal radiographs enabled the measurement of the optical density at different time points [43, 106, 107].
While Cepera et al. (2012) and Angeletti et al. (2010) reported results in favour of LLLT, Matos et al. (2020) did not find statistically significant results for LLLT [43, 106, 107]. As can be seen from Table 8, radiological parameters were underreported. While Cepera et al. (2012) did not mention any of them, the other studies did not report all the required parameters, such as exposure time, amperage, and voltage [43, 106, 107].
Garcia et al. (2016) and Ferreira et al. (2016) both used CBCT as an assessment method [108, 109]. Ferreira et al. (2016) evaluated the outcomes by using a software to measure the optical density at three points and finally calculating a mean value of the optical density [109]. The results were in favour of LLLT [109].
Garcia et al. (2016) were the only authors who did not perform a bone density measurement method [108]. In the CBCT scans they conducted, measurements of the distance between the suture margins at three fixed points and the maximum possible distance were used for evaluation. In addition, a qualitative analysis in which the observers had to classify the continuity or discontinuity of the suture palatina, nasopalatine duct and anterior nasal spine,

was performed. The appearance of the margins of the suture was classified as well. This was based on a defined score using four levels. In the quantitative analysis, only one of the four measurement points was statistically significant. However, in the qualitative analysis, their results were in favour of LLLT [108].

4 Discussion

4.1 Discussion on the Results of this Study

4.1.1 Discussion on Results of Animal Studies

As presented in Table 9 and Table 10, a total of twelve studies on animals were included in this review. Overall, a variety of analysis methods were chosen. One of the most common was the histological examination of the number of osteoblasts, osteoclasts, vessels, connective tissue area, bone formation and inflammatory cells. For this evaluation method, the majority of the results from the individual studies indicated that these parameters were increased by LLLT. This was demonstrated at the assessment at time points which ranged from approximately seven days up to 30 days [114, 115, 117-119, 121]. Only in the number of vessels there were no significant differences in some studies. [117-119, 121].

As stated in section 1.3, the interaction between osteoblasts and osteoclasts is required for bone remodelling and regeneration.

Some studies included the activity of the osteoclasts as a factor in the evaluation of the efficiency of LLLT [114, 115, 117, 118]. However, as can be seen from the results, there is no consistency whether the number of osteoclasts is higher, lower or equal to the control group. While some studies stated an increase in osteoclast number and activity as a positive outcome, others stated the opposite, a decrease in osteoclast number and activity, as positive [114, 115, 117, 118]. It seems that there is no clear consensus on this matter. Consequently, it appears that it cannot be answered with certainty whether a higher, lower or unchanged number of osteoclasts compared to the control group can be considered a sign of increased bone regeneration. It appears that this might not be a reliable indicator to draw conclusions about bone regeneration. Therefore, this outcome criterion is not used in this review for drawing conclusions about bone regeneration.

Rosa et al. (2017 & 2014) conducted two studies in which Raman spectroscopy was performed [113, 114]. While the evaluation of the cortical bone did not seem to yield significant results, a significant result was reported for the midpalatal suture in terms of hydroxyapatite. However, the collagen disposition was not significantly different to the control group [113, 114]. This might indicate that the apposition of hydroxyapatite is enhanced by LLLT, which also suggests

a correlation of an upregulation of bone regeneration. Thus, not only the cellular component in numbers, but also its metabolic product seems to be increased.
This conclusion is consistent with the statements of the study by da Silva et al. (2012) [112]. They examined the bone cells from the sutura palatina using polymerase chain reaction. An increase in cell proliferation rates and increased messenger ribonucleic acid expression of osteoblastic markers such as alkaline phosphatase, runt-related transcription factor 2, osteocalcin, type I collagen and bone sialoprotein were found [112]. It may be concluded that LLLT not only increases the number of cells, but also stimulates cell metabolism, which could enhance bone regeneration.
Additionally, it seems noteworthy that in the study by da Silva et al. (2012) a single LLLT application led to this result [112].

Metric measurements of new bone formation and comparisons of individual suture widths were also conducted through histological analysis. This assessment method also seems to demonstrate a positive benefit on bone regeneration of the sutura palatina by LLLT [111, 114, 116-121].
In addition, Eslamian et al. (2020) evaluated the bone density of the sutura palatina using occlusal radiograph optical density evaluation and CT scan optical density evaluation [120]. The results are consistent with those obtained in the histological measurements [120].
Mohaghegh et al. (2020) also performed the evaluation of bone density in occlusal radiographs and CT scans [121]. They conducted a histological examination of osteoblasts, new bone formation, vascularisation, connective tissue and suture width as well. In addition to LLLT, they also investigated the influence of mesenchymal stem cell injections on bone regeneration. In order to adhere to the topic of this review, only the group of solely LLLT is included in the evaluation. The effect of stem cell injection is not considered further in this review. The only positive result reported was for the LLLT group in terms of the number of osteoblasts. It is striking that the histological evaluated results and optical density in occlusal radiographs and micro-CT scans did not favour LLLT. New bone formation and the sutural width did not show significant results for all experimental groups [121]. It is challenging to establish a connection between this and the results of other studies.
This is further complicated by the fact that the laser parameters were only partially explained. However, it is noticeable that laser application was performed for only three times and a low energy density with 4-6 J/cm^2 was applied [121]. Nevertheless, this alone might not indicate a reason for a non-positive result for LLLT, since other studies with a low energy density or few applications has demonstrated positive outcomes [115-118]. A possible conclusion might be that the relation between low energy density and few laser applications leads to an insufficient dose and a lack of efficiency of LLLT.

However, when the results of the studies by Mohaghegh et al. (2020) and Eslamian et al. (2020) are compared, it seems interesting that the histologically measured distance of the sutura width coincides with the results of the bone density in occlusal radiographs and the CT scan [120, 121]. It can thus be concluded that the bone density measurements obained in occlusal radiographs and CT scans are in correlation with the results of the histological measurement and therefore might represent a valuable method for evaluating the bone regeneration of the sutura palatina.
In addition, no significant difference was observed between the results of the occlusal radiographs and the CT scans [120, 121]. It can therefore be concluded, that a CT scan is not necessarily a superior method of evaluating bone density compared to occlusal radiographs. Especially in consideration of the radiation exposure and the possibility of conducting several occlusal radiographs at different time points on subjects, it appears reasonable to perform the evaluation of bone regeneration using occlusal radiography.
Nevertheless, it should be considered that a CT scan provides additional opportunities for evaluation, such as measuring the width of the bone margins of the sutura palatina.

The available evidence from animal studies does not permit the drawing of conclusions regarding the optimal laser parameters. As presented in Table 9 a large heterogeneity in the dosage, for example energy density and irradiation time, as well as in the frequency of application, prevents to draw a conclusion.
In some cases, the comparison is further complicated by a lack of information on the parameters. It is striking that a dosage of 100 mJ/cm^2 and 0.1 milliseconds as well as 160 J/cm^2 over 0.42 seconds resulted in a positive outcome in favour of LLLT [112, 120]. Furthermore, a laser application of 120 seconds or even 10 minutes appear to lead to positive results [111, 113, 114]. This extensive range of values illustrates the problem that a statement about a dose-related effect is not yet possible.

Three studies assessed a single LLL application [111, 112, 120]. Eslamian et al. (2020) and Saito and Shimizu (1997) found no statistically significant results for the single irradiation, while da Silva et al. (2012) reported statistically significant results favouring LLLT [111, 112, 120]. The main difference between the studies seems to be in the dosage of LLLT. While da Silva et al (2011) reported an application of 160J/cm^2 in 0.42 seconds, Eslamian et al. (2020) reported 100 mJ/cm^2 over 0.1 milliseconds [112, 120]. The parameters of Saito and Shimizu (1997) have not been fully clarified in the study report [111]. An energy of 126 J with an irradiation time of 21 minutes was reported. No value for the energy density was stated [111]. It is important to consider, that these results can only be compared to a limited extent, given that the evaluation method differed. Eslamian et al. (2020) performed a histological

measurement of the sutural width and a bone density analysis using occlusal radiographs and CT scan [120]. Saito and Shimizu (1997) performed a histological measurement of the newly formed bone and mineral apposition [111]. Da Silva et al. (2012) performed a polymerase chain reaction analysis [112]. It may be the case that an effect of single irradiation with LLLT can be detected at the molecular level after seven days using polymerase chain reaction, whereas no effect can be detected in histomorphometric parameters.
Furthermore, taking into account that only three studies investigated on single irradiation with LLLT, it appears noticeable that comparatively high and low doses did not lead to positive results for LLLT [111, 120]. Nevertheless, it is not possible to conclude from these results whether a single irradiation with LLLT is beneficial for bone regeneration of the sutura palatina in animals.

There might be an indication of an upper threshold for the doses of LLLT. When comparing different energy densities in the study by Tas Deynek and Ramoglu (2019), it was shown that only the low-dose LLLT had a positive effect [119]. The energy density was 18 J/cm^2 with an irradiation time of 3 min. The irradiation was performed twice [119].
Altan et al. (2015) also compared different laser doses [115]. They reported an energy density of 6,300 J/cm^2 and an irradiation time of 1,980 seconds for the high-dose LLLT. The low-dose group was reported with an energy density of 5 J/cm^2 and an irradiation time of three seconds, while the mid-dose group was reported with an energy density of 20 J/cm^2 and an irradiation time of 13 seconds. A power density of 1.6 W/cm^2 was stated for each group [115]. It is noteworthy that the values for irradiation time, energy dose and energy density for the high-dose group were reported with a comparatively high value. Furthermore, these values appear to be inconsistent with the mathematical comparison to the specified power density. However, it is unclear which of the values is the source of the discrepancy, and whether it could be a simple transcription error. Nevertheless, it seems reasonable to assume that a comparatively high energy density and irradiation time was used in the high-dose group.
However, statistically significant differences were reported across all LLLT groups. Apart from that, no significant difference in new bone formation was observed for the mid-dose group [115].
However, the doses of the low- and mid-dose groups are within the range of the doses of the low-dose group in the study by Tas Deynek and Ramoglu (2019) [115, 119].
The positive result for LLLT in the study by da Silva et al. (2011) with the value of 160 J/cm^2 contrasts with these findings [112]. It is important to note that a single irradiation was performed. The animal study on dogs by Santiago et al. (2012) also demonstrated results in favour of LLLT with higher values for the energy density in the range of 90-120 J/cm^2 with a total of 20 irradiations [110]. Laser applications were performed at two-day intervals. The

irradiation time was not reported. However, the comparison of this study with other animal studies should be taken with caution, as it was conducted on dogs, whereas the other studies were conducted on rats. Nevertheless, the results seem to be largely consistent with the other animal studies. [110]. With cautious consideration due to aforementioned discrepancies in the values, the high-dose group in the study by Altan et al. (2015) also had results that were in favour of LLLT with an energy density of 6,200 J/cm^2 and an irradiance time of 1,980 seconds, which is 33 minutes [115]. The irradiation was conducted four times [115]. Therefore it can be concluded, that the results of animal studies do not allow a statement about an upper threshold of the laser dose.
Nevertheless, it seems that the interaction between energy density, irradiation time and the number of applications is correlated. One possibility is that a single or few applications at a high dose could result in a comparable positive outcome to that of frequent applications at a lower dose. Conversely, it may be assumed that frequent applications of higher doses do not result in a positive effect of LLLT. However, these statements are only assumptions based on the isolated results of the examined studies. In the authors opinion, no statement can be made about an upper threshold for the LLLT dose in the context of the overall results.

However, a common finding seems to be that the laser application directly after RME might have a detectable effect when evaluated at seven, 14 or even 30 days. This has been demonstrated at the molecular level by polymerase chain reaction or Raman spectroscopy, as well as by histological and radiological examination.

The limitations of the results of the animal studies are limited in the following ways:
The comparability of the results is limited by the use of different laser doses and application protocols. In addition, the varying evaluation methods complicate comparisons. However, with the exception of the histological evaluation of the osteoclasts, no contradictory results were obtained for any of the evaluation methods, which allows a certain degree of comparability. Additionally, the beneficial effect of LLLT has been demonstrated for most of the different laser parameters. Nevertheless, it is important to bear in mind that the above results primarily refer to the application of LLLT in rats. The obvious anatomical differences between animals and humans alone, as well as the differences in metabolic processes, can only imply the potential benefits of the LLLT therapy in humans. For example, the depth of penetration of the LLL into deeper bone regions in humans may be diminished, and therefore the effect of LLLT could be different than it was observed in rats.

