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Key words: Concentrated Growth Factors, Mphi laser, Regeneration, Wound Healing.

Application of Concentrated Growth Factors (CGF) and Mphi Laser to Treat Defects in the Oral and Maxillofacial Region. A two - case report.

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ABSTRACT

The application of Concentrated Growth Factors (CGF) in oral and maxillofacial surgery (OMS) and, in general, in regenerative medicine is steadily increasing. The purpose of this study is to present a review and case reporting on the use of CGF for tissue regeneration in the oral maxillofacial region.

MATERIALS AND METHODS

Literature search was carried out using Medline search and manual search using the keywords: "concentrated", "growth factors", "tissue engineering", "regenerative medicine" and "blood". The review followed the method recommended by PRISMA and included clinical studies with adequate information. Papers with lack of data were excluded. Additionally, authors' experience on this topic was reported with the description of two relevant cases. In both patients, bony defects were filled with autologous fibrin rich CGF and synthetic alloplastic materials, and then treated with Mphi laser. Results: There were no published data on the combined use of Mphi laser and CG Fin clinical applications in the OMS region. Two case reports on the surgical regenerative management of oral lesions CGF and Mphi laser were described. Postoperative recovery was uneventful. Laser was effective in reducing postoperative pain, swelling, bleeding, speech impairment, analgesic use, trismus and wound healing. There was no difference in wound healing after one and 3 months. Conclusion: The innovative application of Concentrated Growth Factors (CGF) in combination with Mphi laser in Oral and Maxillofacial Region defectsproduced rapid improvement and minimized complications. The treatment is fairly simple and cost effective.

I. INTRODUCTION

Growth factors are molecules capable of facilitating several biological activities, such as cell proliferation, differentiation and repair. The use of concentrated growth factors (CGF) in dentistry is a relatively new concept. Since its inception, CGF have been used to enhance regeneration and healing for a variety of procedures, such implant placement, socket preservation, bony reconstruction and tissue regeneration [1]. The use of Multiwave-Locked System laser devices, such as Mphi laser [2], represents an innovative adjunctive therapy for the enhancement of wound healing after CGF treatment. A unique feature of MLS® Laser Therapy is the patented wave technology involving the use of two different and synchronised emissions,one with continuous/ frequenced mode and 808 nm wavelength, the other with pulsed mode and 905 nm wavelength, that makes it one of the most efficient lasers for improving wound healing. Mphi laser has many therapeutic indications: sprains, muscle tears, tendinitis, brachial neuralgia, craniofacial pain, bursitis, lumbago, arthritis, articular pain, edema, hematoma. MLS® Laser Therapy produces its effects through anti-inflammatory and analgesic properties [3]. These effects are beneficial in the enhancement of wound healing and management of complications that can occur in surgical procedures. A previous study on the use of Mphi laser on treatment of craniofacial pain yielded promising results [5]. Research on laser therapy is widespread: up to the present time more than 28,200 articles are listed on PubMed, of these over 14,400 papers discussed pain associated with oral surgery. A systematic review on the application of LLLT on pain management [4] showed mixed results due to multiple inconsistencies in classification of wavelengths, outcome measures, study methods, recording techniques, degree of difficulty in oral surgery and duration of surgery.

Throughout typical wound healing, the fibrin substance is imperative in hemostasis, and forms the primary framework for the new extracellular matrix [6]. Fibrin permits the attachment of cells (for example, platelets and white blood cells - WBCs) and proteins to the bone tissue, fibroblasts and osteoblasts, endothelial cells, and smooth muscle cells. Also, keratinocytes attach to fibrin. Fibrin subsequently encourages wound healing by acting as conveying locations for the attachment of cytokine, growth factors and cell adhesion molecules [1]. In animal studies, fibrin accumulated in hypodermal tissue and revealed to be a significant factor in angiogenesis [7]. Additionally, numerous reports showed that wound healing is led by fibrin structure (i.e. concentration, quantity of division points, porosity and permeability). The fibrin substantial configurations are determined by several factors comprising clotting rate, Factor XIII concentration, thrombin, chloride ions, pH, etc [1]. Enhancing these environments is one of the goals of the CGF procedure. Pathological modifications of these fibrin regulators occur in some disorders, for example diabetes, and this undoubtedly tips to instabilities in wound healing. Accordingly, patients affected by these diseases are the subjects who benefit the most from the CGF procedure. Furthermore, not only the use of PRP and PRF have been reported to promote faster healing, but there are findings indicating that fibrin glue by itself can be utilised to improve wound healing [8]. With no anticoagulants used, the platelets start to be stimulated intuitively together with the coagulation cascade. The subsequent matrix/membrane complex has a high fibrin content and functions synergistically with growth factors [8]. In addition to CGF, employed as an autologous store of growth factors, synthetic alloplastic or xenoplastic materials can be used. The course of bone regeneration depends on various factors including, but not limited to, the size, the type and extent of the deficiency, the patient medical status, demographic variables and smoking status, provided that coagulum formation process is not impaired [8]. The typical healing time of oral bony defects is normally up to 12 months for small lesions, two years for medium-size lesions, and five years for larger cystic lesions [9]. Once the lesions were removed, bone defect was totally filled with blood clot/coagulum. A series of events occur after the preliminary blood clot formation, which include clot contraction and serum elimination, resulting in marginal serum-filled gaps amongst bony partition and coagulum exterior [9, 10]. This may notably affect angiogenesis and wound healing. Furthermore, the area created by the dental lesion elimination may originate a favourable environment for microbial proliferation and increase the possibility of infection. Thus, it is essential to stabilize the newly formed blood clot to facilitate wound healing [8]. Numerous methods of clot preservation have been documented including, but not limited to, guided bone regeneration and guided tissue regeneration using autografts, allografts and xenografts. Recently, the innovative application of autologous concentrated growth factors (CGF) has been well received [11]. Growth factors are naturally occurring substances, such as steroids or proteins, capable of promoting cellular growth, proliferation, healing, differentiation, and angiogenesis [12]. Blood growth factors are principally found in blood plasma and platelets. Of these, the most important are: platelet derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and insulin like growth factor 1 (IGF 1) [13, 14]. Historically, the initial production of platelet-rich plasma (PRP) [15] was presented in 1998 and the second, platelet rich fibrin (PRF) [16], in 2000. Blood obtained through patient venepuncture was used to generate fibrin-rich gel PRF [16–18]. CGF was originally, discovered by Sacco and co-workers [19]. CGF revealed a superior tensile strength, extra growth factor content, better viscosity and greater adhesive strength than PRF [20]. The usage of autologous fibrin provides many advantages including safety, no side effect, easy technique, cheap, and efficacy for the patients [20, 21].

II. MATERIALS AND METHODS

This study attempted to carry out literature review and cases report on the use of Mphi laser in conjunction with CGF applications in the oral and maxillofacial region. Literature search was carried out using Medline search and manual search using the keywords: "concentrated", "growth factors", "tissue engineering", "regenerative medicine" and "blood". The review followed the method recommended by PRISMA and included clinical studies with adequate information. Papers with lack of data were excluded. No publication was found on this topic. The authors presented their experience with the above mentioned technique by describing two cases on the application of Mphi laser in conjunction with CGF in the regeneration of bony patients with large cystic lesions in the upper and lower jaw, respectively. CGF was prepared (Figure 1) according to the procedure using patient's blood through venepuncture (total blood collected 40 ml), which was allocated into two red and two white sterilised 10 ml Vacutainer® tubes. These four tubes were instantly centrifuged with Medifuge MF 200 (Silfradent, Italy) following the manufacturer's recommendation. After spinning, sedimentation of the Vacutainer's content was allowed for 20 min until further processing. The top 2ml layer comprised the platelets poor plasma (PPP) containing serum, the next 2ml layer was platelets rich plasma (PRP), the third 0.7ml was the stem cells/white layer, while the fibrin-rich mass with CGF was in the central part of the tube constituting the CGF clot, the remaining 4ml and 1ml precipitated portions were red blood cells and sedimentary blood fragments, respectively. The final CGF mixture was collected by tipping off the top PPP and meticulously collecting the clot layers. Using a sterile Petri dish, the CGF clot was detached from the red blood portion using scissors (12). Fabrications of CGF sticky bone and membrane were followed by the manufacturer's protocol. For sticky bone, Geistlich Bio-Oss® (bovine demineralized freeze dried bone, Geistlich Biomaterials) and Osteon (hydroxyapatite and calcium triphosphate, Genoss®) were used instead of calcium triphosphate. Digital radiographic and clinical assessments were performed at one, three and six month review. The patients were monitored and were asked to report post operative pain, swelling, bleeding, speech impairment, analgesic use, trismus and wound healing.

