Key words: HILT, Nd:YAG laser, photomechanical effect, physiotherapy, laser therapy

Hilterapia®: From molecular and cellular effects to clinical studies

Tamara Viliani, Francesca Cialdai, Chiara Risaliti and Monica Monici

ASAcampus JL, ASA Res. Div., Dept. Experimental and Clinical Biomedical Sciences "Mario Serio"
University of Florence, Florence, Italy

ABSTRACT

Laser therapy has been widely used in many different fields of medicine and has proved to be effective in various pathologic conditions through its anti-inflammatory, anti-edema, and analgesic effects. Despite the richness of literature and the numerous clinical trials that prove the effectiveness of phototherapy, the molecular and cellular mechanisms underlying the therapeutic effects induced by laser emissions of different wavelengths are not completely understood. The study these molecular mechanisms is rather complex due to the different characteristics of the various tissues and body areas (in particular, the different optical properties) and the variety of parameters used in clinical trials, such as wavelength, continuous or pulsed mode, frequency, time of exposure. The aim of this review is to focus on the Nd:YAG laser source used for Hiltherapy and to analyze different studies, both preclinical research and clinical applications, in order to help understand the mechanisms of action of this laser source and the therapeutic effects when it is applied in clinics.

INTRODUCTION

In the course of history, different civilizations have learned that light can have a strong effect on cells and tissues. Starting from Romans, Greeks, and Egyptians, ancient people often used exposure to sun with the aim to obtain positive therapeutical effects. During the 19th century, red light was used to prevent scarring in patients affected by smallpox [1]. Throughout the 20th century, many advances were made with a rapid evolution from arc lamps to modern lasers, which allow us to use high-intensity (when needed), focalized, monochromatic radiation, or to use multiple wavelengths. Since the 70s lasers have been used both in surgery, for tissue ablation, and in many other medical fields, such as physiotherapy, sports medicine, rehabilitation medicine, etc., thanks to the development of laser systems with improved emission modalities.

The effect of laser radiation on biological tissues depends on various parameters, such as wavelength, power, frequency, emission regime (continue or pulsed), exposure time, and, last but not least, tissue optical properties. Proper choice of the treatment parameters allows physicians to control photochemical, photothermal, and photomechanical effects produced by laser irradiation to achieve therapeutic efficacy avoiding or minimizing side effects.

When radiation hits the surface of a biological tissue, about the 3% of it is reflected, due to the change in the refractive index between air and tissue. The remaining radiation propagates within the tissue, where it is partly adsorbed and partly scattered. The absorption of light energy is essential for an effect to occur at cell and tissue level. Light is absorbed by chromophores. They are molecules belonging to the tissues and responsible for tissue properties (e.g. coloring), vary from tissue to tissue, and determine the response of the tissue to the radiation of a given wavelength.

Generally speaking, laser radiation can induce three different kinds of effects in biological tissues: photochemical, photothermal, and photomechanical effects [2]. The photochemical effects occur when the light energy absorbed by a molecule (chromophore) is used for a structural or conformational rearrangement of the molecule, or for a chemical reaction. The photothermal effect takes place when the energy associated with the photons is converted into heat. At tissue level, the results of photothermal interactions depend on the interaction time and the thermal relaxation time of the tissue [3]. The photothermal interactions have been studied under different points of view, since they are crucial in surgery for tissue ablation, while in other medical applications they are useful for inducing moderate peripheral vasodilation, muscle relaxation and enhancement in the rate of biological reactions. Photothermal interactions are also important in laser safety. In non surgical lasers, the temperature of the treated tissues should not exceed 43°C to avoid side effects [3]. In addition to the above effects, the photothermal interactions are also responsible for secondary photomechanical effects. Heating can induce transient modifications of extracellular matrix (ECM) components, such as collagen and other macromolecules, as well as transient fluid dynamics in the ECM, effects that in turn cause mechanical stress on cells, modifying cell morphology and tissue texture. While photochemical effects are mostly induced by Ultraviolet (UV) and Visible (Vis) wavelengths, Near Infrared (NIR) wavelengths, such as that of the Nd:YAG laser emission (1064 nm wavelength), mostly induce photothermal effects and, consequently, photomechanical effects. However, effects of the NIR wavelengths closest to the visible spectrum on mitochondrial enzymes have been reported [4].

In more recent years, lasertherapy has been defined as a form of photobiomodulation (PBM), a generic term to indicate effects of light irradiation on tissues. The term refers to the changes that light (from many different surces) can elicit in biological processes, inducing their stimulation or inibition. PBM is a fashinating way to stimulate and cure tissues pathologies, and new frontiers emerge in a wide range of cellular responses, pain processes, inflammation pathways, and wound healing.

Hilterapia® is a distinguished High Intensity Laser Therapy (HILT) with patented laser pulse (FDA approved in 2003). The laser source is a solid crystal, Nd: YAG, with pulsed, NIR emission at 1064 wavelenght. It falls in the so called "therapeutic window", where the absorption by the major tissue cromophores is lower, allowing laser radiation to penetrate deeper. The emission wavelength (1064 nm), and the related photon associated energy, mostly induces photothermal effects. The pulsed emission is characterized by very high peak power, allowing the propagation of high density photon packages in deep tissues. These properties ensure some advantages. Indeed, high power pulsed radiation cycles permit to penetrate tissues in depth without damaging or disrupting them. In order to analyze photothermal and consequent photomechanical effects, pulse duration and duty cycle need to be considered. The pulse duration (t:on 200 μs) is shorter than the interval between pulses (t:off in the order of ms). Therefore, heat is dissipated without side effects and can diffuse in the targeted tissues producing temperature gradients. The transmitted heat can induce transient modifications of the biological microenvironment [3,5]. These modifications mostly involve the extracellular matrix (ECM), which can translate them into changes in mechanical stress acting on cells, which are connected to ECM via membrane proteins. It has long been known that the ECM performs structural functions, but more recently it has been demonstrated that the ECM has a key role in tissue homeostasis and in the regulation of cell behavior. Thus, the secondary photomechanical effects caused by the Nd:YAG laser can promote ECM remodelling and influence cell-matrix interactions.