4.1.2 Discussion on Results of Clinical Studies

Five clinical trials were included in this review. Overall, the evaluation of the clinical trials presented several challenges, which are described in greater detail below.

The evaluation method in four of the studies was based on bone density measurement using occlusal radiographs or CBCT scans [43, 106, 107, 109]. Three studies evaluated the optical density in occlusal radiographs to draw conclusions about the bone density of the sutura palatina [43, 106, 107]. The study by Ferreira et al. (2016) used CBCT scans to measure the optical density of the sutura palatina [109]. As outlined in section 4.1.1, the methods of measuring optical density in occlusal radiographs appear to provide information on bone regeneration of the sutura palatina. This was shown in the CT scan as well. The authors of this review consider the evaluation by means of CBCT scans to be comparable to that of CT scans and assume that this form of evaluation also provides conclusions about the bone regeneration. Regarding the method of occlusal radiographs or CBCT scans for the evaluation of bone density, both methods seem to provide conclusions on the evaluation. As described in the section 4.1.1 it is assumed that the CBCT scan does not provide more accurate results. This method might not be superior to occlusal radiographs.
This is also reflected in the findings of both significant and non-significant results for LLLT on occlusal radiographs [43, 106, 107]. One advantage of occlusal radiographs is that a lower radiation exposure is required. This approach enables the assessment of the bone regeneration at different time points throughout the healing process.
In case of the occlusal radiographs not all of the set parameters were specified in the studies. However, each study mentions a certain degree of standardisation of the evaluation, which could be interpreted as an indication that the radiological parameters were standardised for all patients [43, 106, 107]. A comparison of the assessment based on different radiological parameters and the resulting findings is not possible due to the partial lack of parameter information. However, this would only be of interest as a side note and is not directly relevant to the topic of this review.

In the study by Matos et al. (2020), the energy density was stated to be 238.85 J/cm^2 with an energy of 3 J. The diameter of the laser beam was specified as 0.4 mm, while the spot size was reported as 1.26E3 cm^2. The power density was stated to be 238.85E3 mW/cm^2 with a power of 300 mW [43].
Upon closer examination, these values appear to be contradictory. The spot size of 1.25E3 cm^2 does not seem applicable in practice due to the size of the area. Furthermore, this does not correspond a circle with a diameter of 0.4 mm. With regard to the reported irradiation time per point of 10 seconds, a power of 300mW and a power density of 238850 mW/cm^2, these

values seem to be correct. Nevertheless, a further comparison with the energy density of 238.85 J/cm^2 reveals a discrepancy. It can be assumed that a calculation or topographical error may have occurred in the study report.

The exact value given, especially with regard to energy density, is therefore not considered a reliable statement for the evaluation in this review. Regardless, it appears that a comparatively higher energy density was used.

This assumption is based on the high stated energy density value of 238.85 J/cm^2 and the high value of the stated power density [43]. Therefore, the result of the study was included taking into account a relatively higher energy density.

Furthermore, the study by Mathos et al. (2020) seems to differ from the other studies with regard to the laser parameters, as a comparatively high energy density was apparently used [43].

The stated patient flow in the study by Matos et al. (2020) requires further analysis [43]. Initially, they stated 40 patients evenly distributed between the groups. As a consequence of the loss of patients during the follow-up period, the sample size was reduced. In the flow chart, a total of six patients were excluded, while the text mentioned a total of seven excluded patients. However, the sample size evaluated, as indicated in the flow chart and in the text, was consistent throughout the report [43]. It is suspected that this discrepancy was due to an error in the transmission of the numbers. However, this discrepancy is considered inconsequential [43]. It is therefore concluded that this discrepancy is unlikely to have affected the results of the study. Accordingly, this was not incorporated into further analyses, including the risk of bias assessment.

Regardless of the aforementioned issue, Matos et al. (2020) reported that LLLT had no significant impact on the ossification of the sutura palatina [43].

Despite the issue of the interpretation of the reported laser dose, it is assumed that Matos et al. (2020) used a higher energy density than that reported in the other studies [43]. From the authors' point of view, it is not possible to conclude whether this represents the upper limit for LLLT based on a single study.

This is further supported by the animal studies, where the use of higher values of LLL was reported as well [110-112, 115, 119]. As stated in section 4.1.1, it was not possible to demonstrate in the animal studies a correlation between high energy density and irradiation time in terms of the absence of an effect of LLLT. Even high energy density values of up to 6,300 J/cm^2 with an irradiation time of 1,980 seconds, which exceeds the energy density and irradiation time of Matos et al. (2020), led to positive results [43, 115]. Nevertheless, some of the animal studies also indicated that the higher doses of LLLT had no effect compared to the control group [111, 115, 119]. While no definitive conclusion can be drawn regarding the upper

threshold, the results may suggest a potential diminishing effect of LLL on its outcomes with increasing doses.
Furthermore, an irradiation area that is too small might also have an influence on the results of the LLLT. Even assuming that the light is distributed further in the tissue by light scattering, a sufficient distribution of the LLL could fail to occur if the spot size is too small.
Whether a comparatively small irradiation area in Matos et al. (2020) could have led to a lack of effect of the LLL remains unclear, especially in consideration, that the size of the irradiation area is not certain [43].

The risk of bias assessment also demonstrated the classifications into *high* risk and *some concerns*. However, the authors of this review consider the *high* risk ratings of the domain risk of bias due to deviations from the intended intervention to be less serious. This assumption is based on the consideration, that the influence of this domain is rather low due to the intervention and assessment method. This is because the evaluation of this domain is largely based on whether the participants and their caretakers were aware of the assigned intervention. Such factors could influence the behaviour of the participants or caretakers in the study, which may affect the outcome of the intervention group. However, the impact of this effect is considered minor due to the evaluation methods and the nature of the therapy. It seems unlikely that bone regeneration was influenced by the behaviour of the individuals involved, apart from the conscientious implementation of the therapy.
Nevertheless, it should be mentioned that none the studies were classified as *low* risk of bias. On average, a certain degree of risk of bias must be assumed, which is apparently in the range of *some concerns*. This might further diminish the confidence in the results of the studies.

A GRADE evaluation was carried out to provide an additional indication of the certainty of the results. The implementation of GRADE in this systematic review was subject to certain limitations. It was not possible to use any calculated values, which would be available in a meta-analysis, for the evaluation. Such data would have allowed a more objective evaluation to be conducted. Consequently, the evaluation was largely based on the individual and partly subjective judgement of the authors.
Furthermore, the GRADE assessment was limited to a single question: Whether LLLT provides a benefit for bone regeneration of the sutura palatina after RME. Therefore, the GRADE analysis offers a limited evaluation of the results of this review. Possible further conclusions, which are discussed in this review, are not part of the evaluation by GRADE.
This also applies to the results of animal studies that were included in the GRADE analysis.
Furthermore, in the case of the study by Garcia et al. (2016), only one subgroup was included in the GRADE analysis [108]. Two different evaluation methods were used in the study. Only

the subgroup of quantitative results in which the distance of the sutura palatina was measured in the CBCT scan, was included into the GRADE assessment [108]. None of the animal studies observed the associations between the distance measurements of the bone margins in the CT scan and histological analyses. However, this method is considered a valid method by the authors of this review, and was therefore included in the GRADE assessment.

The results were evaluated at four measurement points. Only at one of the points evaluated did the measurement reveal a significant difference compared to the control group. The authors of this review do not consider this result to be relevant for drawing a conclusion in favour of LLLT compared to the control group. However, the qualitative evaluation by Garcia et al. (2016) demonstrated statistically significant results in favour of LLLT [108].

In the study by Matos et al. (2020), the impact of LLLT on bone regeneration of the sutura palatina and on pain sensation in RME was investigated [43]. For this review, only the subgroup in which bone regeneration was evaluated was included into the GRADE assessment [43].

The GRADE classification resulted in *very low*. This indicates that the certainty of the result on the assessed question seems to be very low. This statement is in accordance with the assumption that a rather subjective evaluation of the GRADE was inevitable, as well as with the fact that this is a systematic review. Given the study design, it is not possible to provide a higher level of significance, as would be possible in the context of a meta-analysis, for example. A GRADE evaluation addressing the question of the influence of LLLT in RME on treatment duration or relapse was not conducted due to a lack of further studies.

Furthermore, the comparability of the studies is partly limited by the use of different laser parameters, application protocols and evaluation methods were used. This was also reflected in the GRADE evaluation. To assess the efficiency of different laser parameters or application protocols with GRADE, the current study situation does not seem to provide enough comparable data.

In the GRADE assessment the effect of LLLT on bone regeneration after RME was investigated. The included studies revealed three studies indicating a beneficial efffect and two without a positive effect of LLLT. Considering the GRADE evaluation of *very low*, it seems uncertain whether LLLT has a positive effect on the bone regeneration of the sutura palatina. However, the results might indicate a tendency towards a positive effect of LLLT on bone regeneration. The authors of this review suggest that the results in favour of LLLT appear to outweigh the others.

This statement is supported by the detailed consideration of the laser parameters used by Matos et al. (2020) [43]. However, considering the GRADE and RoB evaluation, this statement should only be interpreted as a mere tendency.

Additionally, this can be supported by the results of the qualitative evaluation by Garcia et al. (2016) [108]. Moreover, this tendency also appears to be consistent with the results of the animal studies discussed in section 4.1.1.

Overall, the applications of LLLT and the time point of evaluation varied. Different LLLT applications between 8 and 12 times, over a period of 8 weeks or even 70 days were reported [43, 106-109].

Furthermore, the laser parameters used were differed between the studies. Due to this heterogeneity of the studies, a reasonable interpretation of the results in terms of laser parameters applied, application frequency or time point of evaluation appears to be limited. It appears reasonable that an application of eight or more treatment sessions would be appropriate. The irradiation of multiple points along the sutura palatina at each treatment session might be an effective method in order to irradiate the entire involved area.

With regard to the evaluation method, it seems reasonable to evaluate the development of bone density using occlusal radiographs. This would allow to draw conclusions about the ossification at different points in time. It might be beneficial to conduct this evaluation over an extended period of several months, up to 6 months. This allows to obtain results in relation of the effect of the LLLT over the entire period of the retention phase.

In consideration of the laser parameters, a spot size of 0.04 cm^2 or greater might be reasonable. The application of energy densities of 10-34 J/cm^2 with an irradiation time of 10-60 seconds indicated positive outcomes [107-109]. Comparable laser parameters in animal studies led to positive results favouring LLLT as well [113-115, 119]. In contrast, Angeletti et al. (2014) reported a positive result with an energy density of 140 J/cm^2 and an irradiation time of 84s [106]. It is noteworthy, that in the animal studies, energy densities of up to 160 J/cm^2 as single irradiation for 0.42 seconds, or 90-120 J/cm^2 as multiple irradiation at an unknown irradiation time, also demonstrated positive results [110, 112]. In contrast to these results, lower doses of 5 J/cm^2 at an irradiation time of 3 seconds demonstrated results favouring LLLT in animal studies [115]. Even an energy density of 100 mJ/cm^2 and an irradiation time of 0.1 msec, with multiple irradiations applied, appeared result in positive outcomes in favour of LLLT [120]. In consideration of the aforementioned data, it is assumed, that the correlation between irradiation time and energy density seems to be an influencing factor in the effective application of LLLT. On this topic, partial lack of data report in the studies additionally complicate this evaluation. Thus, the data situation does not provide sufficient evidence to draw a definitive conclusion on this topic.

With regard to the wavelength, it appears, that no statement can be made in consideration to the heterogeneity of the studies. Only two CS implemented an identical wavelength of 780 nm [107, 109]. As previously stated in section 1.5.5, it is assumed that specific wavelengths

stimulate particular cells or cell components. However, the comparison of the wavelengths would not be sufficiently reliable due to the differences in the laser parameters and evaluation methods used. Consequently, the issue whether a certain wavelength is an optimum to improve the bone regeneration of the sutura palatina cannot be assessed.