Figure 1: White and Red Vacutainer® tubes showed different colours and layers after spinning, used for CGF preparation of sticky bone and membrane (Adapted from Dr Ezio Gheno, 2015)

Ideally, there should be a control treatment site on a contra-lateral side to compare the effectiveness of Mphi laser and CGF treatment to the sham/control side. However, due to lack of suitable cases for a split mouth study, these two cases were treated as clinical audit

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III. RESULTS

The search found only six CGF related articles that, however, did not meet completely the inclusion criteria. These six articles illustrated the application of CGF in the oral and maxillofacial region (OMR) including: sinus lift, ridge augmentation, gingival recession, implantology, maxillofacial reconstruction.

The cases reported below showed good results, indicating that the innovative clinical application of CGF in OMR is promising. No post-operative complications associated with CGF procedures were reported in the two cases. Mphi laser was effective in reducing postoperative pain, swelling, bleeding, speech impairment, analgesic use, trismus and wound healing. Apparently, there was no difference in wound healing after one and three months.

CASE REPORT

Case 1

A female patient, 55 year old, was presented to a private specialist Oral Surgery clinic for a complaint of pain and swelling in the anterior lower jaw region. Her medical history was unremarkable. Clinical assessment indicated inflammation in the lower vestibule, tender and fluctuant to touching in the lower right lateral incisor and first premolar area.

As the involved teeth were splinted together in a fixed porcelain fused to metal bridge, no mobility was detected (Figure 2). After clinical assessment, cone beam computed tomography (CBCT) scans were acquired, displaying two well outlined round cystic defects (diameter ~ 3 cm), located in the right anterior area of the mandible (Figure 3).

Figure 2: Intra-oral photo of lower right lateral and first premolar splinted together by porcelain fused to metal bridge

and demonstrating a fair amount of bone loss at the lower right lateral incisor and first premolar, with intact lingual bony plate.

The surgical management involved total elimination of two cystic defects (lower right lateral incisor and second premolar), apicoectomy of the involved teeth and concealing the deficiency with CGF mixture of fibrin rich sticky bone and membrane. After CGF clot preparation, surgical process was carried out under local anaesthesia. Subsequently, a mucoperiosteal buccal flap was raised between lower left first incisor and lower right second premolar. An interchanging dulled and piercing division was used to detach and eradicate the two cystic lesions from bone. After enucleation/ cystectomy, apicoectomies of the involved teeth were performed. The resultant bony deficiencies were rebuilt by packing of CGF fibrin-rich clot sticky bone reinforced with Geistlich Bio-Oss® and Osteon, which totally covered the cystic defects (Figure 4). Ultimately, the flap was sutured in place with resorbable chromic sutures. At the end of the treatment, Mphi laser was applied at the surgical site following the manufacturer's protocol. The total CPW energy used was 0.637 Joules at an energy density of 1.27 J/cm², frequency of 1500 Hz, lasing time per application 0.04 second at 25% intensity. Two laser applications, at the apical and coronal half, were employed at each implant on buccal and lingual side. Post-operatively, the patient was given thorough oral hygienic instruction and dietary program. Prescription

Figure 3: Cone beam computed tomography (CBCT) and 3D reconstruction of patient's oral and maxillofacial region shows defects at the lower right anterior section of the mandible.

Figure 4: Outline of treatment for two dental cysts using CGF sticky bone and membrane.

of antibiotics (Amoxicillin/Clavulanic and metronidazole) and analgesics (combined paracetamol and ibuprofen) were given. Postoperative follow-ups were uneventful and were done at first day, first week, one month, three months and six months. No post-operative complications associated with CGF treatment were noted. Digital radiographic and clinical assessments were performed at one, three and six month review. The patient was monitored for postoperative pain, swelling, bleeding, speech impairment, analgesic use, trismus and wound healing. Mphi laser helped to reduce postoperative pain, swelling, bleeding, speech impairment, analgesic use, trismus and wound healing. There was no difference in wound healing after one and 3 months. Through the ensuing six months, an even and stable building of the deficiencies by freshly produced bone was noted.

Case 2

A healthy 81 years old lady with no significant medical history, presented to a specialist Oral Surgery Clinic for surgical management of perio-implantitis of her two existing implants in the upper first premolar and molar area. Though the patient did not complain of any particular troubles, digital imaging indicated areas of bone loss surrounding the coronal third of her two implants spreading bucco-lingually.

Clinical evaluation indicated slight gingival inflammation in the buccal aspect of the two implants though the sulcular mucosa appeared normal. A digital peri-apical imaging of the implants showed moderate bone loss in their coronal thirds (Figure 5). Treatment options for the defect encompass conservative and radical surgical management. Conservative treatment includes debridement followed either by traditional or CGF bone and tissue regeneration (GBR and GTR).

Radical treatment involved surgical removal of the two mentioned implants. The patient

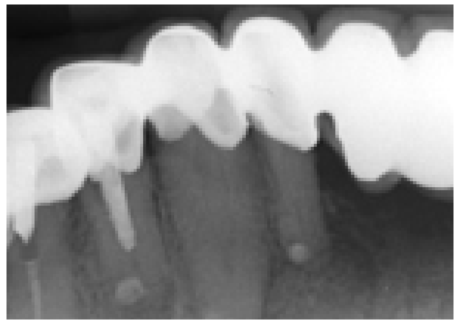

Figure 5: Post-operative peri-apical radiography showed cystic defects were filled CGF containing sticky bone and membranes.

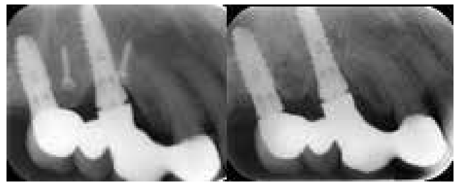

Figure 6: Left x-ray showed perio-implantitis defect at coronal third of upper first premolar and molar. Right x-ray illustrated defects after CGF treatment.

chose conservative CGF GBR and GTR.

This treatment comprised of raising a bucco-palatal muco-periosteal flap followed by a total removal of soft granulated peri-implantitis tissue, debridement of the infected bone, removal of two remaining GBR screws and smoothing of exposed implant titanium threads. The exposed implant surfaces were conditioned with CGF stem cells and PRP prior to application of CGF sticky bone and membrane to restore the entire peri-implantitis defects (Figure 6).

The CGF sticky bone and membrane were prepared instantaneously, prior to operation, as explained in case 1, using four 10 ml Vacutainer® tubes. Once the defects were completely filled with sticky bone and membrane, the flap was closed using chromic resorbable sutures then coated with PPP to create a fibrin seal to enhance wound healing (Figure 7). At the conclusion of the procedure, Mphi laser was used to irradiate the surgical wound following the manufacturer's protocol. The total CPW energy used was 0.637 Joules at an energy density of 1.27 J/cm², frequency of 1500 Hz, lasing time per application 0.04 second at 25% intensity. Two laser applications, at the apical and coronal half, were employed at each implant on buccal and lingual side. Similar prescription antibiotic regimen (Amoxicillin/ Clavulanic and metronidazole) and analgesics (combined paracetamol and ibuprofen) and post surgical oral hygiene instruction were given. Postoperative follow-up were uneventful and were carried at first day, first week, one month, three months and six months. The patient was observed and reported for post operative pain, swelling, bleeding, speech impairment, analgesic use, trismus and wound healing. No post-operative complications associated with CGF therapy were recorded.

Digital x-ray assessments were performed at one, three and six month review. Mphi laser helped to reduce postoperative pain, swelling, bleeding, speech impairment, analgesic use, trismus and wound healing. There was no difference in wound healing after one and 3 months.

Figure 7: Outline of treatment for peri-implantitis for upper right first premolar and first molar using CGF sticky bone and membrane.

DISCUSSION

Traditionally, regeneration of bony defects following eradicating big cystic defects in the oral and maxillofacial region, such as maxilla and mandible, may, at times, be coupled with complications. For example, shrinkage of blood clot, serum exudation, and development of lifeless gaps, as well as a risk of minor infection, considerably affect the regenerative courses of the jawbones.

The above issues have brought attention to the medical scientific community through research and publications [1,8]. Conventionally, it is not uncommon to have a total eradication of cystic defects and covering the finishing bony lesion with primary wound suturing. The main dilemma of the surgeon is to find the best way for bone defect reconstruction. According to the available literature [8], large bony defects are commonly filled and reconstructed with autotransplants obtained from the iliac ridge, ribs or donor sites in the oral cavity. Application of autotransplants enables primary wound healing, preservation of bone contours and fast regeneration. However, a drawback of this approach is the need for additional surgical procedure, highly specialized personnel, general anaesthesia and very high expenses [8,9]. Application of growth factors in guided bone regeneration procedure has been well-known for an extended period of time. This technique is applicable in implantology, specially due to its versatility in various augmentation techniques, and in unfavourable anatomic situations (horizontal and vertical augmentation, sinus lift etc.) [14]. CGF can be applied alone or mixed with bone autotransplants or other bone graft substitutes. The above-mentioned indications exemplify small bony defects that can be easily restored.