In vitro preclinical studies investigated in depth the efficacy of Nd:YAG laser in inducing photothermal and photomechanical effects (see **§ 2)**. Contextually, clinical applications of Hilterapia® showed very good results in osteoarticular and neuromuscuar diseases, with consequent improvement of patient quality of life. Years of daily use by clinicians and many studies published in national and international journals demonstrate the effectiveness of Hilterapia® in rehabilitative medicine and other fields of application (see **§ 3)**. Its first clinical applications were developed in sport traumas and pain therapy, but quickly its effectiveness has been confirmed in degenerative and inflammatory osteoarticular and musculoskeletal diseases.

The aim of this paper is to review both preclinical research and clinical trials on HILT that can help shed light on the mechanisms of action and therapeutic effects, respectively.

2. EFFECTS OF HILTERAPIA® AT CELLULAR AND MOLECULAR LEVEL

It is well-known that mechanical factors are necessary for maintaining tissue homeostasis. Cells are continuously exposed to compressive stress, shear stress, stretching, gravity etc. Consequently, cells reorganize their morphology and reprogram their functions for adapting dynamically to the environmental conditions. Internal and external forces regulate cell shape and many studies have shown that mechanical forces can affect apoptosis, gene expression, protein synthesis, differentiation etc [6].

As reported above, Hilterapia® is based on a high power, pulsed Nd:YAG laser source. Its emission induces in the tissues photothermal effects, which can produce photomechanical effects in the cell microenvironment. Considering the importance of mechanical stimulation on tissue homeostasis, some

in vitro studies on the action mechanisms of Hilterapia® at cellular and molecular level have been devoted to compare the effects of pulsed Nd:YAG emission with those induced by mechanical/gravitational stress due, in particular, to loading/ unloading conditions.
In a study of Monici et al. [7], carried out on human mesenchymal stem cells (hMSC), the authors analyzed and compared the effect of Nd-YAG laser radiation with those caused by gravitational factors in order to help understand the molecular mechanisms of hMSC differentiation and the role of mechanical factors in regulating this process. Cell differentiation is the process during which immature (unspecialized) cells take on individual characteristics and reach their mature (specialized) shape and function. During this process, a differentiating cell undergoes an epigenetic reprogramming which causes major changes in cell phenotype and function [8]. In the study, cells were cultured in a Random Positioning Machine or in a hyperfuge to simulate microgravity (unloading conditions) and hypergravity (increase in loading, gravity > 1x*g*), respectively, or irradiated with a pulsed Nd:YAG laser (73 seconds, 1064 nm wavelength, 200 µs pulse duration, 10 Hz repetition rate, 458,65 mJ/cm^2 energy fluence, laser source: Hiro 3, ASA, Arcugnano, Italy) . The results showed that gravitational alterations and photomechanical stress were both effective in inducing specific differentiation patterns in hMSCs. In fact, the expression of Sox9 and Runx2, which are major differentiation markers of chondrogenesis [9] and osteoblastogenesis [10], respectively, was lower than controls in samples exposed to simulated microgravity (unloading conditions), but it was significantly increased in samples exposed to hypergravity (gravity > 1x*g*) and Nd:YAG laser treatment [7]. In addition to this, the genes *MEN1, NF1 and GLI1*, involved in the commitment of hMSCs into the osteoblast lineage [11], bone development and remodelling [12], control of chondrocyte and osteoblast differentiation [13], resulted significantly upregulated after exposure to hypergravity and laser treatment. In contrast, the nuclear receptor PPARγ, the major differentiation marker of adipogenesis [14], significantly increased after exposure to modeled microgravity, whereas it decreased following hypergravity exposure and Nd:YAG laser treatment. The same behaviour was observed in other genes involved in the regulation of adipocyte biological function [15], such as FABP4 [7]. Following the exposure to Nd:YAG laser treatment, an overexpression of *Runx-2* and other genes encoding typical osteoblastogenesis markers, such as *ALP and BMP-2*, was observed also in a later study where hMSC were cultured in 3D scaffold, consisting of decellularized equine bone. This study demonstrated that Nd:YAG laser treatment can stimulate the differentiation towards the osteoblastic lineage and can favor and accelerate the development of three-dimensional bone constructs (data not published). Together with the above changes in expression of major differentiation markers of adipogenesis, chondrogenesis and osteoblastogenesis, the authors found that the exposure to gravitational/ photomechanical stress induced cytoskeleton alterations in hMSC [16]. The outcomes of these studies demonstrate that Nd:YAG laser radiation induces photomechanical effects. In fact they are comparable to those induced by hypergravity (gravity > 1x*g*, that is in load increase conditions), while unloading conditions (microgravity) produce opposite effects. It is well known that mechanical stress, such as loading, is of key importance in maintaining the homeostasis of tissues with antigravity functions, such as bone, cartilage and muscle.
It has long been known that the cytoskeleton plays a key role in mechanotrasduction due to its complex and dynamic network of proteins and its ability to sense and mediate cell-cell and cell-matrix interactions [6].