Based on the currently available data, it appears, that no further statement can be made about the benefits of LLLT. From the authors' point of view, statements about a possible reduction of the relapse would be desirable.
Based on the current studies, only the assumption that an upregulation in bone regeneration could potentially result in a reduction of the relapse can be made.
Another aspect, whether LLLT could enable a shortening of the retention phase or treatment duration, is not addressed by the current studies. On this topic, it may be assumed that an upregulation on bone regeneration could have a positive effect on shortening the retention phase or treatment duration, is possible.

4.1.3 Limits of this Study

The analysis of the data was limited by several factors, which are described in the following section.
On the one hand, the studies partly lacked information regarding the laser parameters applied or the evaluated outcome data. Additionally, it appeared that transcription errors in the text had resulted in an inaccurate study report in a few instances.
Furthermore, the evaluation of the clinical studies using the GRADE approach resulted in *very low* and the risk of bias is approximately at *some concerns*. Additionally, the analysis by GRADE only covered a subset of the statements presented in this review. It was applied exclusively to CS and a single outcome. Consequently, GRADE did not include the entirety of the studies and statements of this review.
Additionally, as presented in Table 7, Table 8, Table 9 and Table 10 the study designs are vary with respect to certain baseline parameters such as laser doses, application protocols, evaluation methods and evaluation times. Moreover, only five clinical studies on the topic could be identified, which further limited this issue.
Consequently, the evidence, which this review can provide, is thus considered low.
In the opinion of the authors, a meta-analysis is not appropriate given the limited numbers and heterogeneity of the clinical studies. Thus, an improvement of the evidence did not appear feasible.

4.2 Discussion in Comparison with Further Studies with Different Study Designs, Systematic Reviews and Meta-Analyses

A study by Pirmoradian et al. (2020) investigated the relapse of palatal expansion distance without a retention appliance in rats [123]. They observed a benefit for LLLT in the first months. However, in the last month of observation, the distance between the teeth appeared to decrease again and no difference was observed compared to the control group. Pirmoradian et al. (2020) indicated that this was an effect of the tooth inclination rather than the loss of dimension of the palatal expansion [123]. The extent to which this statement can be reliable remains unclear. The authors of this review are of the opinion that the result of a single animal study is an insufficient foundation for a general statement about the relapse of palatal expansion after LLLT. However, the study to indicates that the positive effects of LLLT at the cellular level and in relation to new bone formation described in section 4.1.1 could have an influence on a reduced relapse of the palatal expansion.

While the studies discussed in this review have addressed the evaluation of bone density, Abdelwassie et al. (2022) focused on the evaluation of orthodontically defined linear and angular measurements [124]. LLLT was performed in patients treated with RME using a bone anchored appliance for the palatal expansion. They observed no significant difference for LLLT compared to the control group [124].

For evaluation, CBCT scans were conducted before palatal expansion and after the retention period of six months. Although no CBCT scans were performed immediately after palatal expansion as a comparator, it can be reasonably assumed that a strictly followed protocol for palatal expansion would enable comparability of subjects and groups. It was reported that all patients underwent the same amount of palatal expansion over the same period of time [124]. Abdelwassie et al. (2022) reported that the bone anchored appliance was left in situ for the purpose of retention for six months, which is approximately until the time of the second CBCT scan [124].

It is possible that the results demonstrate no effect of LLLT, as a bone anchored retention is capable of safely maintaining the expanded skeletal and dental dimensional changes without significant relapse.

Thus observed results might only apply to bone borne RME using a bone borne retention for six month and the evaluation after the retention period of six month. It may be the case that their results do not permit any further conclusion on a possible benefit of LLLT for RME.

No further studies for comparison that used similar evaluation methods of the effect of LLLT in RME were identified. The evaluation method applied might be reasonable to draw a more

direct conclusion on the clinical benefits. The measurement of clinically relevant orthodontic dimensions might offer a more direct conclusion about a possible benefit of LLLT with regard to the relapse after palatal expansion. Furthermore, this method may be additionally performed in studies that determine bone density by means of CBCT scans.
The conclusion of Abdelwassie et al. (2022) was that LLLT in RME with bone anchored appliances did not result in significantly differences on the skeletal and dental dimensions after the retention period of six months [124]. Nevertheless, it remains unclear, whether this effect is maintained in different treatment methods of RME, for example using dental fixed appliances, or at a later evaluation time after nine or twelve months.
In any case, this issue demonstrates that the comparison of studies on LLLT in RME is not only challenging to assess due to the varying evaluation methods and laser parameters, but also due to the impact of the different treatment methods on the comparability of the study results.
Nevertheless, in the view of the authors of this review, the question of whether a possible upregulation of the bone regeneration of the sutura palatina could enable a reduction on relapse cannot be answered on the basis of this single study.

A total of four systematic reviews and one meta analysis on the effect of LLLT on RME were found [41, 125-128].

The systematic review by Davodi et al. (2018) focused on the evaluation of four randomised controlled clinical trials [41]. These were all included in the present study as well.
The Jadad Scale was used for the purpose of the risk of bias assessment. An overall moderate risk was reported, which is consistent with the RoB assessment of this review. An evaluation using GRADE was not performed [41].
Overall, they reported a benefit of LLLT on bone regeneration. No consensus was reached regarding the dosage. They stated that the observed studies applied LLLT in the initial therapy phase. Additionally, they assumed that an application to at least 3-4 points along the sutura palatina is beneficial [41]. The statements regarding the LLL dosage and application are consistent with the results of this review.
In contrast to our findings, Davodi et al. (2018) concluded that CBCT scans are superior to occlusal radiographs and lead to more accurate results [41].

Skondora et al. (2018) conducted a systematic review including four clinical studies and eight animal studies [127]. Each of them were included in this review as well [127]. The CS included were identical as in the systematic review by Davodi et al. (2018) [41, 127].

A risk of bias analysis was performed using the Cochrane RoB tool for CS. The analysis resulted in a high risk of bias for the study by Ferreira et. al. (2016) with regard to the randomisation process and high subject loss in the control group [127]. These findings were not consistent with the assessment in this review.
Similar to the assessment performed in this review, Skondora et al. (2018) reached the same conclusion, that blinding of the subjects and researchers has a minimal impact due to the study design. In accordance with the results of this study, they identified a lack of reporting on randomisation and allocation concealment as well [127].
With regard to the laser dose used, they were also of the opinion that they varied greatly in the studies and that no statement could be made about its effective application [127].
Including animal studies and CS, Skondora et al. (2018) concluded that LLLT effectively stimulates bone regeneration, resulting in improved long-term outcomes with a reduced relapse [127]. They thus suggested a possible shortening of the retention phase. Nevertheless, they mentioned that further research is required to substantiate these findings [127].

Lai et al. (2021) observed in their systematic review on the use of LLLT in RME in clinical and animal studies [126].They included six clinical and eight animal studies. The clinical studies contained of a single case report. In the opinion of the authors of this review, one of the included studies did not perform LLLT but rather conducted a surgical laser application with penetration of the gingiva [126]. These studies were excluded from the present research due to the study design.
The remaining CS included by Lai et al. (2021) were identical to those reported in the two aforementioned reviews. A risk of bias analysis was not reported [126].
They did not find a consensus on the dosage of LLLT. They suggested that there is an upper threshold for the effective dose of LLLT [126]. These statements are in line with those of this review.
The rating of the evidence of their study was considered as low. Nevertheless, they concluded that LLLT does improve bone regeneration after RME [126]. Similar to Davodi et al. (2018), they recommended to apply LLLT in the early phase of the therapy [41, 126].
In addition, they reported an effect of LLLT on the frequency of application, which is why frequent application was recommended [126]. The authors of this review consider this statement reasonable, but it cannot be given with certainty regarding the current data situation.

In the systematic review by Farzan et al. (2022) the effect of LLLT on the ossification of the sutura palatina after RME was examined. They identified four CS that met the inclusion criteria. In contrast to the other aforementioned systematic reviews, they included the study by Matos et al. (2020) [128].

A risk of bias analysis was also performed using the Cochrane RoB2 tool. It is notable that the results of the individual domains differ, at least in part, from those of this review. However, the overall risk of bias is partly similar that of the present study. A notable discrepancy is, that Farzan et al. (2022) evaluated a *high* risk of bias for the studies by Matos et al. (2020) and Garcia et al. (2016) [128].
In contrast with the position taken by the authors of this review, they concluded that CBCT scans are superior to occlusal radiographs as an evaluation method. With regard to the laser protocol, they recommended to start the therapy with the initial treatment phase. They also pointed out the great heterogeneity of the study situation and no explicit statement was made about the most effective laser parameters. They concluded that bone formation is increased by LLLT. In addition, they concluded that a reduction of the retention phase is possible by the use of LLLT [128].

Chaves et al. (2023) conducted a meta-analysis including five CS [125]. The study addressed the effect of LLLT on the ossification of the sutura palatina after RME. The same CS were included as in the present review [125].
A risk of bias analysis was performed using the Cochrane RoB 2 tool. A *high* risk of bias was identified for three studies in the domains addressing risk of bias in the measurement of the outcome only. Risk of bias arising from the randomisation process was rated with *some concerns* for all studies. All other domains were rated as *low* risk. In general, the classification of the studies in the individual domains differed from that in the present review. Nevertheless, the results of the overall risk of bias did in part overlap with those of this study, even though it was not explicitly mentioned in the study by Chaves et al. (2023) [125]. The GRADE assessment was conducted as well. Similar to this review, the corresponding question addressed in the GRADE evaluation was whether LLLT accelerates bone regeneration after RME. The result was a rating of *very low* level of evidence certainty. Despite the availability of additional parameters in the meta-analysis in order to assess GRADE, the result is consistent with this review [125].
The meta-analysis was conducted by calculating the results at different time points. Thus, the data from the studies were compared for the time point after one, two, three and four to six months [125]. This appears to be a sensible approach, as it enables a differentiated view on the results in relation to the timepoint of evaluation.
It should be noted, that for the evaluation of the meta-analysis, only three studies were included at the time point after one month and only two studies were compared at the subsequent time points. In addition, the results by Matos et al. (2020), which did not report a significant outcome for LLLT, were consistently included at each time point. Thus, this study was compared with two other studies after the one-month period, and with only one other study at subsequent

evaluation points in time. This resulted in a comparison of only two extracted values at most evaluation time points. Each individual calculation at the different time points were included in the funnel plot, resulting in a multiple representation of the studies that were used at multiple time points of evaluation [125].
In conclusion, in their meta-analysis Chaves et al. (2023) stated that they could not demonstrate any benefit of LLLT for bone regeneration after RME. However, they attributed this to the low level of evidence and the lack of studies [125].
The authors of this review suggest that the results of the meta-analysis might further be reduced in evidence due to the analysis of few variables compared at each chosen time point. A meta-analysis of study results at different time points is considered reasonable. However, given the current study situation and lack of data, an evidence-based implementation seems difficult.

In comparing the aforementioned statements of the systematic reviews and meta-analyses, the following appears to stand out.
A risk of bias analysis was conducted in a total of four studies. In general, a comparison of the results of the individual analyses of the studies reveals discrepancies when the individual domains are considered. A comparison of the overall risk of bias reveals partial similarities in the results [41, 125, 127, 128].
There was an extensive overlap in the CS included in the studies. The study by Matos et al. (2020) was only included in the meta-analysis conducted by Chaves et al. (2021) and the systematic review conducted by Farzan et al. (2022) [41, 125-128].
It appears that there is a general consensus that the current data are not sufficient enable an evidential statement [41, 125-128].
None of the authors of the systematic reviews or meta-analyses was able to provide a detailed statement regarding the effective laser dose or application protocols [41, 125-128].
With regard to the results of the four systematic reviews, there is a consensus on the assumption that the application of LLLT can lead to a positive effect on bone regeneration. [41, 126-128]. These statements are largely consistent with those from this review.
In contrast, a single meta-analysis found no evidence of benefit for bone regeneration using LLLT [125].