The good results obtained in the two clinical case reports indicated that the innovative clinical application of Mphi laser and CGF in OMR is promising, though the exact mechanism of action is not discussed as it is beyond the scope of this paper. The application of Mphi laser and CGF in the reconstruction of large cystic defects has not been reported yet. The presented cases are a pioneering attempt of reconstructing and restoring bone defects of the upper and lower jaws in combination with the use of synthetic alloplastic bone substitutes, secondary surgical procedures and chemical additives. The only method that is somewhat comparable with the presented cases is a lateral sinus lift procedure with filling dead spaces between the sinus mucosa and bony palate with pure CGF blocks [8, 20]. The published data addressing this topic suggested that newly formed bone of acceptable quality (density) and quantity was formed within 3–6 months, and had less postoperative complications. Moreover, the procedure is economically acceptable to the patient [20, 21].

Application of CGF sticky bone and membrane is one of the most up-to-date methods for reconstruction of bone defects in the OMR [8, 20]. Concentrated growth factors are applicable alone or mixed with bone graft material. The two cases presented in this article demonstrate the efficiency of CGF in significantly shortening bone-healing time, particularly in massive bone defects, reducing the incidence of postoperative complications, and enabling better restoration of surrounding periodontium. The method is relatively simple, with minimal risk of infection and allergic reaction, and economically feasible.

In an ideal scientific study, there should be a control group. However, the current cases were not suitable for a split mouth study and were treated as clinical audit. More research should be carried out, particularly, prospective split mouth study to confirm CGF and Mphi laser effectiveness and efficacy in tissue regeneration for the oral and maxillofacial region.

CONCLUSION

Majority of current regenerative technologies in OMR still faced with three main issues: compatibility, failure and cost. The use of autologous materials such as CGF may represent a potential solution to these dilemma. The combination with Mphi laser application may represent a valuable aid in managing post operative discomfort. Further research should be conducted, especially, prospective split mouth study to validate the effectiveness of the CGF and Mphi laser combined treatment in tissue regeneration for the oral and maxillofacial region.

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Key words: thendinopathies, MLS® therapy, NIR radiation

MLS® Laser Therapy in the treatment of patients affected by Tendinopathies

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ABSTRACT

Tendon diseases are widespread in the population and constitute a high percentage of the consultations to the physician for musculoskeletal disorders. They are painful, debilitating and negatively affect patient's quality of life. Some tendons are particularly vulnerable to degenerative pathology; these include the Achilles, elements of the rotator cuff, patella, foot extensors and tibialis posterior tendons.

Although tendinopathies are common, their treatment is not easy and often combined therapies are needed to alleviate symptoms, promote functional recovery and prevent recurrence. Among the resources available for treating tendinopathies, laser therapy showed to be effective in reducing pain and disability in some types of tendinopathy. This study aimed to evaluate the efficacy of a high power, dual wavelength NIR laser source in the treatment of patients affected by tendinopathies. Seventeen patients with symptomatic tendinopathies were enrolled for this study and divided into subgroups, based on anatomical district and anatomical structures affected by the disease. Patients were evaluated by Visual-Analogue Scale (VAS) before and after laser treatment, that was administered 3 times / week, for a total of ≈ 8 session/patient. At the end of the treatment, each subgroup showed an improvement in pain symptoms; considering all the patients, a 56,9% reduction in the mean VAS score was observed after laser treatment. In conclusion, our results suggest that MLS® therapy can be effectively applied for pain control and function improvement in patients affected by tendinopathies.

INTRODUCTION

Tendinopathies are common diseases with an incidence of about 30% of all physician examinations for musculoskeletal disorders [1]. Such conditions have an adverse impact on patient's quality of life, because of pain, stiffness and limitations of movements that can result. For these reasons, tendinopathies are responsible for hundred thousands of work hours lost. In the last years, the increase in sport activities, life expectancy, and other factors such as environment, diet, systemic diseases and some drug therapies have led to a rise in the incidence of tendinopathies, which therefore, nowadays, do not affect only athletes but also the general and elder population [2,3].

Although tendinopathies may involve tendons of any joint, the most affected are those of wrist and hand (for example, finger flexor tenosynovitis), elbow (epicondylitis, or tennis elbow), shoulder (cuff rotator tendinopathy), ankle (Achilles tendinopathy) and knee (patellar tendinitis and popliteal tendinitis) [4-6].

Physiologically, tendon is composed of densely arranged collagen fibers, elastin, proteoglycans, and lipids. These elements are produced by tenoblasts and tenocytes, elongated fibroblasts and fibrocytes, located among the collagen fibers, that represent about 90-95% of the cellular elements in the tendon. The remaining 5-10% includes chondrocytes, synovial cells, endothelial cells and smooth muscle cells. Tendon is sheathed by the epitenon, a particular connective tissue which contains the tendon neurovascular supply and facilitates the gliding of collagen bundles against one another during tendon movement. Muscular force is transmitted to the skeleton at the point where the tendon inserts into the bone. The osteotendinous junctions, as well as the musculotendinous junctions, are the areas most susceptible to mechanical stress and consequently to tendon injury [7,8].

Mechanical etiopathogenesis is, in fact, the most common cause of tendon pathologies; in particular, insertional tendinopathies, tenosynovitis, peritendinitis and tendinosis, also associated among them. These diseases may arise from an edematous injury to the microvasculature, following an acute trauma or, even more frequently, to repeated microtraumas of exogenous origin (exercise machines, footwear...) and /or endogenous (congenital abnormalities, primary or secondary skeletal disorders, functional overuse, leg length discrepancy, muscle tension).

Tendinopathies classification remains difficult and encompasses a variety of histopathologic entities. A possible classification is: (I) acute tendinitis alone: tendon injury with inflammation; (II) chronic tendinosis alone: tendon injury with degeneration at cellular level and no inflammation; (III) chronic tendinosis with acute tendinitis [9] Although cases of tendinopathies with true inflammatory component exist, often many patients have symptoms for a long time and wait for a long time before contacting the family doctor, so that, acute inflammation has probably subsided and it has been replaced by degeneration of collagen fiber structure. Histologic descriptions of tendinopathies have demonstrated disordered collagen arrangement together with non-collagenous matrix increase, cellular alterations and neo-angiogenesis [10]. This process seems to be one of the causes of pain symptoms: in Achilles tendinopathies, the presence of sensory nerves associated with new formed vessels could be responsible of the production of nociceptive and proinflammatory substances [11].

Since it is unclear if these chronic degenerative changes are preceded by an acute inflammatory response, the term tendinosis is more appropriate to describe these clinical aspects in absence of evidence of acute inflammation [12].

Conservative or physical therapies are generally accepted as the first line approach for managing tendinopathies with the purpose of alleviating symptoms, promoting functional recovery and prevent their recurrence [13-16]. These therapies can be used alone or combined with pharmacological agents. In the last few years, for example, the use of oral supplements has been proposed to support the physiological turnover of tendon tissue, in order to prevent inflammation and degeneration [17-20]. Surgical approaches are usually reserved for the most hostile cases, with conservative therapies failure for at least 6 months [21,22]. Physical therapies include eccentric exercises, electrotherapeutic modalities, such as Extracorporeal Shock Wave Therapy, soft tissue therapies, splints and orthosis. Among the resources available for treating tendinopathies within the field of physical therapy, laser therapy showed positive effects. In some in vivo studies on the efficacy of laser therapy in the treatment of Achilles tendinopathies, the following results have been reported: modulation of inflammatory response following trauma, analgesic effect, antioxidant effect, stimulation of healing process by increasing collagen I production and tenocyte proliferation [23]. However, relatively few controlled clinical studies on laser therapy applied to the management of tendinopathies have been reported and, sometimes, showing controversial results and methodological flaws.

The present study aimed to evaluate the effectiveness of a high power, dual wavelength NIR laser source in the treatment of patients affected by tendinopathies.

MATERIALS AND METHODS

Patients

Seventeen adult patients, 13 M and 4 F, mean age 47 yrs (range 15-80 yrs), were treated on an outpatient basis, with an average of 8 sessions/patient. The patients suffered from acute or chronic tendon diseases in the following anatomical districts: knee (5 patients: 3 Pes Anserine Tendinopathy -Gracilis, Sartorius and Semitendinosus tendons - and 2 patellar tendon), shoulder (4 patients: 2 acromioclavicular joint, 1 supraspinatus tendon and 1 long head of biceps tendon), ankle (3 patients: Achilles tendon) and foot (5 patients: 4 foot extensor tendon and 1 tibialis posterior tendon) see Fig. 1.