The results of a further study focused on cytoskeleton and extracellular matrix, showed that exposure to Nd:YAG laser treatment induced reorganization of the microtubule network and increase in actin stress fibers [17]. As it is known, stress fibers are involved in the formation of focal adhesions, structures composed by integrins and responsible for cell-matrix interactions [18]. The authors explored also the possibility to utilize pulsed Nd:YAG laser irradiation for modulating the production of extracellular matrix (ECM) molecules by cells of the connective tissues. The ECM is a complex network consisting of numerous proteins (such as collagen and fibronectin), glycoproteins, proteoglycans. It has a key role in providing structural support, but more recently it has been demonstrated that the ECM is also important for cell adhesion, intercellular communication, and cell migration. ECM components are produced and released by cells, but mechanical forces also take part in the process and alterations of such forces can influence the ECM composition [19, 20]. In fact, the increase in mechanical stress acting on cells generally induces an increase in ECM production. By using the above reported laser treatment parameters, authors analyzed the expression of some major ECM

components in different cell types. Collagen II and aggrecan were assessed in chondrocytes while the expression of collagen I and fibronectin was studied in fibroblasts. The results showed that laser treatment significantly increased the ECM molecules in both cell types. Fibronectin, a protein that binds integrins and is involved in different processes, such as cell adhesion, migration, and differentiation, also changed its distribution. Following laser treatment, it assembled in thick and ordered fascicles around fibroblasts instead of the randomly distributed network of fascicles observed in control samples. A significant decrease of metalloproteinases 1 (MMP-1) expression, the major lytic enzyme involved in ECM degradation [21], was found in the treated samples. In addition, the expression of α5β1 integrin, which has a key role in fibronectin matrix assembly, was also evaluated. Immediately after laser treatment, a decrease in α5β1 integrin expression and changes in its distribution on the cell surface were observed in fibroblasts and chondrocytes. This result suggests that laser treatment can induce a reorganization of the fibronectine network associated with a redistribution of its mechanical receptor on the cell membrane. Moreover, given the enhanced expression of aggrecan, which is considered a marker of chondrocyte maturation, authors assayed the expression of Sox 9, a transcription factor involved in chondrocytes differentiation and functions, as the synthesis of ECM molecules. As expected, a significant increase in expression of Sox-9 was found after laser treatment. The findings of this study demonstrated that irradiation by pulsed Nd:YAG laser affects fibroblast and chondrocyte behavior similarly to mechanical stress [17].
Further support to the hypothesis that cell sense pulsed Nd:YAG laser irradiation as a mechanical stress, and respond to it by activation of mechanotransduction machinery, was supplied from the results of another research where the effect of laser treatment (73 seconds, 1064 nm wavelength, 200 μs pulse duration, 10 Hz repetition rate, 458,65 mJ/cm^2 energy fluence) on the production of ECM molecules by fibroblasts and chondrocytes was compared with the effect of loading. Again, the authors found that photomechanical stress induces cytoskeleton remodelling, redistribution of membrane integrins, increase in production of ECM molecules and the effects are similar to those observed in the same cells exposed to cyclic hypergravitational stress (10×g) [22]
A further study was carried out on fibroblasts and endothelial cells, which have a key role in tissue repair process, being the major synthesizers of ECM molecules and cooperating to the formation of new vessels [23]. The cells were exposed to Nd-YAG laser irradiation or to unloading conditions, which can also strongly affect the composition of the ECM because it changes the balance of mechanical forces in the cell microenvironment, and the effects of the two treatments were compared. The results confirmed that in cultured fibroblasts and endothelial cells exposed to Nd:YAG laser treatment there was a reorganization of fibronectin fibrils with the formation of ordered fibronectin fascicles, while unloading induced a strong, but less organized, increase in fibronectin fibrils. Interestingly, the same research revealed that, in sub-confluent endothelial cell cultures, Nd:YAG laser irradiation induced cell spreading and formation of an organized cell monolayer with "paved" appearance, while untreated cells in control samples remained randomly distributed[23]. In conclusion the set of results collected in the above described research demonstrate that cell response to Nd:YAG laser irradiation is very similar to that induced by loading and often opposite to the one produced by unloading, thus suggesting that the biological response occurs via mechanotransduction machinery, as proved by the involvement of cytoskeleton modification and reorganization of integrin receptors.

2.1 SUMMARY

Summarizing, the findings of the studies presented above support the hypothesis that HILT can induce photomechanical effects. Firstly, the data collected from research conducted so far show evidence of cytoskeleton remodelling and changes in the expression level of cytoskeletal proteins, such as tubulin, vimentin and actin [16, 17]. Since it is well known that changes in mechanical stress affect the cytoskeleton structure [20], the results obtained in fibroblasts, chondrocytes and endothelial cells demonstrate that the Nd:YAG laser radiation can modulate mechanical forces acting on cells, thus promoting the reshaping of cytoskeleton. Secondly, all the results presented in this review demonstrate that laser treatment promotes major changes in ECM components, such as collagen, fibronectin and aggrecan. More specifically, the studies reveal that the Nd:YAG laser treatment induces a significant increase in collagen II and aggrecan expression in chondrocytes and a significant increase in collagen I and fibronectin in fibroblasts[17]. Moreover, after laser treatment, there is a reorganization of fibronectin fibrils in different cell lines [23]. Changes in ECM components as well as in their assembly could translate into modifications of cell-ECM interactions and could influence important cell processes, like cell spreading, adhesion and motility. This hypothesis is also supported by the results obtained assessing integrin α5β1, which shows a decreased expression and redistribution after laser treatment [17]. Finally, the outcomes presented above also show that the Nd:YAG laser treatment promotes Sox9 and Runx2 expression in hMSCs, whereas it reduces PPAR-γ expression[7]. Sox9, Runx2 and PPAR-γ are major differentiation markers of chondrogenesis, osteoblastogenesis, and adipogenesis, respectively. Interestingly, according to these studies, the effect of laser treatment on the expression of these markers is comparable to that of hypergravity (loading conditions, $g > 1$), but opposite to that of microgravity (unloading conditions). The fact that laser treatment promotes chondrogenesis and osteoblastogenesis, maturation processes of cells belonging to tissues with antigravitational function, further supports the hypothesis that cell response to pulsed Nd:YAG laser irradiation occurs, at least in part, via mechanotransduction machinery [6]. Even if further studies are needed, the findings of the studies conducted so far are an essential first step to understand the molecular and cellular mechanisms of Hiltherapy.