4.3 Implication in Clinical Practice and Further Research Recommendations

With regard to implementation in clinical practice, it seems sensible to consider the following limitations. The GRADE analysis was only applied in a limited context to the totality of studies

and evaluated study results in this review. Additionally, the evaluation resulted in a rating of *very low*. Furthermore, GRADE was solely performed to evaluate whether LLLT can increase bone regeneration after RME. This result provides only indirect evidence of a clinical benefit. It is therefore not possible for the authors of this review to make a recommendation based on the research question addressed by GRADE.
In view of the overall poor evidence of the studies and the lack of consistency in laser dose and application protocols, the authors do not yet consider it possible to make a recommendation for implementation in clinical practice.

Further research is required to investigation the effect of LLLT on bone regeneration after RME.
A larger sample size, involving more than 20 subjects per group, would be beneficial in order to generate a higher level of evidence.
It seems appropriate to conduct further research, especially with regard to the laser dosage. For instance, a comparison of different laser dosages and application frequencies in clinical studies will provide further information on the medical application of LLLT.
In addition, an assessment of the effect of LLLT on bone regeneration in the follow-up after 1-6 months at several points in time would provide further insight into the long-term effects of LLLT.

In order to improve the data situation on the influence of LLLT on relapse after RME, further studies with evaluation methods corresponding to this topic would be necessary.
A review of the literature revealed no studies investigating the influence of LLLT on a possible shortening of the retention phase of RME. Another field of research could be whether, for dental fixed appliances, LLLT could positively influence the relationship between the opening of the sutura palatina and the buccal tooth movement. Studies addressing these issues could potentially be conducted using alternative assessment methods not related to radiation exposure. Such studies might provide a more comprehensive understanding of the effect of LLLT on RME.

5 Conclusion

Considering the *very low* level of evidence evaluated in the GRADE assessment, the effects of LLLT on the upregulation of new bone formation in the sutura palatina after RME are uncertain.

However, a detailed analysis of the studies included in the GRADE assessment revealed that there might be an indication that LLLT upregulates bone regeneration of the sutura palatina after RME. This statement is supported by the results of the animal studies.
Taking additional consideration of the results outside the GRADE analysis into account, the following conclusion is drawn: It appears that LLLT may have a positive effect on the bone regeneration of the sutura palatina after RME. The null hypothesis is therefore rejected. Nevertheless, in the context of this statement, it seems important to emphasise that the evidence on this topic is still very low. Further research, especially CS, is needed.

However, a statement whether LLLT has a clinical benefit for the patient, for example a shortening of the treatment duration or a reduction of the relapse, cannot be evaluated at present.
The authors of this study hold the opinion that a reduction of the relapse would represent a great benefit for the patients, which is why further research on this topic appears to be sensible. The duration of orthodontic treatment extends over several years. Depending on the treatment protocol, the retention phase after RME is six months or even longer. In view of these time frames, a shortening of the retention phase by applying LLLT appears to be less relevant as a benefit for the patient. Nevertheless, no statement can be drawn on this topic on the basis of the current data. Further research on this issue is necessary.

6 Bibliography

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7 Appendix

Search History: National Library of Medicine (via PubMed®)
Date: up to 14.03.2021

Set	Search Term	Results
# 19	#15 AND # 18	28
# 18	# 16 OR # 17	14,758
# 17	"Laser Irradiation"[Title/Abstract]	9,713
# 16	"low level light therapy"[MeSH Terms]	6,054
# 15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	4,843
# 14	"palatal distraction"[Title/Abstract]	18
# 13	"palatal osteotomy"[Title/Abstract]	13
# 12	"paramedian osteotomy"[Title/Abstract]	11
# 11	"maxillary distraction"[Title/Abstract]	231
# 10	"MARPE"[Title/Abstract]	43
# 9	"SARPE"[Title/Abstract]	78
# 8	"SARME"[Title/Abstract]	137
# 7	"maxillary surgery"[Title/Abstract]	255
# 6	"palatal surgery"[Title/Abstract]	205
# 5	"palatal expansion"[Title/Abstract]	676
# 4	"RME"[Title/Abstract]	1,118
# 3	"maxillary expansion"[Title/Abstract]	1,568
# 2	"maxillary osteotomy"[MeSH Terms]	225
# 1	"palatal expansion technique"[MeSH Terms]	2,892

Table 1: Search History National Library of Medicine up to 14.03.2021

Search History: Cochrane Database (via The Cochrane Library)
Date: up to 14.03.2021

Set	Search Term	Results
# 19	#15 AND #18	154
# 18	# 16 OR # 17	360581
# 17	(“Laser Irradiation“):ti,ab,kw (Word variations have been searched) *(Word variations have been searched)*	697
# 16	MeSH descriptor: [Low-Level Light Therapy] *explode all trees*	1014
# 15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	777
# 14	(“palatal distraction“):ti,ab,kw *(Word variations have been searched)*	0
# 13	(“palatal osteotomy“):ti,ab,kw *(Word variations have been searched)*	0
# 12	(“paramedian osteotomy“):ti,ab,kw *(Word variations have been searched)*	1
# 11	(“maxillary distraction“):ti,ab,kw *(Word variations have been searched)*	18
# 10	(MARPE):ti,ab,kw *(Word variations have been searched)*	18
# 9	(SARPE):ti,ab,kw *(Word variations have been searched)*	14
# 8	(SARME):ti,ab,kw *(Word variations have been searched)*	68
# 7	(“maxillary surgery“):ti,ab,kw *(Word variations have been searched)*	18
# 6	(“palatal surgery“):ti,ab,kw *(Word variations have been searched)*	274
# 5	(“palatal expansion“):ti,ab,kw *(Word variations have been searched)*	221
# 4	(RME):ti,ab,kw *(Word variations have been searched)*	166
# 3	(“maxillary expansion“):ti,ab,kw *(Word variations have been searched)*	286
# 2	MeSH descriptor: [Palatal Expansion Technique] *explode all trees*	168
# 1	MeSH descriptor: [Maxillary Osteotomy] *explode all trees*	15

Table 2: Search History Cochrane Database up to 14.03.2021

Search History: Web of Sciences Core Collection (via Web of Sciences™)

Date: up to 14.03.2021

Set	Search Term	Results
# 24	#23 AND #14 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	28
# 23	#22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	26,633
# 22	TS=(“Laser Phototherap*") *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	411
# 21	TS=(“Laser Biostimulation“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	102
# 20	TS=(“Low-Power-Laser-Therap*“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	83
# 19	TS=(“Low-Level-Laser-Therap*“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	2,857
# 18	TS=(LLLT) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	2,18
# 17	TS=(“Photobiomodulation Therap*“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	540
# 16	TS=(“Low-Level-Light-Therap*“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	358
# 15	TS=(“Laser Irradiation“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	22,992
# 14	#13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	4,585
# 13	TS=("maxillary osteotomy") *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	435
# 12	TS=(“palatal distraction“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	25
# 11	TS=(“palatal osteotomy“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	10
# 10	TS=(“paramedian osteotomy“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	7
# 9	TS=(“maxillary distraction“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	265
# 8	TS=(MARPE) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	56
# 7	TS=(SARPE) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	65
# 6	TS=(SARME) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	126
# 5	TS=(“maxillary surgery“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	182
# 4	TS=(“palatal surgery“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	197
# 3	TS=(“maxillary expansion“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	1,833
# 2	TS=(RME) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	1,833
# 1	TS=(“palatal expansion“) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	919

Table 3: Search History Web of Sciences Core Collection up to 14.03.2021

Search History: National Library of Medicine (via PubMed®)

Date: 14.03.2021 to 09.08.2023

Set	Search Term	Results
#20	#15 AND #18 AND #19	3
#19	("2021/03/14"[Date - Publication] : "2023/08/09"[Date - Publication])	3,833,168
#18	#16 OR #17	17,951
#17	"Laser Irradiation"[Title/Abstract]	11,877
#16	"low level light therapy"[MeSH Terms]	7,166
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	5,579
#14	"palatal distraction"[Title/Abstract]	19
#13	"palatal osteotomy"[Title/Abstract]	13
#12	"paramedian osteotomy"[Title/Abstract]	11
#11	"maxillary distraction"[Title/Abstract]	253
#10	"MARPE"[Title/Abstract]	113
#9	"SARPE"[Title/Abstract]	107
#8	"SARME"[Title/Abstract]	172
#7	"maxillary surgery"[Title/Abstract]	278
#6	"palatal surgery"[Title/Abstract]	235
#5	"palatal expansion"[Title/Abstract]	885
#4	"RME"[Title/Abstract]	1,375
#3	"maxillary expansion"[Title/Abstract]	1,967
#2	"maxillary osteotomy"[MeSH Terms]	245
#1	"palatal expansion technique"[MeSH Terms]	3,274

Table 4: Search History National Library of Medicine from 14.03.2021 to 09.08.2023

Search History: Cochrane Database (via The Cochrane Library)

Date: 14.03.2021 to 09.08.2023

Set	Search Terms	Results
#1	MeSH descriptor: [Maxillary Osteotomy] explode all trees	20
#2	MeSH descriptor: [Palatal Expansion Technique] explode all trees	274
#3	(“maxillary expansion“):ti,ab,kw (Word variations have been searched)	380
#4	(RME):ti,ab,kw (Word variations have been searched)	235
#5	(“palatal expansion“):ti,ab,kw (Word variations have been searched)	336
#6	(“palatal surgery“):ti,ab,kw (Word variations have been searched)	379
#7	(“maxillary surgery“):ti,ab,kw (Word variations have been searched)	22
#8	(SARME):ti,ab,kw (Word variations have been searched)	75
#9	(SARPE):ti,ab,kw (Word variations have been searched)	18
#10	(MARPE):ti,ab,kw (Word variations have been searched)	32
#11	(“maxillary distraction“):ti,ab,kw (Word variations have been searched)	18
#12	(“paramedian osteotomy“):ti,ab,kw (Word variations have been searched)	1
#13	(“palatal osteotomy“):ti,ab,kw (Word variations have been searched)	0
#14	(“palatal distraction“):ti,ab,kw (Word variations have been searched)	0
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	1033
#16	MeSH descriptor: [Low-Level Light Therapy] explode all trees	1354
#17	(“Laser Irradiation“):ti,ab,kw (Word variations have been searched)	811
#18	# 16 OR # 17	426665
#19	#15 AND # 18 with Cochrane Library publication date Between Mar 2021 and Aug 2023, in Cochrane Reviews, Cochrane Protocols, Trials, Clinical Answers, Editorials, Special Collections	40

Table 5: Search History Cochrane Database from 14.03.2021 to 09.08.2023

Search History: Web of Sciences Core Collection (via Web of Sciences™)

Date: 14.03.2021 to 09.08.2023

Set	Search Terms	Results
#1	TS=("Laser Phototherap*") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	423
#2	TS=("Laser Biostimulation") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	114
#3	TS=("Low-Power-Laser-Therap*") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	101
#4	TS=("Low-Level-Laser-Therap*") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	3355
#5	TS=(LLLT) Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	2532
#6	TS=("Photobiomodulation Therap*") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	1008
#7	TS=("Low-Level-Light-Therap*") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	525
#8	TS=("Laser Irradiation") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	27597
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	32206
#10	TS=("maxillary osteotomy") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	605
#11	TS=("palatal distraction") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	23
#12	TS=("palatal osteotomy") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	10
#13	TS=("paramedian osteotomy") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	8
#14	TS=("maxillary distraction") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	280
#15	TS=(MARPE) Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	134
#16	TS=(SARPE) Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	94
#17	TS=(SARME) Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	152
#18	TS=("maxillary surgery") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	205
#19	TS=("palatal surgery") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	247
#20	TS=("maxillary expansion") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	2331
#21	TS=(RME) Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	2216
#22	TS=("palatal expansion") Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	1199
#23	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC	5623
#24	#9 AND #23 Editions: WOS.SCI,WOS.SSCI,WOS.AHCI,WOS.ISTP,WOS.ISSHP,WOS.BSCI,WOS.BHCI,WOS.ESCI,WOS.CCR,WOS.IC Timespan: 2021-03-14 to 2023-08-09	9

Table 6: Search History Web of Sciences Core Collection from 14.03.2021 to 09.08.2023