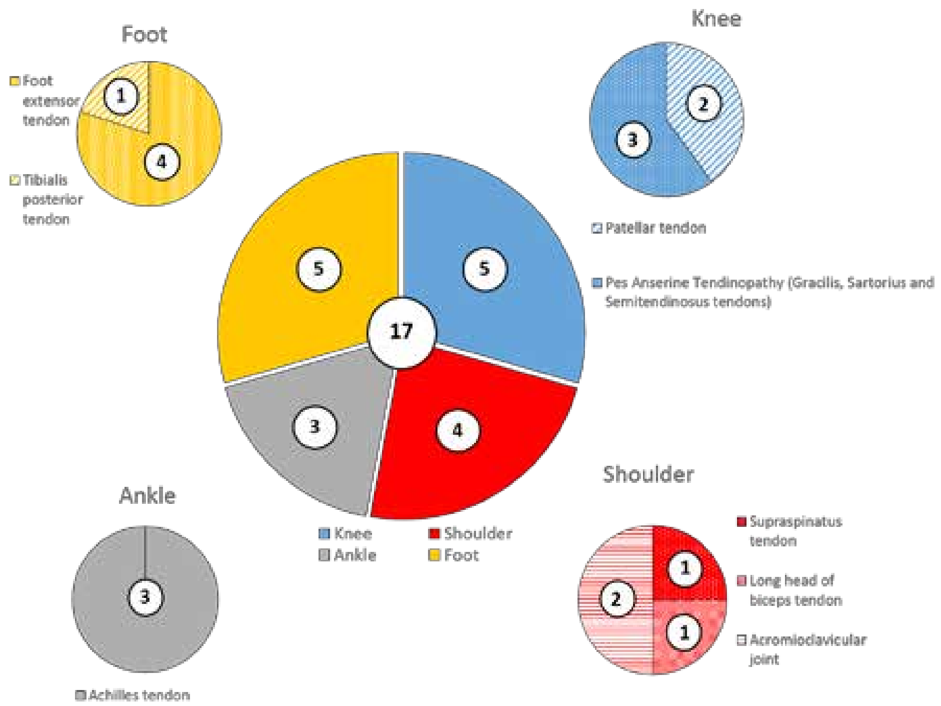


Fig 1: Distribution of tendon diseases according to the anatomical district (Big pie chart). Small pie charts show, within each district, the specific tendons involved.

Inclusion criteria required the presence of symptomatic tendinopathies assessed following clinical and instrumental evaluation. Exclusion criteria were: therapy with oral anticoagulants, non-compliant patients (cognitive impairment or psychiatric disorder), neoplastic pathology, skin diseases. Before treatment, all the patients were informed about the technique and laser beam properties, and they signed an informed consent to the treatment. The evaluation of each patient was performed by means of pain VAS scale [24]. The VAS is a visual analog test which evaluates the subjective painful symptomatology; the score ranges from 0 (lack of pain) to 10 (strogest imaginable pain). It was administered to the patients before and at the end of the whole treatment. The patients were treated 3 times / week, for a total of ≈ 8 session/patient.

Laser treatments

The laser source was a Multiwave Locked System laser (MLS®, ASA Srl, Vicenza, Italy). It is a commercially available laser source built in compliance with EC/EU rules, which received FDA approval and is widely used in clinics. MLS® laser is a class IV NIR laser with two synchronized sources (laser diodes). These emit at different wavelengths, peak power and emission mode. The first one is a pulsed 905 nm laser diode with 25 W peak optical power. The pulse frequency may be varied in the range 1-2000 Hz, thus varying the average power delivered to the tissue. The second laser diode (808 nm) may operate in continuous (power 1.1 W) or pulsed mode (repetition rate 1-2000 Hz, 550mW mean optical power, with a 50% duty ratio independently of the repetition rate). The two laser beams are emitted synchronously and the propagation axes are coincident.

Treatment modality

The patients received the following energy dose:
Knee: 5,27 J/cm^2
Shoulder: 5,63 J/cm^2
Ankle: 14,69 J/cm^2
Foot: 14,69 J/cm^2

Data Analysis

The data were analyzed using paired Student's t-test to compare the values found pre and post treatment in all the patients and into each subgroup. The level of significance was set at 0.05.

RESULTS

Seventeen patients affected by tendinopathies were enrolled in the study; one of them (patient affected by tibialis posterior tendinitis) underwent only the first session and decided to interrupt the treatment, therefore the related values were excluded. Patients consisted of 13 males and 4 females; mean age was 47,6 (15-80) (Table I). At the end of the treatment patients showed improvement in pain symptoms: mean value changed from 6,58 ± 2 to 3 ± 2,4, with a 56,9% reduction in the VAS score after treatment (Fig.2). In order to analyze the data in more detail, the patients were divided, as described in "Material and Methods" section, into subgroups based on anatomical district and anatomical structures affected by the disease (Table II). For each group, VAS score differences were evaluated. The score of patients affected by knee tendinopathies highlighted a statistically significant improvement ($p < 0,005$) at the end of the treatment compared to basal score; the mean value decreased from 6,8 ± 1,4 to 3 ± 2,2. Although in the other anatomical districts considered the mean changes in VAS score did not result statistically significant, however there was an improvement in pain symptoms and a corresponding decrease in the average VAS score. In particular, in patients affected by shoulder, ankle and foot tendinopathies the average score changed from 7,25 ± 1,5 to 3,5 ± 2,64; from 5,3 ± 2,5 to 2 ± 2,6 and from 7 ± 2,94 to 2,75 ± 3,2, respectively (Fig.3 and Table III).
In percentage, after treatment VAS score was reduced by 55% in the subgroup of patients affected by knee tendinopathies and by 51% in the subgroup of patients affected by shoulder tendinopathies. Higher percentages were found in the subgroups of patients affected by ankle and foot tendinopathies, where VAS

Table I - Group baseline characteristics

PATs. NUMBER	MEAN AGE	SEX	VAS Before treatment (mean)
17	47,6 (15-80)	13 M, 4 F	6,58 ± 2

Table II - Subgroups baseline characteristics

ANATOMICAL DISTRICT	PATs. NUMBER	MEAN AGE	SEX	VAS Before treatment (mean)
KNEE	5	44,2	4 M, 1 F	6,8 ± 1,48
SHOULDER	4	53,25	4 M	7,25 ± 1,5
ANKLE	3	71,5	2 M, 1 F	7± 2,94
FOOT	5	37	3 M, 2 F	6,58 ± 2

Table III - Mean VAS Score for patients divided into subgroups before and after treatment application.

ANATOMICAL DISTRICT	VAS Before Treatment	VAS After Treatment
KNEE	6,8 ± 1,48	3 ± 2,2
SHOULDER	7,25 ± 1,5	3,5 ± 2,6
ANKLE	7 ± 2,94	2± 2,64
FOOT	6,58 ± 2	2,75 ± 3,2

Fig 2: Mean VAS Score for all patients before and after treatment application.

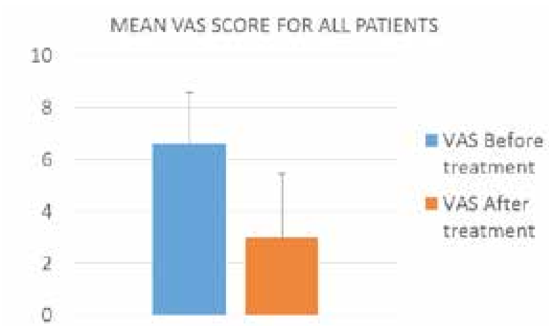
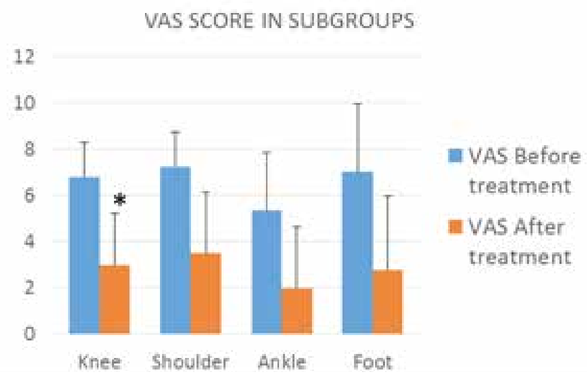


Fig 3: Mean VAS Score for patients divided into subgroups before and after treatment application.



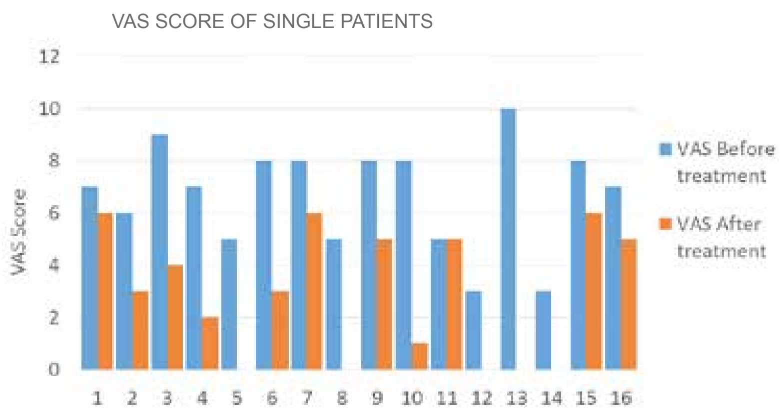


Fig 4:
VAS Score of single patients before and after treatment application.

scores decreased by 62% and 60%, respectively. No patients reported adverse events.