3.0 HILTERAPIA® CLINICAL RESULTS

Tissues and cellulars finding produced by laser light irradiation through Hilterapia® make it an extremely useful tool in a lot of medical field, in particular in rehabilitative practice. Positive clinical results are found in sport traumas, osteoarthritis and musculoskeletal disorders, wound and chronic ulcers, and in some other struggling conditions.

3.1 SPORT TRAUMAS AND LESIONS

First clinical experiences started in the late 90's, mainly in sportsman affected by lower legs traumas or lesions, in muscles or tendons. In this field main objective is to heal the athlete and reduce the recovery time, allowing a fast return to competitive activity in optimal conditions.

Most sports injuries involve muscles, tendons, ligaments and joints. Injuries are often related to the type of practiced sport, such as epicondilitis in tennis, knee suffering in jump, shoulder problems in volleyball. Moreover acute injuries, such as contusions, distorsions, and muscle strains are common.

In 1997 efficacy of Hilterapia® was described in 97 injured athletes [24] were pain and oedema were reduced with excellent results in 73% of cases, allowing a rapid return to agonistic activity. A wider sport traumatology cases serie was studied in a later study [25]: in 405 cases affected by sports traumatology, clinical and instrumental evaluation was conducted. Improvement was confirmed in 85% of the cases, revealed by subjective and clinical assessment, and confirmed by throught instrumental evaluation.

Studies were also conducted in various selected districts, as pubalgia [26], ankle ligaments [27], patellar tendinopathy [28], muscle strains [29], intersection syndrome [30]. Pubalgia, today defined as "groin pain syndrome", is a specific insertional tendinopathy, a relevant and common complaint in sportsmen, caused by inflammation in tendons of the muscles at the level of the pubis, due to repeated microtrauma in this area. This condition is very frequent in football player, due to typical athletic gesture, and it is of difficult resolution. A rest period is always requested, toghether with phisiotherapy, and often complete recovery time is quite long. In 31 athletes affected by pubalgia treated with Hilterapia® [26], research found a complete and rapid recovery in 14 cases, partial but finally complete recovery in 13, while only 4 athletes needed a longer time to recovery.

In sport ankle lesions recovery time speeding up was revealed [27]: in acute ligamentous lesions same results were obtained in three weeks laser treatment instead of six weeks traditional treatment. Also in patellar tendinopathy in sportsman [28], faster recovery was found compared to C02 laser treated patients, and effective results were reached in muscle lesions in atlethes with 1st degree muscle strain [29].

Thanks to its effectivenes, rapidity of pain relief and recovery fastening, Hilterapia® has been currently used in sport settings from ninety onwards, with public testimonials in football, motorcycle championship, national fencing team, and so on.

Beyond the studies on sports lesions, research applied during years also on degenerative and inflammatory joint disease, and in soft tissues disorders.

3.2 OSTEOARTHRITIS AND MUSCULOSKELETAL DISORDERS

From the first 2000's onwards, Hilterapia® has been studied and applied in the management of all the main osteoarthritis sites, both in degenerative forms and flogistic pathologies, such as Juvenile arthritis or Lupus arthropaty, and in soft tissue pathologies. Hilterapia® clinical effectiveness is sustained by several studies conducted in a wide range of troublesome and common diseases, such as knee osteoarthritis, shoulder affections, low back pain and spinal disorders, osteoporosis, muskuloskeletal pain, as far as inflammatory arthropathy (LES, juvenile arthritis) or emophilic arthropathy.

Knee diseases

A considerable number of international studies in last years focused on lasertherapy in knee OA, because it is a major cause of disability in the elderly, considering its global prevalence and incidence. Cartilage alterations are a main topic in orthopaedic and physiatric research, and PBM therapy is one of the most studied approach between non-surgical and non-pharmacological interventions [31]. Hilterapia® has been studied and confirmed as an optimal resource therapy in this field. Suggestions in cartilage regeneration were found [32,33], and clinical results like reductions in knee pain, increases in ROM, and increased functionality were consistently observed: VAS, Womac Score, ROM goniometry improvement were reported [34-43].