Appendix

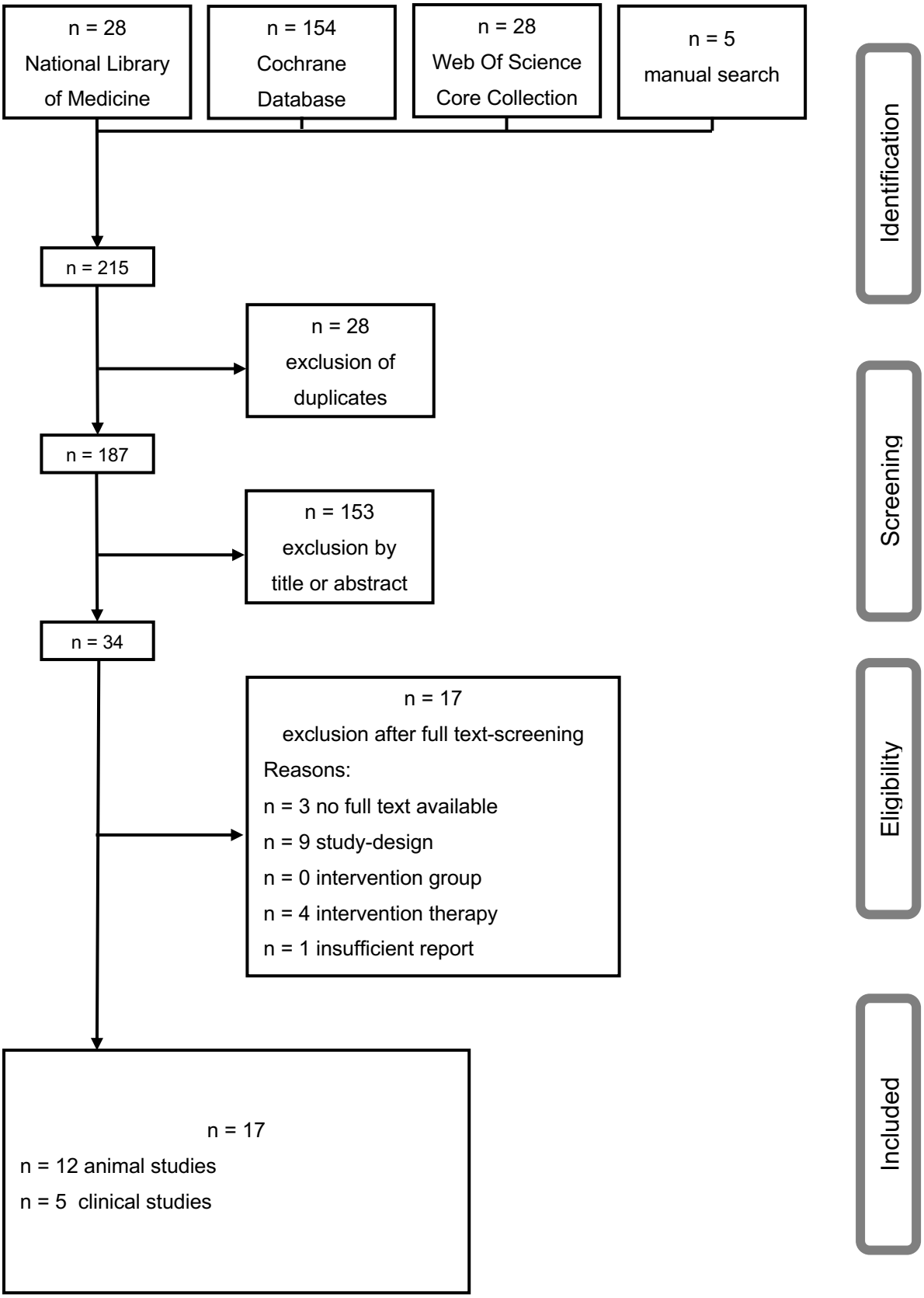

Figure 1: Flowchart Selection of Studies - Literature Research up to 14.03.2021

Appendix

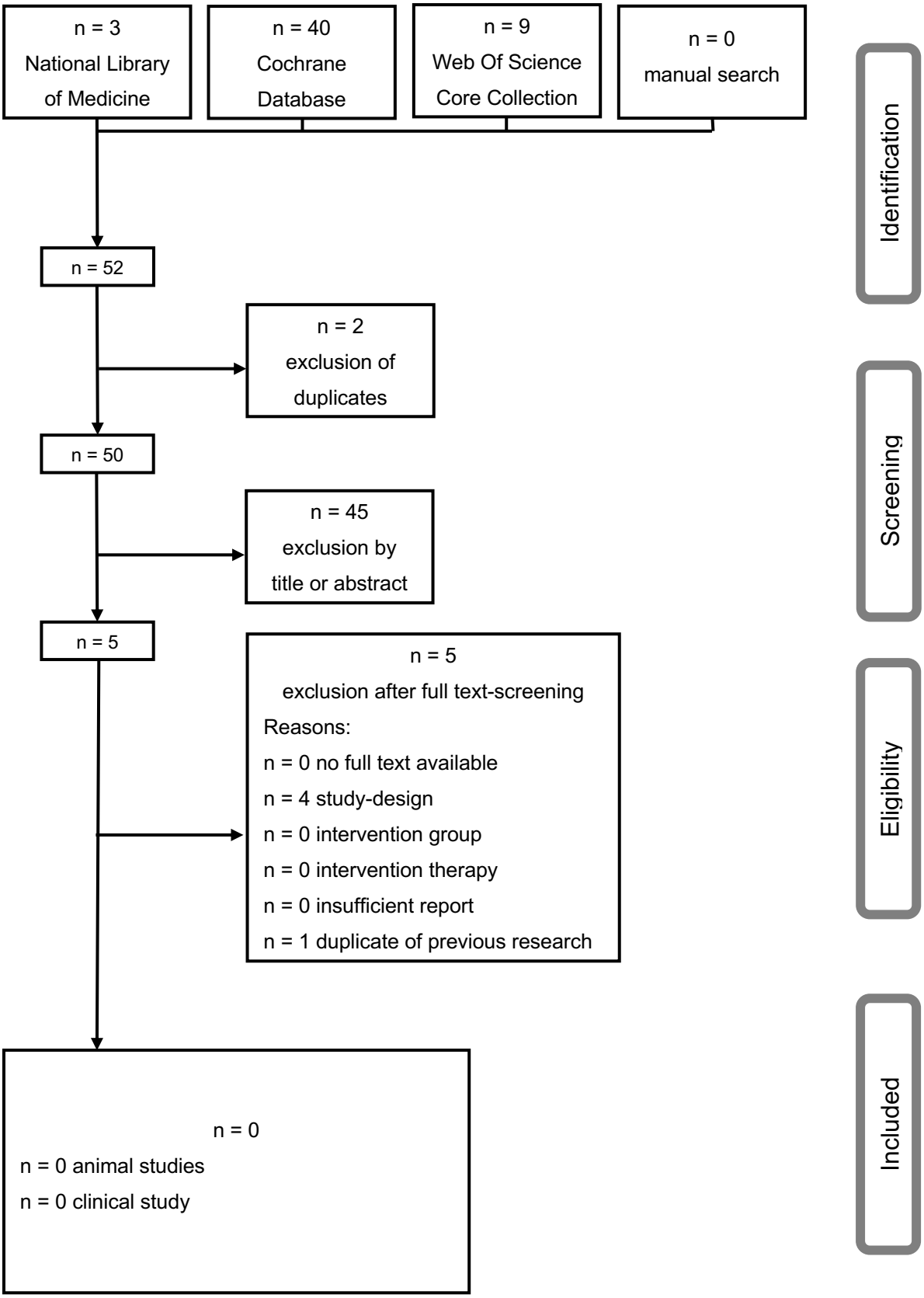

Figure 2: Flowchart Selection of Studies - Literature Research 14.03.2021 - 08.09.2023

Appendix

Author	Year Published	Signalling Question	Expansion Device and Protocol	Total of Participants	Control Group
Cepera, F. et al. (2012) [107]	2012	Effect of LLLT on bone regeneration at the midpalatal suture after RME	Dental fixed expander with Hyrax screw 4 activations on the first day (1 full turn) 2 daily activations afterwards (half turn) Approximately 8 days of activation 90 days of retention phase	27 patients 8.2 - 12.1 years old Laser group 14 patients Control group 13 patients	Yes
Angeletti, P. et al. (2010) [106]	2010	Effect of LLLT on bone regeneration at the midpalatinal suture after SARME	Surgical assisted rapid maxillary expansion by LeFort 1 osteotomy. Dental fixed expander with Hyrax screw. Activation intraoperatively by 1.6 mm. 4 days later activation with a turn of 0.2 mm twice daily, 0.4 mm expansion each day. 4 month retention phase	13 patients 18 - 33 years old Laser group 7 patients Control group 6 patients	Yes
Garcia, V. J. et al. (2016) [108]	2016	Effect of LLLT on the repair at the midpalatal suture after RME	Hyrax expansion screw set in an acrylic splint. Activated a quarter turn (0.20 mm) two times a day 6 month retention phase	39 patients 6.2 – 12.4 years old Laser group 20 patients Control group 19 patients	Yes
Ferreira F. N. et al. (2016) [109]	2016	Effect of LLLT on bone regeneration at the midpalatal suture after RME	Dental fixed expander with Hyrax screw. One full turn at moment of installation, afterwards two half turn daily activations (1/4 turn in the morning and 1/4 turn at night) Activation phase for approximately 14 days. 4 month retention phase	14 patients 8–14 years old Laser group 10 patients Control group 4 patients	Yes
Matos, D. S. et al. (2020) [43]	2020	Effect of photobiomodulation therapie at the midpalatal suture after RME	Dental fixed expander with Hyrax screw. Four ¼ turns (one full turn) initial activation. From the 2nd day after insertion, 2 daily ¼ turn activations Activation approximately for 15-21 days 6 month retention phase	34 patients 6-12 years old Laser group 18 patients Control group 16 patients	Yes

Table 7: Clinical Studies - Study Design

Appendix

Author	Laser Parameters				Evaluation Method	Results
	Type	Wavelength	Dosage	Application Frequency		
Cepera, F. et al. (2012) [107]	Diode Laser	780 nm	Spot size: 0.04 cm^2 Power: 40 mW Time per point: 10 s Energy per point: 0.4 J Total energy: 4 J Energy density per point: 10 J/cm^2	Number of application points per treatment: 10 Applications were made in the following stages: 1. from the start of expansion screw activation until 5 days later 2. immediately after the end of expansion for 3 consecutive days 3. 7 days after stage 2 4. 7 days after stage 3 5. 7 days after stage 4	Occlusal radiographs were taken at: T1, before RME (25 radiographs) T2, immediately after achieved expansion (25 radiographs) T3, 3 to 5 days after expansion (25 radiographs) T4, 33 to 35 days after expansion (26 radiographs) T5, 93 to 95 days after expansion (27 radiographs) Comparing density changes over time intervals. Radiograph parameters not stated. Digital optical density measurement by histogram equivalent to the grey scale.	Results favouring LLLT for T2 - T5 ($p = 0.017$) and T4 - T5 ($p = 0.001$). No statistically significant difference for T2 - T3 and T3 - T4. LLLT showed improved the opening of the midpalatal suture and bone regeneration.
Angeletti, P. et al. (2010) [106]	Diode Laser Ga-Al-As medium	830 nm	Spot size: 0.06 cm^2 Power: 100 mW Time per point: 84 s Energy per point: 8.4 J Energy density per point: 140 J/cm^2 Total energy per treatment session: 25.2 J at an energy density of 420 J/cm^2	Number application points per treatment: 3 Each patient had 8 laser sessions. 24 hours after surgery, afterwards at an interval of 48 hours.	Digital radiographs were taken at: F0 preoperatively postoperative days F1 = 30, F2 = 60, F3 = 90, F4 = 120, F5 = 210 Radiograph parameters: 8mA, 70kVp Optical density evaluation by the number of pixels. Comparing optical density at the timepoints of radiographs.	Reports results favouring LLLT at the timepoint F1 ($p = 0.022$), F2 ($p = 0.007$), F3 ($p = 0.004$), F4 ($p = 0.003$) and F5 ($p = 0.003$). No results not favouring LLLT are reported. After 7 months total ossification of the MPAS was not observed.
Garcia, V. J. et al. (2016) [108]	Laser In-Ga-Al-P medium	660 nm	Spot size: 0.26 cm^2 Power: 100 mW Power density: 332 mW/cm^2 Time per point: A: 60 s B: 30 s Energy per point: A: 6 J B: 3 J Energy density per point: A: 23 J/cm^2 B: 12 J/cm^2	Number of application points per treatment: 6 A: At four points along midpalatal suture B: At one point each side of the suture A total of seven applications on days 1, 7, 14, 28, 42, 56, and 70 of the retention phase	Cone beam computed tomography (CBCT) scan at the day of the first laser treatment and at day 75. CBCT parameters: 68kVp, 6.3mA, voxel size 0.07mm Qualitative study Description of the continuity or discontinuity of the anterior and posterior cortical, inferior suture, anterior nasal spine, and nasopalatine duct. Classification of the appearance of the inferior suture and superior suture margins into four levels. Quantitative study: Measuring the distance of the margins of the suture at posterior-superior suture distance,	Qualitative Analysis: Patients treated with LLLT showed more approximation. LLLT: 65% approximate anterior nasal suture, 50 % significant approximation and 30 % full approximation. 90% shows signs of cortical of nasopalatine duct reorganized. Control group : 53% approximate anterior nasal suture, 42% significant approximation and 21 % full approximation. 68% shows signs of cortical of nasopalatine duct reorganized. Concluding that 27 % of the irradiated