DISCUSSION

The results obtained in this study show that the treatment with a high power, dual wavelength NIR laser source is effective in inducing inhibition of pain referred by patients affected by tendinopathies. Since predisposing factors to pain and following rate of response to treatment are different depending on anatomical area, patients were divided into subgroups and results were evaluated considering the subgroup and the scores of each patient individually. The subgroup of patients affected by knee tendinopathies was the only subgroup where a significant change ($p < 0{,}005$) of VAS score was reported at the end of the treatment, compared to the basal score (from 6,8 ± 1,4 to 3 ± 2,2). It is important to point out that a patient of this subgroup (see fig. 4, patient 1) was affected by congenital joint laxity; therefore, at the end of the treatment, its score decreased only from 7 to 6 points of the VAS scale (Fig.4). Excluding the values of this patient, in the knee subgroup VAS score decreased from 6,75 ± 1,7 to 2,25 ± 1,7.

A positive result in terms of pain reduction, even though not statistically significant, was obtained also in the subgroup of patients affected by shoulder tendinopathies, where the mean VAS score decreased from 7,25 ± 1,5 to 3,5 ± 2,64. In this subgroup, the lack of statistical significance can be attributed to the small sample size and to a single patient poorly responsive to the treatment (see fig. 4, patient 7, VAS score from 8 to 6). During the treatment, this patient did not follow the doctor's advice and continued sport activity. This behavior partially nullified the effect of therapy and delayed the improvement of symptoms. (Fig.4).

Also in the subgroup of patients affected by ankle tendinopathies, the statistical significance was jeopardized by the small sample size and strongly affected by a single patient who did not report any improvement after the treatment (see fig. 4, patient 11). On the contrary, the other patients of this group had a strong improvement (5,5 ± 3,5 to 0,5 ± 0,7).

In the last subgroup, foot tendinopathies, one patient (affected by tibialis posterior tendinitis) did not finish the treatment, as mentioned above. Although variation was not significant, VAS score decreased from 7 ± 2,94 to 2,75 ± 3,2. In this subgroup half of the patients had excellent results (0 VAS score at the end of treatment) but the other half presented clinical complications (Fig.4). Indeed, a patient was affected by Sudeck's disease, an inflammatory disease of connective tissue that usually occurs after an injury in the arm, hand, shoulder, foot or leg and is characterized by the recurrence of pain, swelling, mobility disorders, skin changes, differences in temperature at the location of the wound after healing. The other patient had a not completely resorbed hematoma that obliged him to additional care (therapeutic massage). In conclusion, about the 70% patients had concrete improvements of symptoms after laser therapy, the 50% had very good results and almost the 30% of patients had excellent results. The patients who had no improvement (only 1) or only a slight improvement showed clinical complications or additional diseases associated with tendon diseases. These conditions would probably have required a therapeutic plan with a higher number of sessions to obtain the positive effects observed in other patients.

Despite the different problems of the patients enrolled and the small sample size, the findings here presented are in agreement with those obtained by other authors in literature, who reported that NIR laser treatment induced significant improvement in pain symptoms, range of motion and function. Tumilty et al. [23] reported that laser therapy promoted reduction of inflammation in the lateral epicondyle of the elbow: measurement of grip strength, a diagnostic tool in the assessment of patients with lateral epicondylitis, was significantly improved in treated patients compared to control group (WMD, weighted mean difference, 9.59 Kg). The same author demonstrated that NIR laser radiation (810 nm), used in combination with the application of an eccentric exercise program, led to clinical improvement in the patients affected by Achilles tendinopathy [25]. In a study of Stasinopoulos et al. [26], positive results induced by a 904 nm laser radiation in the treatment of tendinopathy were also observed in combination with an exercise program, highlighting the importance of combining different therapeutic tools.

Nevertheless, in literature are present several studies where no improvement of the symptoms was reported. Different methodologies and laser parameters, heterogeneity in terms of populations studied, physiotherapy intervention employed and, often, small sample size led to discrepancies among the results reported. Therefore, it is evident that further research is needed to obtain more accurate quantitative data and to establish a homogenous methodology for the use of laser therapy in the treatment of tendinopathies.

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Key words: CAPD, Event Related Potentials, Laser, attention problems, respiratory chain, ATP, Wire and Fire, Learning disabilities, conduct disorder

Hypothesis for a future application of a Laser-device in patients with symptoms of a developmental auditory processing disorder

Part I: Methodological basics

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ABSTRACT
This article provides a conceptualisation of research studies which should evaluate whether changes of electrophysiological late event related potential pattern (latency, amplitudes) could be used to reflect clinical changes from therapeutic intervention with LASER light in patients with symptoms of central auditory processing disorder. The contingent negative variation (CNV) of event related potentials reflects a synchronization of together firing wired neural assemblies responsible for auditory processing, suggesting an accelerated neuromaturation process when applying a LASER device stimulation. It will be discussed whether a LASER stimulation might be useful for a clinical improvement of distraction symptoms caused by auditory processing deficits. A model is presented explaining these effects by inducing the respiratory chain of the mitochondria.

INTRODUCTION
It is well accepted that an acoustical environment (noise and reverberation) in classroom conditions is a critical factor in the educational achievement of many children. Such populations being at risk for academic failure encompass children with language impairment, dyslexia, attentional deficits and general developmental delay [1]. An increasing number of children appear to have hearing impairment in spite of normal auditory thresholds. Parents and teachers describe difficulties in listening in the presence of background noises and difficulties in understanding rapid or degraded speech. In these cases, listening problems result from dysfunctions of auditory processing inside the brain and will be considered as central auditory processing disorder (CAPD) [3, 4, 5, 6]. It is reasonable to assume, that poor neural acoustic representation will lead to serious problems in the maturation of the auditory pathways and hence the development of auditory process ability. Recent research results suggest that neuroplasticity and neuromaturation are dependent on stimulation [1, 3, 7]. Therefore, comprehensive management of CAPD should include auditory stimulation to achieve functional changes within the central auditory nervous system. Thus, young children would be expected to benefit from a great degree of neuroplasticity. Stages of neuromaturation are i) neurostimulation, ii) neuromodulation iii) neurorelaxation and iv) neurodifferentiation [7, 8]. This article refers mainly to the neurostimulation part: if a relevant circuit is turned on, it fires and the blood flows to this circuit. The brain scan (functional Magnetic Resonance Tomography (MRT)) is running like this. Neurostimulation is effective in preparing the brain to build new circuits (internal neuroplastic stimulation). Energy based stimulation (light, sound, electricity, vibration, movement, substance) may help to revitalize dormant circuits to achieve homeostasis from external and internal sources. The purpose of this article is to introduce a conceptualization of studies for auditory-perception improvements of children with symptoms of an auditory processing disorder when applying laser light. A model will be presented to explain possible results using electron modelling and proton exchange inside the respiratory chain.

(RE)-WIRING A BRAIN WITH LASER LIGHT
Already Francis Crick speculated the challenge to find a way to turn on certain

neurons, while leaving others unaffected [9]. Light might be used to turn on specific clusters (classes) of neurons, thus wiring these neurons not by substance-based (chemical) signals rather than by physical signals. Energy from light use light sensitized molecules thus transforming light into energy [10, 11]. Thus, different wavelengths of the light spectrum may have different effects on the organism. Wilden et al. [12] already reported, that LASER stimulation with distinct wavelength may vitalize the cell by increasing the mitochondrial ATP (adenosine-tri-phosphate)-production. With regard to radiation phenomena and its enhanced electron flow in the cellular energy transfer (respiratory chain), these authors postulated already that the experimentally found increase of ATP-production could be explained by means of low-level laser light on a cellular level. These investigation are mainly based on patients with tinnitus and sudden hearing loss, while developmental hearing problems are not considered.
Studies of brain development show that sensory stimulation in the case of the visual centres of the brain is critically important, and influences the actual organization of visual brain pathways. Increase in visual stimulation may result in morphological alterations within the visual parts of the brain [13, 14]. Strategies for management of auditory processing disorder are usually direct remediation, environmental modifications and compensatory strategies. One of a possible new strategy for reducing the deleterious effects of auditory noise is the use of Laser light, providing discrete wavelengths (frequencies) to improve auditory clarity and avoidance of ear pressure, tinnitus and background noise. The purpose of direct stimulation of auditory processing on the level of neurostimulation is to maximize neural plasticity and possibly accelerate maturation, improving auditory performance.
Studies of brain development show that sensory stimulation of the auditory centres of the brain is critically important, and influences the actual organization of auditory brain pathways [1, 15]. Increase in auditory stimulation may result in morphological alterations within the auditory parts of the brain [3]. The ability of the auditory cortex to reorganize continuously throughout life span reflects the ability to acquire new skills and behaviours. Long-term potentiation is related to increases in the synaptic activity and efficacy following strong and repeated stimulation of a sensory system. There have been reports of morphological and structural alterations within nerve cells including increase in size and postsynaptic density along with alterations in late event potentials [3, 4, 16].
Usually cells wire and fire together i.e. in rhythm. Neurons work usually in large groups of neuronal assemblies, communicating electrically through distributed networks throughout the brain [7, 8]. If the neurons are not synchronized, they cannot generate enough strong, sharp signals to stand out against the background noise of all the other neuronal signals inside the brain. Neurons do not necessarily fall silent, but they continue to fire at a slower rate. Therefore, these cells mess up the function of the "normal" cells. This occurs in epilepsy, Alzheimer disease, brain injuries and learning problems because cells are out of synchronization, even if the neurons are far away from the "sick" neurons. Light might be used to turn on specific clusters (classes) of neurons. Light frequencies carry energy and provide different types of information. In this context, it could be already shown that distinct frequencies from a low level laser stimulate mitochondrial respiratory chain complexes by turning on and off processes inside the cell [17]. Single cells without eyes have light sensitive molecules on their outer membranes that supply them with energy. Halobacterium for example reacts differently on wavelengths (frequencies) [18]. Energy from light use light sensitized molecules transforming light into energy. Thus, different wavelengths of the light spectrum have different effects on the organism. Szent-Györgyi [19, 20] discovered, that when an electron is transferred from one molecule to another within our bodies, the molecules can change their colour, i.e. they change the type of light they emit. Where does the energy come from and what are the energy analogues?