A randomized controlled clinical trial [35] compared the effects of Hilterapia® vs viscosupplentation in 41 patients suffering from symptomatic knee OA. Positive results of the two type of treatment were analogous: improvement was found in Womac and Lequesne Scale at the end of the treatment and at 4 months follow-up, with Hilterapia® being less invasive and safer than articular infiltrations. Analogous study was conducted later [36], comparing two treatment protocols, only differing in the number of sessions (10 sessions or 5 Hilterapia® sessions). Hilterapia® was found to produce a rapid antalgic effect, in the very first sessions. Furthermore the duration of HILT effects seemed to be dose-related, because the shorter protocol showed a rapid pain relieve, but a tendency to regression. A clinical investigation was conducted [37] in 30 Knee OA patients, comparing Hilterapia®, LLLT and ultrasound therapy results. In this study Hilterapia® had a more analgesic effect compared to LLLT e US, toghether with functional test improvement (walking distance and squat), and a better patient's satisfaction index.
Many other experiences confirmed the efficacy and safety of Hilterapia® in painfull knee [34-43], because knee pain is approachable according to the clinical phase, in a periarticular soft tissues approach or with the objective of treating intraarticular space, benefiting from regenerative properties of the device. Results of LLLT and HILT treatment, in combination with exercises were compared in knee OA patients [41]: Hilterapia® resulted more effective (VAS and WOMAC Scale) than LLLT treatment. Efficacy of pulsed Nd:YAG laser, Hilterapia®, in the treatment of patients with knee osteoarthritis was evaluated also in another study [42]. The study included 50 patients with diagnosed grade II to III arthrosis, were treated, and conclusions were that HILT significantly reduced pain, stiffness and problems with normal daily activities. Investigation of the effects of pulsed Nd:YAG laser plus glucosamine/chondroitin sulfate in patients with knee osteoarthritis was carried out: the addition of HILT determined a plus in patients improvement. In 96 gonarthrosis patients HILT enabled prompt analgesic effects in KOA treatment [43].
All these researches showed high efficacy and safety in KOA patients treatment, inside rehabilitative settings.

Shoulder diseases

Acute or persistent Shoulder pain is a very common condition, associated with high social cost and patient burden. It is mostly due to tendon inflammation (bursitis or tendinitis), glenohumeral osteoarthritis, or rotator cuff tendon tear. So painful shoulder is a very common complaint, increasing after the age of 50 especially in working populations. In this affection a lot of studies found efficacy and safety of Hilterapia®, from the first reported studies [44-50], till nowadays [51-53]. Painful shoulder syndromes were several times investigated. Subacromial Impingement Syndrome (SAIS) was studied in some forms: Hilterapia® showed its advantage versus ultrasound (US) therapy in the treatment of SAIS [53]: participants diagnosed with SAIS showed greater reduction in pain and improvement in articular movement, functionality and muscle strength of the affected shoulder after 10 treatment sessions of HILT than did participants receiving US therapy over a period of 2 consecutive weeks. Hilterapia® and manual therapy were found to be more effective than other interventions in minimizing pain and disability and increasing ROM in patients with SAIS. The effect of HILT is confirmed in a study [49] on seventy patients with SAIS, evaluated with SPADI Scale and subscales. Forty patients who were diagnosed with 1 - 2 stage impingement syndrome pain were treated and analized [51]: post-program comparation revealed a statistically significant reduction in ultrasonography dimension of supraspinatus and VAS and significant increase in ROM of shoulder flexion and abduction, in favour to the treated group with Hilterapia®.
It's possible to conclude that high level laser therapy produces great improvement in shoulder mobility in impingement syndrome. Improvement is found in the short and long term**.**

Spinal disorders

Neck and Low back pain treatment remains a struggling argument in

medical literature, and international guidelines don't totally agree [54]. Back pain represent a main topic of rehabilitative treatmens, and the various proposed protocols generally combine physiotherapy with instrumental options.
Almost 20 years of clinical practice and demonstrations, support the efficacy of HILT trough Hilterapia® in spinal pain of various origin. Special efficacy was reported in several studies on low-back pain [55-63]: in mechanical LBP wheter acute o chronic form [61-63], in LBP from disck erniation [55], in sciatic nerve radiculopaty [56, 57] pain decrease and improvement in functional tasks were reported. Its efficacy, in terms of VAS, and disability scores (Roland Disability Questionnaire and Modified Oswestry Disability Questionnaire) is reported in several researches [60-63], were lasertherapy is combined with exercises and compared with other standard physical therapies.
Also in neck pain Hilterapia® showed high efficacy, in combination and compared with other classical intervents. It was compared with ultrasound and trancutaneous electrical stimulation in 84 cervical spondilosis patients [64]: HILT plus exercise was more effective than US/TENS plus exercise. Other studies report efficacy of Hilterapia® in chronic neck syndrome [65], cervical myofascial pain syndrome [66], in cervical radiculopathy, [67], in cervical spondilosis [68].
A recent systematic review and meta-analysis in the treatment of spinal disorders confirmed the efficacy of this type HILT treatment [69]. Osteoporosis, which is a main source of vertebral pain, also improved with Hilterapia® [70-72].
Analogous positive results were found in soft tissues and musculoskeletal disorders [73-82], such as epycondilitis [73, 74], plantar fascitis [75,76], carpal tunnel syndrome [78]. Particularly severe tendon and ligament injiuries (triceps tendon rupture, Achilles tendon partial rupture or fibrillar degeneration, subachillar bursitis and partial abruption of Achilles tendon insertion, medial collateral ligament partial rupture, lateral and medial meniscus and MCL partial rupture) were assessed by musculoskeletal examination, thermography, musculoskeletal sonography and VAS [79, 80]. Results showed promoting repair in tendon and ligament structures in all cases, reducing pain in all cases and favouring restoration of the function in all cases. An interesting case report on Tieze Syndrome patient was conducted [77]: Hilterapia® allowed managing severe pain not responding to drugs treatment. The result obtained in 9 sessions was a complete elimination of pain, which persisted at 40 days follow up, and the patient returned to her normal activities.