					anterior- inferior suture distance, anterior- nasal-spine suture distance and the maximum distance.	patients had a greater degree of approximation. The approximation in the anterior suture is greater than in the posterior. Quantitative Analysis: Result favouring the LLLT only for posterior-superior distance of sutura palatina. (p = 0.04) results at the anterior nasal spine, inferior distance and maximum distance measured were not statistically significant
Ferreira F. N. et al. (2016) [109]	Diode Laser Ga-Al-As medium	780 nm	Spot size: 0.04 cm^2 Power: 70 mW Time per Point: 20 s Energy per Point: 1,4 J Energy density per point: 35 J/cm^2	Numbers of application points per treatment: 4 incisal papilla the regions right and left to the palatal raphe posterior region along the midpalatal suture Twice a week in the first month and once a week in the second month, totalising 12 sessions	CBCT, after achieved expansion (T0) and 4 month later (T1) after retention period. CBCT scan parameters: 80kV, 90mA, voxel size 0.075mm Optical density (OD) values were measured by a software at three points: The alveolar crest, half the distance between the alveolar crest and the incisive foramen, a third point between the two other points. Mean OD of the three measured points was calculated for T0 and T1 for conducting intergroup comparison.	Comparing intergroup optical density at T0 and T1: Statistically significant results favouring LLLT (p = 0.00) In the control group no statistical significance (p = 0.2) Comparison at T1 between LLLT and Control group significant difference (p = 0.05) In both groups complete ossification of the palatal suture after 4 months.
Matos, D. S. et al. (2020) [43]	Diode Laser	980 nm	Beam Diameter: 0.4 mm Spot size: 1.26E3 cm^2 Power: 300 mW Power Density per point: 238.85E3 mW/cm^2 Time per Point: 10 s Energy per point: 3 J Total energy: 18 J Energy density per point: 238.85 J/cm^2	Number of application points per treatment: 6 12 applications over 10 weeks During Activation phase on Day 1, 5, 10, and 15 Afterwards once a week for 8 weeks	Digital occlusal radiographs at screw fixation (R1), and after 1 (R2), 2 (R3), 3 (R4), and 6 months (R5). Radiograph parameters: 70 kV, exposure time 0.25s. Using a software, which measures pixel value of previously defined selections and comparing to a step wedge. Evaluation of density changes over period of time.	Bone formation between groups was not significantly different (p = 0.2273). Time interval for this value not stated. After 3 months, the bone formation was not yet complete in both groups.

Table 8:Clinical Studies - Laser-parameters, Evaluation Method and Result

Appendix

Animal Studies						
Author	**Year Published**	**Laser Parameters**				**Control Group**
		Type	**Wavelength**	**Dosage**	**Application Frequency**	
Eslamian, L. et al. (2020) [120]	2020	Diode laser	808 nm	Energy density: 100 mJ/cm^2 Irradiation time: 0.1 msec	Group A: on day 7 Group B: on day 7, 9, 11, 13, 15 Group C: Control with retention Group D: Control after expansion	Yes
Altan, A. B. et. al. (2015) [115]	2015	Diode laser Ga-Al-As	820 nm	Fiber diameter: 2mm Group low dose: Power: 50 mW Irradiation time: 3 s Power density: 1.6 W/cm^2 Energy dose: 0.15 J Energy density: 5 J/cm^2 Group medium dose: Power: 50 mW Irradiation time: 13 s Power density: 1.6 W/cm^2 Energy dose: 0.65 J Energy density: 20 J/cm^2 Group high dose: Power: 100 mW Irradiation time: 1,980 s Power density: 1.6 W/cm^2 Energy dose: 198 J Energy density: 6,300 J/cm^2	5 days of expansion Consolidation period of 8 days total Total of four applications reported.	Yes
da Silva, A. P. et al. (2012) [112]	2012	Diode laser Ga-Al-As	830 nm	Spot size: 0.00785 cm^2 Spot diameter: 1mm Power: 30 mW Irradiation time: 0.42 sec Energy density: 160 J/cm^2	One time immediately after expansion	Yes
Mohaghegh, S. et al. (2020) [121]	2020	Diode laser Ga-Al-As	810-830 nm	Power: 250-300 mW Energy density: 4-6 J/cm^2	Three times Twice at the time of retainer placement and after seven days.	Yes
Rosa, C. B. et al. (2014) [113]	2014	Diode laser	780 nm	Spot size: 0.04 cm^2 Illuminated area: 1 cm^2 Power: 70 mW Power density: 1.75 W/cm^2 Irradiation time: 257 s Energy: 18J Energy density: 18 J/cm^2	Three times in 48h intervals 1st, 3rd, 5th day after expansion	Yes
		LED	850 nm	Spot size: 0.5 cm^2 Illuminated area: 1 cm^2 Power: 150 mW ±10 mW Power density: 0.3 W/cm^2 Irradiation time: 120 s Energy: 18J Energy density: 18 J/cm^2		
Tas Deynek, G.; Ramoglu, S. I. (2019) [119]	2019	Diode laser In-Ga-As-P	940 nm +/- 10	Frequency: 50/60 Hz Fiber tip: 300 µm Irradiated area: 1cm^2 Power: 0.1 W Irradiation time: 3 min Low dose: 18 J/cm^2 Medium dose: 42 J/cm^2 High dose: 60 J/cm^2	Two times in the first week after expansion	Yes
Aras, M. H.; Bozdag, Z. et al. (2015) [117]	2015	Diode laser Ga-Al-As	808nm	Illuminated area: ~ 1 cm^2 Power: 250 mW Irradiation time: 20 sec Energy: 5 J Energy density: ~ 5 J/cm^2	Start 4 days after expansion Daily for 4 days	Yes

Aras, M. H.; Erkilic, S. et al. (2015) [118]	2015	Diode laser Ga-Al-As	808nm	Illuminated area: ~ 1 cm^2 Power: 250 mW Irradiation time: 20 sec Energy: 5 J Energy density: ~ 5 J/cm^2	Start 4 days after expansion Daily for 4 days	Yes
Amini, F.; Najaf Abadi, M. P. and Mollaei, M. (2015) [116]	2015	Ga-Al-As Laser	810 nm	Energy density: 4 J/cm^2	Irradiation at four points on day 0, 2, 4, 6, 8, 10, 12, 14 Divided in following protocols Group 2 - 7 Days with LLLT Group 4 - 14 Days with LLLT Group 6 - 30 Days with LLLT	Yes
Rosa, C. B. et al. (2017) [114]	2017	Diode laser	780 nm	Spot size: 0.04 cm^2 Illuminated area: 1 cm^2 Power: 70 mW Power density: 1.75 W/cm^2 Irradiation time: 257 s Energy: 18J Energy density: 18 J/cm^2	Irradiation in 48h intervals on day 1, 3, 5 and 8, 10, 12, depending on allocated group	Yes
		LED	850 nm ± 10	Spot size: 0.5 cm^2 Illuminated area: 1 cm^2 Irradiation time: 120 s Power: 150 mW Power density: 0.3 W/cm^2 Energy: 18J Energy density: 18 J/cm^2		
Saito, S. and Shimizu, N. (1997) [111]	1997	Diode laser Ga-Al-As	830 nm	optical fiber diameter: 0.6 mm Power: 100 mW Power density: 35.3J/second/cm^2 Irradiation Time: 3 min or 10 min Depending on allocated Group - total dosage energy: 126J or 420J	1. Nontreated 2. Treated with palatal expansion only. 3. Two 7-day irradiation groups: once daily on day 0 until day 6 after expansion (a) 3 minutes per day (b) 10 minutes per day Total dosage:126 J and 420 J 4. Two 3-day irradiation groups: Irradiation for 7 minutes per day once daily on (a) days 0 to 2 (b) days 4 to 6 Total dosage: 126J 5. Single irradiation group: Single irradiation for 21 minutes after expansion. Total dosage: 126J	Yes
Santiago, V. C. et al. (2012) [110]	2012	Photon laser device	790-940 nm	Energy density: 90-120 J/cm^2	20 applications every 48 hours, during and after expansion over a period of 39 days Application at four points	Yes

Table 9: Animal Studies Overview

Appendix

Animal Studies				
Author	**Total of Participants**	**Evaluation Method**	**Timepoint of Evaluation Starting from First Laser Application**	**Results**
Eslamian, L. et al. (2020) [120]	40 rats 4 Groups, 10 per Group	Bone density by occlusal radiographs and CT. Histomorphometric analysis of suture width.	28 days	Bone density in the multiple irradiated group was significantly higher than the control group or single irradiation group in occlusal radiographs and micro-ct. No significant difference for the single irradiated group. Histological examination: Mean suture width was smaller in multiple irradiated group compared to control. No significant difference in mean suture width between the single irradiation and control group.
Altan, A. B. et. al. (2015) [115]	28 rats Group sizes not stated 3 LLLT groups, one expansion only group	Histological examination of osteoblasts, osteoclasts, fibroblasts, vessels and TGF-β	8 days	For all LLLT-groups significantly higher amount of osteoblasts, fibroblasts, vessels and TGF-β and significant lower osteoclasts. Vessels, TGF-β expression, and new bone formation were mostly increased in the low dose group, followed by the high dose group. The number of osteoblasts and fibroblasts were highest in the high dose group. Comparing laser groups: Only significant difference was in new bone formation between low dose and mid dose laser application.
da Silva, A. P. et al. (2012) [112]	30 rats 15 experimental group 15 control group Examination of 5 rats from each group 24h, 48h, and 7 days after expansion	Examination of explanted bone cells. Examination of ALP, Runx2, osteocalcin, type I collagen, and bone sialoprotein mRNA by polymerase chain reaction. Measuring of matrix mineralization	24h, 48h and 7 days	LLLT showed decreased doubling time, indicating increased cell proliferation rate between day 3 and 7 for cells harvested after 24 and 48h. Increased doubling time, indicating decreased cell proliferation in cells harvested after 7 days. In all LLLT treated groups, ALP activity was higher. Increase mRNA expression of osteoblastic markers (ALP, Runx2, osteocalcin, type I collagen and bone sialoprotein) for each LLLT group. Also increased mineralization for each LLLT group, highest in the cells harvested 48h after RME.
Mohaghegh, S. et al. (2020) [121]	60 rats Four groups A = Control. B = Low Level Laser C = bone marrow-derived mesenchymal stem cells D = bone marrow-derived mesenchymal stem cells and Low Level Laser	Measurement of bone density in occlusal radiographs and micro-CT. Histological examination: number of osteoblasts, new bone formation, vascularization, connective tissue, sutural width.	28 days	Number of osteoblasts: Only LLLT had significant better results than control. New bone formation: No significant difference in all experimental groups compared to control. Vascularisation: No significant difference for LLLT and LLLT with stem cell therapy. Only stem cell therapy without LLLT had a significant difference to control. Quality of connective tissue: Significant difference for the groups with stem cell therapy with and without LLLT. No significant difference for the only LLLT group. Sutural width: No significant difference in all groups. Occlusal radiographs - Radiographic bone density: Only stem cell therapy combined with LLLT had significant difference. No significant difference for only stem cell therapy or only LLLT. Micro-Ct - Bone density: Same results as occlusal radiographs
Rosa, C. B. et al. (2014) [113]	20 rats 5 per group Group 1: no treatment	Raman spectroscopy to evaluate hydroxyapatite and collagen disposition.	8 days	No significant difference was found for collagen disposition. For Midpalatal suture, the LLLT and LED treatment resulted in statistically significant higher hydroxyapatite mineralisation.