MODEL OF EXPLANATION USING ELECTRON MODELLING AND PROTON EXCHANGE INSIDE THE RESPIRATORY CHAIN.
The model of the cellular photobiological chain reaction caused by visible light to near-IR radiation of specific wavelengths (frequencies) reported by T.J. Karu [21-25] is used. Karu´s model is based on the analogy between the effects of photosynthesis and respiratory chain [26, 27]. While photosynthesis is an anabolic process producing glucose from light energy, H_2O and CO_2, the respiratory chain inside the mitochondria is a catabolic reaction from glucose gaining energy. Use of comparable redox equivalents in different compartments (NADP vs. NAD, FAD vs. FD) makes it attractive to support the "Karu idea".
While photosynthesis is transforming light energy by using chlorophyll as photoreceptor to gain the energy equivalent ATP, the respiratory chain does not really need light for running to gain the energy equivalent ATP. Both processes (photosynthesis, respiratory chain) are running the ATP synthesis by using high proton gradients to build up ATP from ADP and phosphate. This process is called "oxidative phosphorylation". Both processes are similar in terms of function of the ATP synthase. [27].
The respiratory chain process is running "substance-based" in healthy cells without light support. In the case of sick cells, it may be speculated that the energy production is reduced and can be recovered and supported by photooxidation process stimulation apart from substance substitution [26]. This means, there is a light induced transfer of an electron by a physical process instead of a chemical oxidation from a donating to an

accepting molecule, which will be reduced. Absorption of photons by light-absorbing molecules enhance electron transport chain function [17, 21, 28-30]. The energy from the absorbed photon will be transferred to redox centres of the respiratory chain, achieving an increase in ATP synthesis [21, 26]. The light induced increase of ATP synthesis and the construction of a photon gradient lead to an increased activity of the Na^{+}/K^{+} and Ca^{+}/K^{+} Antiporter and other ATP driven ion carriers like the NA^{+}/K^{+} ATPase and the Calcium ATPase. ATP controls the cAMP level, both Ca^{2+} and cAMP stimulate DNA and RNA synthesis which leads to an increased cell repair mechanism [26].

It has been already demonstrated by Karu and others that the so called "antenna pigments", the flavoproteins and the cytochrome a/a3 of the cytochrome oxidase complex can be considered as sensitive light receptors on the cell membrane [22, 31, 32, 33]. Further investigations demonstrated that there is a variety of additional light absorbing molecules (chromophores) capable of absorbing photons at the membrane and mitochondria level [22, 34]. Altogether, specific wavelengths (multiwavelenght sources, NIR wavelength source, low power and high power laser etc.) may induce the respiratory chain of sick neurons thus leading to a modulation of mitochondrial regulation contributing to a molecular and cellular ATP driven repair mechanisms [17, 25, 35]. Monici et al. showed that laser treatment leads to a cytoskeletal rearrangement and expression of early differentiation markers [36] leading to an up-regulation and/or modulation at the protein level (cytoskeleton organization). Further on it may be speculated that epigenetically DNA synthesis can be increased by using distinct wavelengths of the light and NIR spectrum.

EVENT RELATED AUDITORY CORTICAL POTENTIALS (AERP)

Only a few studies have been found in literature having focused on the use of CNV and P300 potential in documenting changes in clinical status.

Recording of the Contingent negative variation (CNV) requires the patient to pay active attention to a stimulus. AERP´s are presumed to be related to attention, recognition, and memory processes. Event related cortical potentials allow the evaluation of brain activities. The contingent negative variation (CNV) is a slow negative potential decrease, which will appear hundreds of ms before target stimulation. CNV is representing a large number of increasing synchronous self-regulatory excitatory activity of neuron populations and is preparing the brain for the following auditory stimulus. In this sense CNV is related to the synchronous firing of wired neurons in order to provide the ability of reaction capacity of a certain brain task.

Other studies emphasized the feasibility of using P300 event related potentials to document levels of auditory dysfunction [37, 38]. There are several studies suggesting that P300 auditory event related potentials in children with CAPD showed longer latency times and smaller amplitudes compared to controls [4, 16, 39]. Jirsa [40] demonstrated a significant decrease in P300 latency time along with an increase in P300 amplitude in the evoked potentials obtained from children with CAPD following an intensive therapeutic 14-week intervention program. The children in the experimental group exhibited improvement on selected auditory tasks and positive changes in overall academic performance. These data were interpreted as indicating that neuroauditory maturation could be influenced by a specific intervention and could be distinctly objectified by means of late event related potential measures. It seems reasonable to assume that changes in the morphology of the waveform correlates with changes of the clinical status. Because maturation processes in highly plastic brains in childhood should be enhanced through sensory stimulation, expectation of improvement of auditory processing abilities must be confirmed by follow up investigation.

CONSEQUENCES

The organic living brain is quite the opposite of an engineered machine with hardwired circuits that can only perform a limited number of actions, but during the day the brain is forming / unforming new flexible neuronal networks. A group of neurons will be used for different purposes at different times. Tasks can be performed using different coalitions (assemblies) of neurons [41]. Learning skills are encoded in the cumulative electrical patterns resulting from the neurons firing together [41, 42]. The pattern, i.e. the population is interesting, not the individual cell. Cells that are, on whatever reason, chronically inflamed, are more sensitive to red and near-infrared light than are well-functioning cells. To heal, the body often needs to create new cells.

Because auditory neuromaturation and neural plasticity depend on distinctive stimulation of auditory neurons, dynamic management of CAPD should begin as early as possible. Studies have to address the question whether use of AERP´s may be more sensitive for prediction of treatment outcomes as it has been already suggested by Walsleben et al. in the case of auditory processing (44). Studies on AERP measures performed before and after specific Laser light stimulation are in progress, to demonstrate possible therapeutic advantages of such a device and will be presented in Part II of this article. Furthermore, we need more information about the distinction of the different kinds of auditory processing disorders and clear cut-off definitions in the electrophysiological data. Our descriptions of performance disorders range from ADHD, visual and auditory processing disorders related to all-inclusive learning disabilities, minimal brain damage or minimal cerebral disorder in kindergarten and school age children. Up to now there is still a great lack of consensus on precise definitions of what a processing disorder encompasses. It is not yet clear how to differentiate a CAPD from other processing disorders [45]. Future research has to address these questions to enhance specificity of the clinical intervention tools and/or programs on auditory neuromaturation. Additionally, it can improve our knowledge of the development of auditory function in children. Intrahemispheric and interhemispheric functional measurements may also give a more precise view into these questions [46, 47]. Part II of this article will describe the experience with an infrared application in patients with auditory processing disorder evaluated by event related potentials using Multiwave looked system (MLS®) laser device (ASA S.r.l.) with wavelengths 808 and 905 nm.

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CONFLICTS OF INTEREST

The author declares that he discloses any financial and personal relationships with other people or organisations that could inappropriately influence (bias) this work.

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Key words: Dog Degenerative Joint Disease, Vet physical therapy, pet pain control, LOAD questionnaire, CBPI questionnaire, animal rehabilitation, laser therapy, carprofen, NSAIDs

Management of the articular degenerative disease of the dog: comparison of physical and pharmacological therapies

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ABSTRACT

Degenerative Joint Disease (DJD) is one of the most common and disabling orthopaedic conditions of pets. The most recent therapeutic approach consists in the combination of different therapeutic options, such as the use of conventional drugs, the use of alternative treatments (i.e. homeopathy, phytotherapy, acupuncture), the oral administration of chondroprotectors (i.e. nutraceuticals), body weight control, rehabilitation and correct home management.