3.3 REGENERATIVE TREATMENT

Hilterapia® efficacy in regenerative treatments is mainly attributable to its photomechanical effect. In fact a distinguishing characteristic of Hilterapia® is its capability to produce photomechanical effects on the treated tissues. Entity of such effect is directly proportional to laser emission intensity, and inversely proportional to impulse duration. Hilterapia® impulse presents ideal features to produce such stimulation, that leads to cellular cytoskeleton reorganization in endothelial, mesenchimal and connective cells, and promote extra-cellular matrix production, similarly to mechanical stimulus. It induces connective cells differentiation and endothelial layers formation, thus promoting tissue repair processes. The efficacy of Hilterapia® in stimulating tissue regeneration and healing has been demonstrated in wound healing [83], chronic ulcers [84], diabetic [85] or neurogenic ones [86], which are generally non healing or long lasting and disabling conditions. Although regenerative and proliferiative effect is evident in skin lesions, regenerative properties are of main relevance also in rehabilitative treatment, favouring healing of non directly visible soft tissues lesions (tendons, burses, etc), whether of degenerative or traumatic origin, and stimulating cartilage repair.

3.4 OTHER CONDITIONS

Inter alia, Hilterapia® showed positive results in many other rehabilitative domain such as balance [87], post mastectomy pain syndrome [88], postburn pruritus [89], linphoedema [90], haemophilic arthropaty [91,92], bells palsy [93], pain management [94], confirming wide and various direct and indirect effects.
In all the cited studies a very high level of safety was reported, considering that it was used also in hemophilic arthropatic patients without side effects.

3.5 SOME PRACTICE DETAILS

From a practical point of view Hilterapia® devices are characterized by pre-imposted programs, togheter with personalized possibilities from the operator. This fact allows a customized treatment. Laser power emission and erogation modality consent a lot of approaches and time saving, for the operator and for the patients. Its particularity are intensity and depth of treatment (some centimeters) which allows healing of deeper structures. Treatment is typically distributed in three phases: the first phase is directed to control muscle contracture in periarticular group muscles

and relax trigger points. The second phase is more specifically addressed to the suffering tissue (es tendon, or articular components, oedema, etc), even through optical windows. Third and last phase is direct to pain irradiation areas. The first session treatment leads to an immediate improvement in pain level reduction, up of 50%. A few laser sessions obtain further pain control, which increases as the sessions continue. This fact makes it possible to start mobilization, while antiinflammatory and restorative effects occurs, so implementing and stabilizing results over the time, in a virtuous circle. Mean session number reccomended is 8-10, carried out daily or every other day. According to cited literature Hilterapia® is an extremely flexible technology, because it allows modulation in intensity, frequency and energy according to the clinical situation and the type of pathology, both in acute and chronic phase.
Adding co-intervention is usual in clinical rehabilitative practice, as combined interventions generally obtain better functional results. Hilterapia® is easily and safely combined with ultrasounds, TENS, ECSWT, and other common physioterapy devices.This is just a summary of ascertained Hilterapia® clinical effects on musculoskeletal system diseases. In this review we outlined the researches of main interest, were Hilterapia® showed interesting results in various affections of rehabilitative concern. Positive influence of adding Hilterapia® to physiotherapy interventions in musculoskeletal pain management is well recognized.

3.6 SUMMARY

Hilterapia® is a main tool in rehabilitative settings as part of an integrated rehabilitation program, for pain management and tissues healing. Beyond the typical effects of LLLT, its specific advantages are:
Transfer in depth of higher energy amount, which enables deep tissues treatment. A strong photomechanical effect, which allows specific tissues reactions A very rapid effect on pain, the basis for carrying out mobilization and exercises. Reduction of treatment times, much appreciated in patients and operators, and a long lasting effect.

REFERENCES

1. Finsen NR. The Red Light Treatment of Small-Pox. Br Med J. 1895, 2(1823):1412-1414. doi:10.1136/bmj.2.1823.1412-a.
2. Jacques SL. Laser-tissue interactions. Photochemical, photothermal, and photomechanical. Surg Clin North Am. 1992, 72(3):531-558. doi:10.1016/s0039-6109(16)45731.
3. Rossi F, Pini R, Monici M. Direct and indirect photomechanical effects in cells and tissues - Perspectives of application in biotechnology and medicine. In: Monici M, van Loon J (eds.) Cell Mechanochemistry. Biological Systems and Factors Inducing Mechanical Stress, Such as Light, Pressure and Gravity. Research Signpost/Transword Research Network, pp. 285-301, Trvandrum, India 2010.
4. Hamblin MR, Mechanisms and Mitochondrial Redox Signaling in Photobiomodulation. Photochem Photobiol. 2018, 94(2): 199–212. doi:10.1111/php.12864.
5. Cialdai F, Monici M. Relationship between cellular and systemic effects of pulsed Nd:YAG laser. ENERGY FOR HEALTH, 2010, 4-9.
6. TschumperlinDJ.100%Mechanotransduction. Compr Physiol. 2011,1(2):1057-1073.doi:10.1002/cphy.c100016 .
7. Monici M, Romano G, Cialdai F, Fusi F, Marziliano N, Benvenuti S, Cellai I, Egli M, Cogoli A. Gravitational/mechanical factors affect gene expression profile and phenotypic specification of human mesenchymal stem cells. JOURNAL OF GRAVITATIONAL PHYSIOLOGY, 2008, 15:191-192. ISSN: 1077-9248.
8. Definition of “cell differentiation” by “NCI Dictionary of Cancer Terms”, National Cancer Institute.
9. Lefebvre V, de Crombrugghe B. Toward understanding SOX9 function in chondrocyte differentiation. Matrix Biol. 1998, 16(9):529-540.doi:10.1016/s0945-053x(98)90065-8.
10. Bruderer M, Richards RG, Alini M, Stoddart MJ. Role and regulation of RUNX2 in osteogenesis. Eur Cell Mater. 2014, 28:269-286. Published 2014 Oct 23. doi:10.22203/ecm.v028a19.
11. Sowa H, Kaji H, Canaff L, et al. Inactivation of menin, the product of the multiple endocrine neoplasia type 1 gene, inhibits the commitment of multipotential mesenchymal stem cells into the osteoblast lineage [published correction appears in J Biol Chem. 2004 Sep 10;279(37):39186]. J Biol Chem. 2003, 278(23):21058-21069. doi:10.1074/jbc.M302044200
12. Alwan S, Tredwell SJ, Friedman JM. Is osseous dysplasia a primary feature of neurofibromatosis 1 (NF1)?. Clin Genet. 2005, 67(5):378-390. doi:10.1111/j.1399-0004.2005.00410.x.
13. St-Jacques B, Hammerschmidt M, McMahon AP. Indian hedgehog signaling regulates proliferation and differentiation of chondrocytes and is essential for bone formation [published correction appears in Genes Dev 1999, Oct 1;13(19):2617]. Genes Dev. 1999, 13(16):2072-2086. doi:10.1101/gad.13.16.2072.
14. Brun RP, Tontonoz P, Forman BM, et al. Differential activation of adipogenesis by multiple PPAR isoforms. Genes Dev. 1996, 10(8):974-984. doi:10.1101/gad.10.8.974
15. Rosen ED, Walkey CJ, Puigserver