Appendix

	Group 2: expansion only Group 3: expansion + Laser Group 4: expansion + LED			No statistical difference was found for hydroxyapatite in the cortical bone. No statistical difference was found for collagen disposition in the cortical bone.
Tas Deynek, G.; Ramoglu, S. I. (2019) [119]	80 rats Group 1: Control 20 Group 2: Low dose 20 Group 3: Medium dose 20 Group 4: High dose 20 Each group: half sacrificed after 7 and 21 days resulting in a sample size of 10	Histologic examination: Counting osteoblasts, osteocytes, connective tissue area, vessels and newly formed bone area. Comparison of the ratio of newly formed bone to the total bone area. Scoring the amount of inflammation.	7 and 21 days	After 7 days: Low-LLL group significantly higher amount of osteoblast, osteocytes, newly formed bone, and ratio of newly formed bone to the total bone area. Connective tissue was lower in the low dose group. No statistically significant difference for number of vessels or inflammatory. Higher amount of osteocytes compared to the control group. No significant difference found for the mid- and high- LLL-group. After 21 days: Low-LLL group significantly higher amount of osteoblast, osteocytes, newly formed bone, and ratio of newly formed bone to the total bone area and number of vessels. No significant difference for these parameters found for mid- and high LLL- group. High- level Laser group had significant higher inflammation on day 21 compared to all other groups.
Aras, M. H.; Bozdag, Z. et al. (2015) [117]	32 rats Laser group: 16 Control group: 16 Each group: Half sacrificed after 7 and 17 days resulting in a sample size of 8	Histological examination: Number of osteoclasts, osteoblasts, and capillaries. Intensity of inflammatory cells and new bone formation.	7 and 17 days	Osteoblasts: After 7 days higher amount in the LLL group but no difference after 17 days compared to control. Osteoclasts: Lower amount in each LLL group compared to control. Capillaries: No significant difference. LLL group had trabecular bone after 7 days, none was observed in the control group. After 17 days greater ossification for LLLT group. Higher inflammation in the control group after 7 and 17 days compared to LLL group.
Aras, M. H.; Erkilic, S. et al. (2015) [118]	32 rats Laser group: 16 Control group: 16 Each group: Half sacrificed after 7 and 17 days resulting in a sample size of 8	Histological examination: Numbers of osteoclasts, osteoblasts, capillaries, and inflammatory cells. Evaluation of extent of new bone formation.	7 and 17 days	No significant difference in number of osteoblasts. Osteoclasts: significant higher in LLL group after 7 days (control group no osteoblasts), no difference after 17 days. Capillaries: No significant difference. Trabecular bone found in LLL and control group after 7 days, but larger amount in LLL group. After 17 days both groups had increased trabecular bone formation, LLL group had better ossification. Control group had higher inflammation after 7 days.
Amini, F.; Najaf Abadi, M. P. and Mollaei, M. (2015) [116]	78 rats 7 Groups 1. Control Group, no expansion or LLLT: 6 2. 7 Days with LLLT: 12 3. 7 Days no treatment: 12 4. 14 Days with LLLT: 12 5. 14 Days with no treatment: 12 6. 30 Days with LLLT: 12 7. 30 Days with no treatment: 12	Histological analysis via metric measuring of the bone regeneration.	7, 14, and 30 days	After 7 days no significant difference. After 14 and 30 days statistically significant difference favouring LLLT. Highest extend of bone regeneration after 7 days, but results favouring LLLT after 14 and 30. days, indicating late effect of LLLT.
Rosa, C. B. et al. (2017) [114]	45 rats Divided into nine groups: 7-day experimental groups 1. control (no treatment) 2. expansion only 3. expansion and laser irradiation 4. expansion and LED	Raman spectroscopy concentration of hydroxyapatite and collagen protein in the midpalatal suture and cortical bone. Histological analyses of inflammatory process, collagen fibre, osteoblastic and osteoclastic activity.	7 and 14 days	Midpalatal suture Raman spectroscopy: 7 Day groups: Collagen peaks: No statistical difference. Hydroxyapatite: Significant difference favouring LLLT and LED. LED group with Significant higher peak than LLLT. 14 days groups: Collagen peaks: Lower peak for LED treatment for 7 days compared to expansion only. Higher peak for LED treatment for 14 days compared to LED treatment for 7 days.

	irradiation 14 days experimental groups 5. expansion only 6. expansion and laser in the 1st week 7. expansion and LED in the 1st week 8. expansion and laser in the 1st and 2nd weeks 9. expansion and LED in the 1st and 2nd weeks			No statistically significant difference for LED/LLLT compared to expansion only group. Hydroxyapatite: Significant difference favouring LED and LLLT with 14 days of irradiation. Highest peaks observed for LLLT. Higher peaks for 14 days LED treatment compared to 7 days LED treatment. Higher peaks for 14 days LLLT compared to 7 days LLLT. Cortical bone Raman spectroscopy: 7 days groups: Collagen peaks: No significant difference. Hydroxyapatite: No significant difference. 14 days groups: Collagen peaks: Higher peak for 14 days of LED treatment compared to 7 days of LED treatment. No statistically significant difference favour LED or LLLT compared to expansion only. Hydroxyapatite: No significant difference. Histological findings: Inflammatory outcome not clearly stated. Collagen disposition: Significant difference for all LLLT/LED groups compared to expansion only. Osteoblast and osteoclast activity: Higher osteoblast activity and lower osteoclast activity for LED and LLLT.
Saito, S. and Shimizu, N. (1997) [111]	76 rats 56 rats for histomorphometric analysis 20 rats for histologic examination Divided into seven groups of 8 rats each Intact group: Nontreated Non irradiation control group Two 7-day irradiation groups Two 3-day irradiation groups Single irradiation group	Bone histomorphometric analysis by measuring of newly formed bone area between day 0 and 6, osteoid area, mineralized width between day 0-3 and 3-6 in the same histological preparation. Therefore injecting calcein on day 0 and 6 and oxytettracycline on day 3 as a marker. Also measurement of mineral apposition rate by dividing the distance of the two periods with the days was carried out. Histologic examination of no specific parameters.	7 days	Histomorphometric examination: 7 Day irradiation group: Newly formed bone area significantly higher for the 7 and 3 days irradiation group favouring LLLT. Mineral apposition rate was increased in LLLT. Mineral apposition rate was significantly higher from day 0 to 3 compared to day 3 to 6 for the LLLT. No difference on that parameter in the control group. Results for the 10 min irradiation group where higher than for the 3 min irradiation group. 3 day irradiation group: Statistically significant higher amount of newly formed mineralized bone area and mineral apposition rate on day 0-2 compared to control. No significant difference between day 3 to 6 compared with control. No significant difference in the osteoid area for each group. No significant difference for the single irradiation group for all parameters. Histologic examination: For each group, extension of the transverse fibres and enlargement of vessels was observed. No pathologic tissue changes, such as sclerosis or excessive intimation was observed.
Santiago, V. C. et al. (2012) [110]	11 dogs RME with LLLT - Group: 5 RME without LLLT: 5 Control group without treatment: 1	Histological examination: Evaluation of connective tissue, blood vessels, cells, palatal bone tissues at edges of the suture via score and number of osteoblasts	40 days	Significant differences favouring the LLLT group for connective tissue of the suture, blood vessels, bone tissue, and total score. No significant difference in osteoblast counts or relation to the width between the edges of the suture and the width of newly formed bone.

Table 10: Animal Studies Overview 2

Study Identification	Domain 1: Risk of Bias Arising from the Randomisation Process					
Author	1.1 Was the allocation sequence random?	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Risk-of-bias judgement	Optional: What is the predicted direction of bias arising from the randomization process?	Comments
	Y / PY / PN / N / NI	Y / PY / PN / N / NI	Y / PY / PN / N / NI	Low / High / Some concerns	NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	
Cepera, F. et al. (2012) [107]	NI	NI	PN	Some Concerns	Unpredictable	• Only randomisation reported • No exclusion/inclusion criteria specified
Angeletti, P. et al. (2010) [106]	NI	NI	PN	Some Concerns	Unpredictable	• Only randomisation reported • No exclusion/inclusion criteria other than age and treatment were specified, no further information on baseline data was available.
Garcia, V. J. et al. (2016) [108]	PY	NI	N	Low	NA	• Randomisation method not directly specified, but mentioned simple random sampling method. • Inclusion and exclusion criteria specified
Ferreira F. N. et al. (2016) [109]	Y	PY	N	Low	NA	• Use of a digital randomisation programme • Inclusion/exclusion criteria specified
Matos, D. S. et al. (2020) [43]	Y	PY	N	Low	NA	• Subjects were drawn at random • Inclusion/exclusion criteria specified

Y = yes N = no NI = no information
PY = probably yes PN = probably no NA = not applicable

Table 11: Risk of Bias Domain 1

Appendix

Study Identification	Domain 2.1: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)									
Author	2.1. Were participants aware of their assigned intervention during the trial?	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Risk-of-bias judgement	Optional: What is the predicted direction of bias due to deviations from intended interventions?	Comments
	Y / PY / PN / N / NI	Y / PY / PN / N / NI	NA / Y / PY / PN / N / NI	NA / Y / PY / PN / N / NI	NA / Y / PY / PN / N / NI	Y / PY / PN / N / NI	NA / Y / PY / PN / N / NI	Low / High / Some concerns	NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	
Cepera, F. et al. (2012) [107]	NI	NI	NI	NA	NA	NI	NI	High	Unpredictable	• No mention of placebo use • No information on this section was directly mentioned in the study, but also no exclusion of patients during study was mentioned. • No exclusion for inconsequent analysed data
Angeletti, P. et al. (2010) [106]	NI	NI	NI	NA	NA	NI	NI	High	Unpredictable	• No mention of placebo use • No information on this section was directly mentioned in the study, but also no exclusion of patients during study was mentioned. • It seems that there were no missing data or deviations.
Garcia, V. J. et al. (2016) [108]	PN	NI	NI	NA	NA	PY	NA	Some Concerns	Unpredictable	• Stated that a placebo mode was used with the same device. • Exclusion of patients with missing outcome data.
Ferreira F. N. et al. (2016) [109]	PY	PY	PN	NA	NA	PY	NA	Low	Unpredictable	• No mention of placebo use • RME treatment and the laser application were performed by the same operator. • RME treatment was performed before assignment to the intervention/control group. • Exclusion of patients due to medication use or failure of outcome data
Matos, D. S. et al. (2020) [43]	PN	NI	PN	NA	NA	PN	PN	Some Concerns	Unpredictable	• Use of the laser device in standby mode as a placebo. • Exclusion of patients who did not follow the treatment protocol or missed the intervention

Y = yes N = no NI = no information
PY = probably yes PN = probably no NA = not applicable