This study compared the efficacy on arthritic pain control of a physical therapy protocol, including MLS® treatment and hydrotherapy, versus traditional nonsteroidal anti-inflammatory drug (NSAID) therapy.

Sixteen Labrador dogs, older than 5 years and affected by osteoarthritis have been included in the study.

After the baseline visit, the animals matching inclusion criteria have been allocated to one of the treatment groups. The treatment efficacy has been assessed at 15 and 45 days via pet owner's evaluation, using the Liverpool Osteoarthritis in Dogs (LOAD) and the Canine Brief Pain Inventory (CBPI), and by the clinical assessment of a technical expert.

In both groups, a general improvement in symptoms has been observed, confirming that both physical therapy with MLS® and drug therapy are valuable aids in the management of pain symptoms associated with degenerative joint disease.

In particular, for the treatment of ostearthrosis, when long term treatments are necessary, MLS® laser therapy is a valid alternative to pharmacological therapy, allowing for treating old dogs without worsening the condition of other compromised organs.

INTRODUCTION

Degenerative Joint Disease (DJD) is a major condition affecting especially old and/or obese dogs, those subjects presenting genetic bone abnormalities or bone conditions and active dogs that are prone to repeated microtrauma due to intense physical activity [1].

Secondary DJD caused by trauma, articular instability or osteochondral lesion is the most common [2].

DJD has a severe impact on quality of life, due to associated pain and biofunctional limitations. Pain is the main clinical symptom of OA, therefore pain management is of outmost importance in osteoarthritis (OA) treatment, allowing improvement in both physical and psychological quality of life of the subject. Currently, there is no resolutive treatment for OA and several approaches have been investigated to address pain, inflammation and progressive degeneration, which are different aspects of the disease, leading to the so-called multimodal approach [3]. This recent approach consists in the combination of different therapeutic options, combining the use of drugs with less conventional treatments, such as homeopathy, phytotherapy and acupuncture; the oral administration of chondroprotectors, i.e. nutraceuticals; dog weight control; rehabilitation and correct home management by the pet owner. The pharmacological treatment of the DJD involves the use of NSAIDs, chondroprotective drugs and other complementary medications. This study investigates the possibility of alternative therapies that may be more suitable, especially for older dogs with unpaired general health for which drug therapy may not be appropriate. Among the different physical therapy options that were taken into account, Multiwave Locked System(MLS®) laser therapy was considered the most suitable for dog DJD treatment. MLS® therapy involves the use of two different and synchronised emissions: one with continuous/frequenced mode at 808 nm wavelength, the other with pulsed mode at 905 nm. The average power of the device is 1.1 W with a peak power of pulsed emission of 25 W. MLS® has been clinically applied for the treatment of several pathologies, including shoulder pain, lumbago, carpal tunnel syndrome, etc. MLS® pulse has been extensively characterized and its effects are well documented [4-6]. In this study a protocol that used MLS® associated with hydrotherapy treatment, was compared with the traditional pharmacological approach in dog DJD. The aim of the study was the assessment of both approaches efficacy in OA treatment, based on dog owner's feedback and the clinical examination results, and the comparison of the results of the two treatments.

MATERIALS AND METHODS

During the reference period, 25 Labrador dogs were assessed, 16 of which met the study inclusion criteria and have been enrolled. The inclusion criteria were collaborative dogs of age > 5 years with a diagnosis of OA in the elbow, hip or knee, confirmed by X-ray. Animals presenting concomitant pathologies, reduced cognitive abilities or adverse reactions to NSAIDs were excluded from the study.

A series of critical aspects, such as scattered clinical conditions, breed specific characteristics, nutritional status, pain multifactor components, pet owner time availability and economical possibilities, should be considered as they may heavily impact on treatment outcome [11]. Labrador dogs have been selected as study subjects to limit breed variability. This specific breed was chosen as it is a diffuse breed with predisposition for joint pathologies, frequently affected by OA. Additionally, Labrador dogs are generally collaborative, which simplifies the physical therapy treatment, and express pain sensation without excessive misrepresentation, as it happens for example with other breeds. The selection of strict inclusion criteria represented a limitation in terms of number of eligible subjects, but it was needed to reduce the risk of confounding factors. The study took place at the rehabilitation centre Thermal Physiopet (Montegrotto Terme, IT), from September 2015 to March 2016. Dogs were allocated to two groups, respectively group A and B, groups were homogenous for age and weight. Group A underwent to physical therapy sessions including MLS® treatment and hydrotherapy. Animals that received medications from the owner were excluded from this group. Hydrotherapy has been performed in specific pools equipped with treadmills, walking speed was set at 32m/min for 3 minutes and water level was set at the superior third part of the dog femur. The exercise was repeated 4 times with 3 minute breaks in between repetition. Animals were observed during the exercise and after the hydrotherapy session: in case of fatigue, the protocol was adjusted accordingly. After the session, the animal was clinically assessed and the laser treatment was performed.

In this study, the following treatment parameters have been applied:

- Animals with pain at palpation > 4: muscle scan phase with 18 Hz frequency and fluence of 4,81 J/cm²
- Animals with pain at palpation < 4: muscle scan phase with 36 Hz frequency and fluence of 4,81 J/cm²
- Animals with flexion-extension pain > 4: the treatment had been carried out on points, covering the whole articular surface with 18 Hz frequency and fluence 3,99 J/cm² for a total of 12,52 J/point
- Animals with flexion-extension pain < 4: the treatment had been carried out on points, covering the whole articular surface with 36 Hz frequency and fluence 3,99 J/cm² for a total of 12,52 J/point.

In general, 100% intensity has been used. It has been reduced to 75%. for animals with dark fur,

- Each trigger point had been treated from one to four times with the following parameters:10 Hz with 25% intensity and fluency 1 J/cm².

The physical therapy protocol was repeated three times a week for the first two weeks, two times a week for the following two weeks and once a week up to the end of the study. Group B was treated with NSAIDs using oral administration of Carprofen (Rimadyl) with a dosage of 4mg/kg once per day (SID) for the first 7 days, followed by a dosage of 2 mg/kg SID for other 7 days. For gastroprotection, omeprazole was orally administered 20 minutes before food intake with a dosage of 0,7 mg/kg SID.

Assessment were performed at day 0 (enrolment and first treatment), 15 and 45 using:

- Pet owner's evaluation with Liverpool Osteoarthritis in Dogs (LOAD) scale and the Canine Brief Pain Inventory (CBPI) scale,
- Technical expert clinical examination, with observation of: lameness degree (score from 0- no lameness, to 4- limb is lifted and no load bearing), muscle tonicity (score from 0 – tonic limb, to 3 – severe hypotonicity), flexion-extension pain by VAS scale (evaluation based on dog behaviour reaction), pain at palpation of the main muscle groups by VAS scale, trigger point number. When more than one limb was affected, the one with the most severe condition was scored. All the visits have been performed by the same operator, blinded to the pet owner's assessment.

During the visit at day 0, dog specific counselling was provided to the owner in terms of dietary advice and physical activity protocol. Data were analysed using the Shapiro Wilk test, data presenting a normal distribution were expressed as mean ± standard deviation, while not normally distributed data or ordinal data

Management of the articular degenerative disease of the dog: comparison of physical and pharmacological therapies. Energy for Health [16]

were expressed as median (min-max). Intraobserver variation related to evaluation during time by the pet owner and the technical expert was considered.
Group A and group B were compared using the Student t-test and two-way ANOVA.
Friedman test was used to analyzed ordinal variables or not normally distributed differences between treatment, time and their interaction.
Statistical significance was set with $p<0,05$.

RESULTS

Each owner completed the LOAD and CBPI questionnaires at days 0, 15, 45. In both groups, an improvement in the animal condition was perceived by the owners, despite it did not reach statistical significance (Table I). The results obtained in group A and B in terms of owner's questionnaire were compared and show no statistical difference (Table II).
Lameness degree was assessed by the technical observer and scored 2,625 ± 0,91 at T0, 1,75 ± 1,03 at T15 and 1,75 ± 0,89 at T45 for Group A, while Group B obtained the following scores: 2,625 ± 0,92 at T0, 1,61 ± 1,19 at T15 and 1,87 ± 1,46 at T45. The degree of lameness decreased in both groups reaching statistical significance respect to baseline, while no difference was observed between the groups (Figure 1).
Flexion-extension pain by VAS scale (Figure 2) statistically improved during time in Group A from 6,37 ± 2,2 at T0 to 5,25 ± 1,89 at T15 to reach the score of 3,62 ± 0,74 at T45. Group B showed VAS value at T0 (6,87 ± 1,72), T15(5,25 ± 1,67) and T45(5,5 ± 1,77), that do not indicate significant modifications from baseline.
Pain at palpation statistically improved for both groups from T0 to T15 (Figure 3). The following scores were assigned respectively to Group A and B: 6,5 ± 1,77 at T0; 5,37 ± 2,13 at T15 and 4,62 ± 1,60 at T45 and 6,37 ± 1,59 at T0; 4,5 ± 1,85 atT15 and 5 ± 2,14 at T45.
Muscle tonicity (Figure 4) improved for Group A (from 1,75 ± 0,71 at T0 to 1,25 ± 1,03 at T15, up to 0,37 ± 0,74 at T45), while no changes were observed for Group B (scored 1,25 ± 1,03 at T0, 1,25 ± 0,99 at T15 and 1,26 ± 0,99 at T45).
Trigger point number (Figure 5) statistically decreased in Group A (5,87 ± 2,17 at T0; 3,75 ± 1,67 at T15 and 1,75 ± 1,39 at T45) while no change was detected in Group B(5,5 ± 2,72 at T0; 4,87 ± 2,64 at T15 and 5,15 ± 2,99 at T45).