P, Spiegelman BM. Transcriptional regulation of adipogenesis. Genes Dev. 2000, 14(11):1293-1307.

16. Monici M, Cialdai F, Fusi F, Romano G, Pratesi R. Effects of pulsed Nd:Yag laser at molecular and cellular level - a study on the basis of Hilterapia®. ENERGY FOR HEALTH, 2009, 3:27-33.
17. Monici M, Basile V, Cialdai F, Romano G, Fusi F, Conti A. Irradiation by pulsed Nd:YAG laser induces the production of extracellular matrix molecules by cells of the connective tissues. A tool for tissue repair. In: BIOPHOTONICS: PHOTONIC SOLUTIONS FOR BETTER HEALTH CARE, 2008b, Popp J, Drexler W, Turchin VV, Matthews DL Eds., PROC. OF SPIE. vol. 6991, p. 69912K1-10, 2008. ISBN: 9780819471895, doi: 10.1117/12.782865.
18. Cronin NM, DeMali KA. Dynamics of the Actin Cytoskeleton at Adhesion Complexes. Biology (Basel). 2021, 11(1):52. Published 2021 Dec 30. doi:10.3390/biology11010052.
19. Chiquet M. Regulation of extracellular matrix gene expression by mechanical stress. Matrix Biol. 1999, 18(5):417-426. doi:10.1016/s0945-053x(99)00039-6.
20. Ingber DE. The architecture of life. Sci Am. 1998, 278(1):48-57. doi:10.1038/scientificamerican0198-48.
21. Kasper G, Glaeser JD, Geissler S, et al. Matrix metalloprotease activity is an essential link between mechanical stimulus and mesenchymal stem cell behavior. Stem Cells. 2007, 25(8):1985-1994. doi:10.1634/stemcells.2006-0676
22. Basile V, Romano G, Fusi F. et al. Comparison Between the Effects of Hypergravity and Photomechanical Stress on Cells Producing ECM. Microgravity Sci. Technol, 2009, 21, 151–157.
23. Monici M, Cialdai F, Romano G, Fusi F, Egli M, Pezzatini S, Morbidelli L. An in vitro study on tissue repair: impact of unloading on cells involved in the remodelling phase. MICROGRAVITY, SCIENCE AND TECHNOLOGY, 2011, 23: 391-401. ISSN: 0938-0108, doi: 10.1007/s12217-011-9259-4
24. Lubich T, Mondardini P, Verardi L, et Al. Impiego del laser di potenza nel trattamento precoce e nel recupero funzionale dell'atleta infortunato. Medicina dello Sport, 1997, 50: 71-83 24.
25. Mondardini P. High Intensity Laser therapy (HILT): state of the art in sporting traumatology and pain therapy. Atti Seminario High Intensity laser in arthrosic pathologies, Fondazione Don Gnocchi, Firenze, 2002, 1-7.
26. Verardi L, Mondardini P. Il power laser Nd YAG come presidio terapeutico nella sindrome retto-adduttoria dell'atleta. Med Sport, 2000, 53: 343-50.
27. Di Caprio F, Ghermandi R. et Al. The Nd:YAG laser in the treatment of the lateral ligament lesions of the ankle. Atti I Convegno Nazionale Terapia Hilt. Firenze, settembre 2006.
28. Buda R, Di Caprio F, Ghermandi R, Buda M. HILT in the treatment of patellar tendinopathy in sportsman. Atti II Convegno Nazionale Hilterapia National Congress, Milano, 2007.
29. Valent A. Muscle lesions in athletes: case comparison between Hilterapia and traditional therapy. Energy for Health, 2009, 03:21-25.
30. Marenghi L, Mainardi G, Zasa M. Management of intersection syndrome in professional motorcycle rider: a case report. Acta Biomed, 2019, 90(4):556-559. DOI: 10.23750/abm.v90i4.7760.
31. Stausholm MB, Naterstad IF, Joensen J. Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: systematic review and meta-analysis of randomised placebo-controlled trials. BMJ Open, 2019;9 (10):e031142.
32. Zati A, Fortuna D, Cardillo I, Gazzotti V, Cameli O, Ferrari G, Bilotta W. High intensity laser therapy in the treatment of gonarthrosis: the first clinical case of the protocol for a multicentric, randomized, double-blinded study. Atti Seminario High Intensity laser in arthrosic pathologies, Fondazione Don Gnocchi, Firenze, 2002. pp.19-25.
33. Buda R, Buda M, Gigolo B, Di Caprio F, Ghermanti R, Zati A: The Nd:YAG laser in the treatment of osteocartilagineous lesions of the knee. Atti I Congresso Nazionale Terapia Hilt, Firenze, 2006, pp. 92-97.
34. Valent A. Clinical results in treatment of gonarthrosis with HILT therapy. Atti II Convegno Nazionale Hilterapia, Milano 2007, pp.99-103.
35. Viliani T, Ricci E, Mangone G, Graziani C, Pasquetti P. Effects of Hilterapia® vs. Viscosupplementation in knee osteoarthritis patients: a randomized controlled clinical trial. Energy for Health, 2009, 03, 15-17.
36. Viliani T, Martini C, Mangone G, Pasquetti P. "High intensity laser therapy in knee osteoarthritis: comparison between two different pulsed-laser treatment protocols". Energy for Health, 2010, [05]: 26-29.
37. Sabbahy S. Clinical experience using Hilterapia® in "knee arthrosis". Energy for Health, 2009, 04:24-27.
38. Munarolo D, De Lazzari F, Giordan N. Randomized, controlled, clinical study to evaluate the efficacy and safety of glucosamine hidrochloride and chondrointin sulphate in combination with physical therapy (HIRO + Kinesitherapy) versus physical ther-