Table 12: Risk of Bias Domain 2.1

Appendix

Study Identification	Domain 2.2: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Adhering to Intervention)								
Author	2.1. Were participants aware of their assigned intervention during the trial? Y / PY / PN / N / NI	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? Y / PY / PN / N / NI	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups? NA / Y / PY / PN / N / NI	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome? NA / Y / PY / PN / N / NI	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes? NA / Y / PY / PN / N / NI	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention? NA / Y / PY / PN / N / NI	Risk-of-bias judgement Low / High / Some concerns	Optional: What is the predicted direction of bias due to deviations from intended interventions? NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Comments
Cepera, F. et al. (2012) [107]	NI	NI	NI	PN	PN	NI	High	Unpredictable	• No use of placebo laser mentioned • No mention of a regulation concerning intervention adherence • No inclusion/exclusion criteria of participants specified
Angeletti, P. et al. (2010) [106]	NI	NI	NI	PN	PN	NI	High	Unpredictable	• No use of placebo laser mentioned • No mention of a regulation concerning intervention adherence • Only basic inclusion/exclusion criteria of participants specified
Garcia, V. J. et al. (2016) [108]	PN	NI	PY	PN	PN	NA	Low	NA	• Placebo laser mode was used with the same device • Considering the inclusion and exclusion criteria, it seems likely that there were no relevant differences in interventions between the groups and participants
Ferreira F. N. et al. (2016) [109]	PY	PY	PY	PN	PN	NA	Low	NA	• No mention of placebo use • RME treatment and laser application were performed by the same operator • RME treatment was performed before assignment to the intervention/control group • Inclusion/exclusion criteria stated • Specified exclusion of patients due to medication use • Considering the inclusion and exclusion criteria, it seems likely that there were no relevant differences in interventions between the groups and participants.
Matos, D. S. et al. (2020) [43]	PN	NI	PY	N	N	NA	Low	NA	• Exclusion of patients who missed the intervention or had incidents during treatment • Use of standby mode as placebo intervention • Reported inclusion/exclusion criteria, but not regarding medication • Exclusion of patients who did not adhere to the intervention protocol and follow-up or who had complications during the intervention • Considering the inclusion and exclusion criteria, it seems likely that there were no relevant differences in interventions between the groups and participants

Y = yes N = no NI = no information
PY = probably yes PN = probably no NA = not applicable

Table 13: Risk of Bias Domain 2.2

Appendix

Study Identification	Domain 3: Risk of Bias Due to Missing Outcome Data						
Author	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Risk-of-bias judgement	Optional: What is the predicted direction of bias due to missing outcome data?	Comments
	Y / PY / PN / N / NI	NA / Y / PY / PN / N	NA / Y / PY / PN / N / NI	NA / Y / PY / PN / N / NI	Low / High / Some concerns	NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	
Cepera, F. et al. (2012) [107]	Y	NA	NA	NA	Low	NA	• Reported missing radiographs for the evaluation at the different time points • Maximum of 2 missing radiographs from a total of 27 patients at an evaluation time point.
Angeletti, P. et al. (2010) [106]	PY	NA	NA	NA	Low	NA	• Not specified in the report, but no missing data in the tables
Garcia, V. J. et al. (2016) [108]	PY	NA	NA	NA	Low	NA	• Reported that participants who had missed a CBCT scan were excluded.
Ferreira F. N. et al. (2016) [109]	N	PY	NA	NA	Low	NA	• Specified exclusion of patients due to medication, failure of outcome data or technical problems • Loss of half of the patients in the control group (originally 8, only 4 analysed) • 10 patients in the experimental group were analysed • Showed in a figure that optical density data were analysed by CBCT scan for all included patients • Sample size calculations were given, indicating the reability of sample sizes for both groups • No results were given in numbers
Matos, D. S. et al. (2020) [43]	N	PY	NA	NA	Low	NA	• Exclusion of patients who missed the intervention or had incidents during treatment • No mention of total number of radiographs, but seems to indicate no missing data based on reported values. This is further supported by the study results and the exclusion of patients who missed appointments, indicating the exclusion of patients with missing outcome data.

Y = yes N = no NI = no information
PY = probably yes PN = probably no NA = not applicable

Table 14: Risk of Bias Domain 3

Appendix

Study Identification	Domain 4: Risk of Bias in Measurement of the Outcome							
Author	4.1 Was the method of measuring the outcome inappropriate?	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Risk-of-bias judgement	Optional: What is the predicted direction of bias in measurement of the outcome?	Comments
	Y / PY / PN / N / NI	Y / PY / PN / N / NI	NA / Y / PY / PN / N / NI	NA / Y / PY / PN / N / NI	NA / Y / PY / PN / N / NI	Low / High / Some concerns	NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	
Cepera, F. et al. (2012) [107]	PN	PN	NI	PY	PN	Some Concerns	Unpredictable	• No information on blinding of the radiographs taken • No detailed explanation of standardised radiographic parameters, but mention of a standardised procedure • Mentioned of a standardised evaluation method of the radiographs • Assumption that due to the standardised computer-assisted evaluation method, even if the observer knew the assigned group of the radiograph, this might not have a major influence on the results • Not mentioned that a second observer or a second observation was performed
Angeletti, P. et al. (2010) [106]	PN	PN	N	NA	NA	Low	NA	• Blinding of the radiographs • Reported fixed standardisation for data collection and evaluation method • Stated only one observer, but three times observation of each radiograph with an interval of 15 days in between.
Garcia, V. J. et al. (2016) [108]	PN	PN	N	NA	NA	Low	NA	• Blinding of the radiographs • Stated standardisation of the data collection and evaluation method • Stated observation by two radiologists
Ferreira F. N. et al. (2016) [109]	PN	PN	N	NA	NA	Low	NA	• Blinding of radiographs • Stated standardisation of data collection and evaluation method, but no detailed description of all parameters and settings • Stated a single observer who performed the observation twice, 30 days apart
Matos, D. S. et al. (2020) [43]	PN	PN	NI	PY	PN	Some Concerns	Unpredictable	• No blinding of radiographs stated • Stated standardised methods for radiographs and evaluation process • Assumption that due to the standardised computer-assisted evaluation method, even if the observer knew the assigned group of the radiograph, this might not have a major influence on the results • No mention of a second observer or the conduct of a second observation

Y = yes N = no NI = no information
PY = probably yes PN = probably no NA = not applicable

Table 15: Risk of Bias Domain 4

Appendix

Study Identification	Domain 5: Risk of Bias in Selection of the Reported Result						Overall Risk of Bias
Author	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from... 5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	5.3 ... multiple eligible analyses of the data?	Risk-of-bias judgement	Optional: What is the predicted direction of bias due to selection of the reported result?	Comments	Risk-of-bias judgement
	Y / PY / PN / N / NI	Y / PY / PN / N / NI	Y / PY / PN / N / NI	Low / High / Some concerns	NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable		Low / High / Some concerns
Cepera, F. et al. (2012) [107]	NI	N	PN	Some Concerns	Unpredictable	• No data binding mentioned • Only one measurement method was applied to the outcome • No pre-specified study protocol was mentioned • Ethics Committee approval stated	High
Angeletti, P. et al. (2010) [106]	NI	N	PN	Some Concerns	Unpredictable	• Only mentioned data blinding for the observation • Only one measurement method was applied for the outcome • No pre-specified study protocol was mentioned • Ethics committee approval stated	High
Garcia, V. J. et al. (2016) [108]	NI	PN	PN	Some Concerns	Unpredictable	• Only mentioned data blinding for the observation • Assessment of two methods for outcome measurement of the CBCT scans • Positive results for the experimental group were reported for all data evaluated, which seems to indicate that no individual positive results were selected for the report • No pre-specified study protocol was mentioned • Ethics committee approval stated	Some Concerns
Ferreira F. N. et al. (2016) [109]	NI	NI	PN	Some Concerns	Unpredictable	• Only mentioned data blinding for the observation • Performed measurements at three points of the CBTB scan • No differentiation of findings for the measurement points • No result data given in numbers • Only indication of the statistical significance of the results • No pre-specified study protocol was mentioned • Ethics committee approval stated	Some Concerns
Matos, D. S. et al. (2020) [43]	PY	PN	PN	Low	NA	• No blinding of the data was mentioned • Only one measurement method was used for the outcome • Stated study registration and ethics committee approval	Some Concerns

Y = yes N = no NI = no information
PY = probably yes PN = probably no NA = not applicable

Table 16: Risk of Bias Domain 5 and Overall Risk of Bias

Study	D1	D2.1	D2.2	D3	D4	D5	Overall
Cepera, F. et al. (2012) [107]	-	x	x	+	-	-	x
Angeletti, P. et al. (2010) [106]	-	x	x	+	+	-	x
Garcia, V. J. et al. (2016) [108]	+	-	+	+	+	-	-
Ferreira F. N. et al. (2016) [109]	+	+	+	+	+	-	-
Matos, D. S. et al. (2020) [43]	+	-	+	+	-	+	-

+ Low - Some Concerns x High

D1 Risk of bias arising from the randomisation process
D2.1 Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
D2.2 Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
D3 Risk of bias due to missing outcome data
D4 Risk of bias in measurement of the outcome
D5 Risk of bias in selection of the reported result

Table 17: Risk of Bias Overview

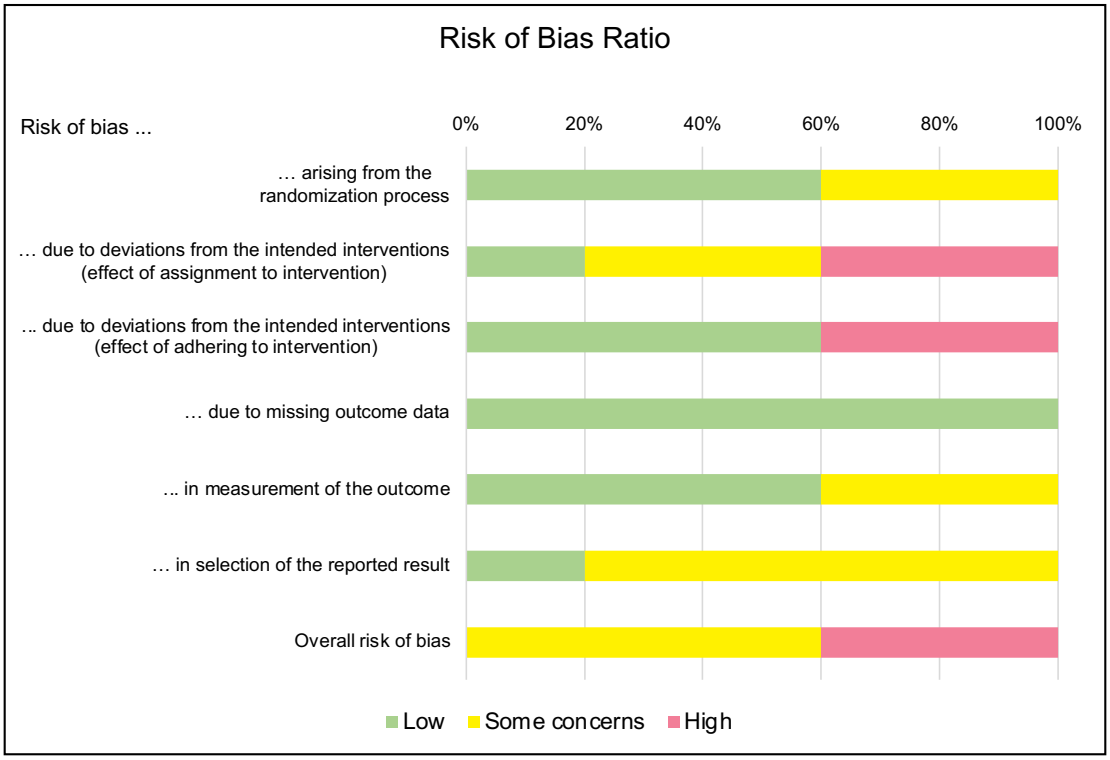

Figure 3: Risk of Bias Ratio

Outcome: Patients treated with LLLT as an adjuvant therapy for RME have increased bone regeneration of the sutura palatina, compared to patients treated with RME only.		
GRADE criteria	Rating	Comment Reasons for down-upgrade
Study design	++++	Randomised controlled trials
Risk of Bias	-1	Some high risk rated domains, many domains rated with some concerns
Inconsistency	-1	No p-, I^2-value or confidence interval evaluation possible, differences in laser-parameters and protocol and timepoint of evaluation. No relevant difference in patients.
Indirectness	0	All studies address the signalling question, no relevant differences in population or intervention.
Imprecision	-1	No confidence interval as indicator for evaluation. Total of sample size included is below 400
Publication bias	0	Small numbers of participants in studies. No Funnel-Plot for evaluation. Most studies state that there is no conflict of interests, sponsoring only by academic and university institutions.
Reasons to upgrade	0	None
Overall Rating	+	Very low

Table 18: GRADE Rating

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9 Tabellarischer Lebenslauf

XXX

Tabellarischer Lebenslauf