DISCUSSION

Pain management in OA is a key point for pet quality of life improvement and pet owners are particularly sensitive to this topic. Recently, pain management protocols have benefited from scientific research progress and allow for a better subject treatment. The current concept in OA treatment involves the combination of pain control, which is the main clinical symptom, with strategies that specifically target the degenerative, inflammatory and oxidative processes involved in OA progression. The so-called multimodal approach is the association of pharmacological treatments, such as the use of ant-inflammatory drugs, and non-pharmacological treatments, involving the use of chondroprotective agents and nutraceuticals, diet control, physical therapy and exercise. The present study aimed at comparing the effects of two different therapeutic approaches: physical therapy versus pharmacological treatment. MLS® therapy has been selected as treatment of choice, due to its large use in the veterinary centre which conducted the study and to practical advantages respect to other physical therapies, such as the fact that laser application does not require trichotomy, a procedure which is not appreciated by dog owners. OA affected dogs generally present impaired mobility, which in turn results in loss of muscular tone. To limit this, MLS® therapy has been associated to hydrotherapy, which allows muscular work, minimizing load bearing [7 -10].
The pharmacologically treated group received Carprofen, one of the most commonly used drugs in the treatment of pain associated to chronic orthopaedic conditions. Carprofen is a COX_2 preferential inhibitor and thus allows OA inflammation and pain control with less than 1% side effects [3].
Another key point for the study was the pet owner's contribution, both in terms of home management of the dog, based on the instruction received during the inclusion visit, and in terms of his evaluation of the treatment outcome assessed using the Liverpool Osteoarthritis in Dogs (LOAD) and the Canine Brief Pain Inventory (CBPI). LOAD questionnaire is more focused on animal motility, while the CBPI questionnaire focuses on pain, therefore they appear to be complementary and were used together to assess the overall health status of the animal. A limitation in the use of these questionnaires is the subjectivity related to the owner sensitivity and his emotional relationship with his dog, that may alter the perception of the real health condition of the animal [12]. To balance these factors, a clinical examination by a trained expert had been included in the study and, in fact, in many occasions this clinical assessment did not correspond to the owner's evaluation. This can be explained by the fact that the clinical examination considered the OA grade of the dog, while the owner was likely influenced in his assessment by the knowledge of the health status of his dog before OA onset.
Another study limitation is related to the need for interpretation of the subject algic response. In relation to this, the evaluation of subjects belonging to the Group A was easier respect to the evaluation of the Group B subjects. Since the physical protocol implied longer treatments, this means that the operator spent more time and got to know more closely Group A dogs compared to Group B dogs, which have been in contact with the operator only during follow up visits. The study results show improvement in symptomatology in both groups.
This is an important achievement, and confirms that both physical and pharmacological therapies are suitable tools for OA pain management.
In our study, no significant differences have been observed between the two treatment outcomes, encouraging to consider the option of prescribing one treatment or the other based on specific animal conditions and characteristics. For instance, when there are restrictions to NSAIDs usage due to dog general health, laser therapy should be preferred as it demonstrated the same pain control and anti-inflammatory effects as drug therapy but without its side effects.
To conduct a successful physical therapy, dog and owner collaboration is essential.
An interesting point that emerged from our study is the advantage of the use of laser therapy over drug therapy for treating trigger points, as only laser allows to exert a local pain relief action.
Due to the limited sample size and follow up duration, this study represents a preliminary investigation and further studies are needed to assess the most appropriate therapeutic approach to pet OA.

CONCLUSIONS

Osteoarthritis is a degenerative condition for which long term animal treatment is required. Any clinical improvement in the pet quality of life should be considered as a relevant achievement. The best clinical approach to articular degeneration involves a multimodal and personalised management of the disease and of the related pain, combining traditional and more innovative treatments, and requires the owner to play an active role in home management.
In conclusion, the results of this study demonstrate that both physical therapy and pharmacological therapy are able to improve the general clinical conditions of OA affected dogs. Physical therapy allows to treat with no side effects even old and compromised animals and can be proposed as a valid alternative to traditional pharmacological therapy.

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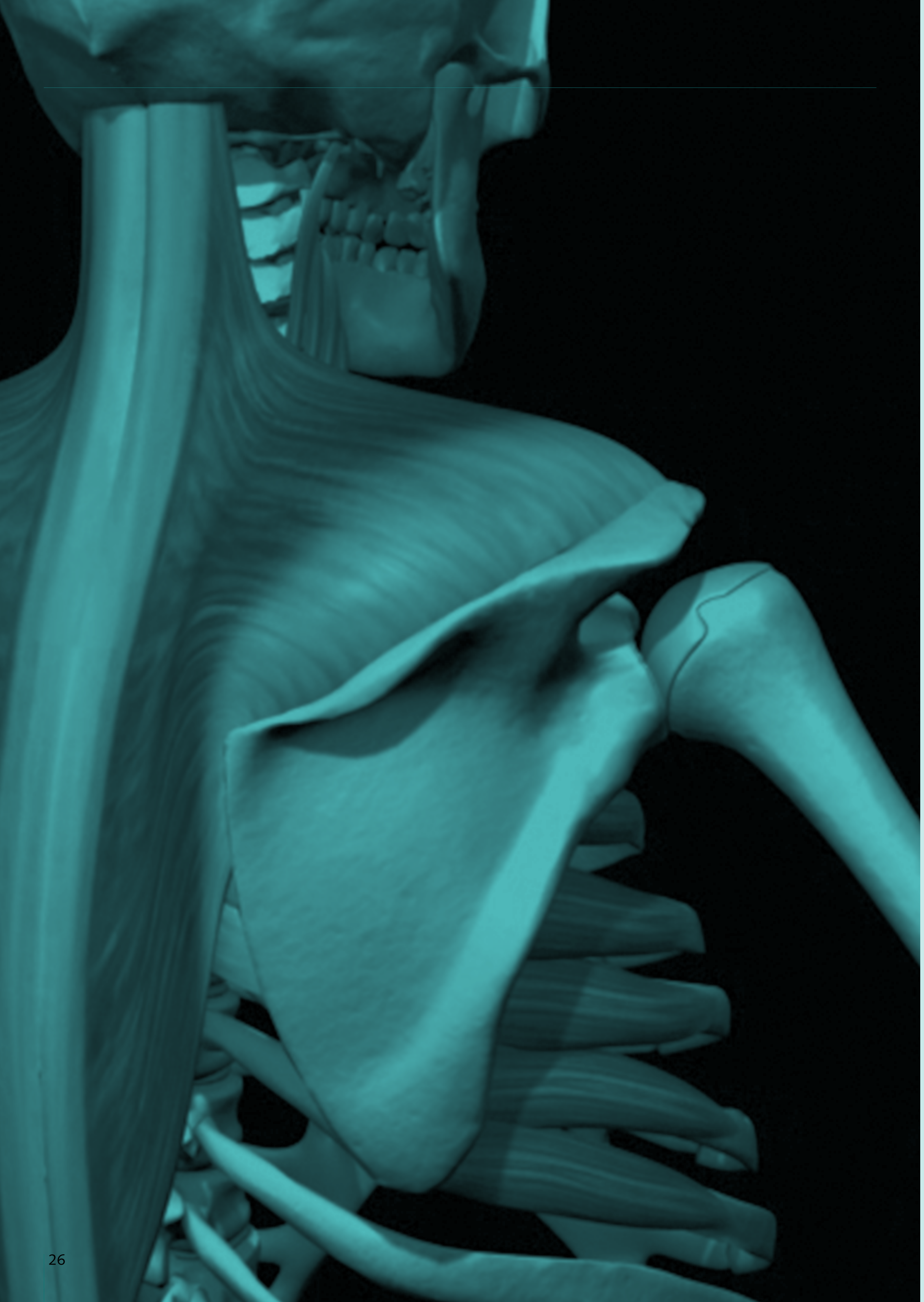

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