apy alone in patients suffering from osteoarthritis of the knee. Med Sport, 2011, 64:159-71.
39. Viliani T, Carabba C, Mangone G, Pasquetti P. High Intensity Pulsed Nd:YAG Laser in painful knee osteoarthritis: the biostimulating protocol. Energy for Health, 2012, 09:18-22.
40. Kheshie AR, Alayat MSM, Ali MME. High-intensity versus low-level laser therapy in the treatment of patients with knee osteoarthritis: a randomized controlled trial. Lasers Med Sci 2014, DOI 10.1007/s10103-014-1529-0.
41. Šifta P, Danilov D. Effects of high-intensity laser on gonarthrosis. Energy for Health, 2015, 14:18-22.
42. Alayat MSM, Aly THA, Elsayed AEM, Fadil ASM. Efficacy of pulsed Nd:YAG laser in the treatment of patients with knee osteoarthritis: a randomized controlled trial . Lasers Med Sci, 2017, DOI 10.1007/s10103-017-2141-x.
43. Stiglic-Rogoznica N, Stamenkovic D, Frlan-Vrgoc L, Avancini-Dobrovic V, Vrbanic TSL. Analgesic Effect of High Intensity Laser Therapy in Knee Osteoarthritis. Coll. Antropol. 2011, 35, Suppl. 2: 183–185.
44. Saggini R, Bellomo RG, Baldassarre V. Therapeutic approach with HILtherapy in the pathology of the shoulder with tenosynovitis of the omeral biceps. Atti I Convegno Nazionale Terapia Hilt, Firenze, 2006, pp 78-86.
45. Melegati G. HILT treatment in calcific tendinopathy of shoulder. A controlled perspectuve study. Atti I Convegno Nazionale Terapia Hilt, Firenze, 2006, pp 88-91.
46. Saggini R. Complex rehabilitation in "painful shoulder" syndrome from partial tear and from calcific tendinopathy of the rotator cuff. Sphera Medical Journal, 2007, 6:16-19.
47. Santamato A, Ranieri M, Ianieri G, Fiore P, Megna G. HILTherapy in the pain of bicipital long caput and/or subacromial conflict. Atti II Convegno Nazionale Hilterapia, Milano, 2007, pp. 3-16.
48. Vissarakis G, Charamidis N. The challenge of shoulder pain. Energy for Health, 2010, 05:20-24.
49. Pekyavas NO, Baltaci G. Short-term effects of high-intensity laser therapy, manual therapy, and Kinesio taping in patients with subacromial impingement syndrome. Lasers Med Sci, 2016, 31:1133–1141 DOI 10.1007/s10103-016-1963-2.
50. Elsodany AM, Alayat MSM, Ali MME, Khaprani HM. Long-Term Effect of Pulsed Nd:YAG Laser in the Treatment of Patients with Rotator Cuff Tendinopathy: A Randomized Controlled Trial. Photomedicine and Laser Surgery, 2018, 36(9) https://doi.org/10.1089/pho.2018.4476.
51. Kamal WA, Saber M, Aiad K, Mostafa MSEM, El- Deen HAB. Effect of High-Power Laser on Shoulder Mobility in Sub Acromial Impingement Syndrome: Randomized Controlled Trial. Journal of Environmental Treatment Techniques, 2020, 8(3): 1157-1162.
52. Yılmaz M, Eroglu S, Dundar U, Toktas H. The effectiveness of high-intensity laser therapy on pain, range of motion, functional capacity, quality of life, and muscle strength in subacromial impingement syndrome: a 3-month follow-up, double-blinded, randomized, placebo-controlled trial. Lasers in Medical Science, 2021, https://doi.org/10.1007/s10103-020-03224-7.
53. Santamato A, Solfrizzi V, Panza F, Tondi G, Frisardi V, Leggin BG, Ranieri M, P Fiore. Short-term Effects of High-Intensity Laser Therapy Versus Ultrasound Therapy in the Treatment of People With Subacromial Impingement Syndrome: A Randomized Clinical Trial. Physical Therapy, 2009, 89(7): 643-652.
54. Corp N, Mansell G, Stynes S, Wynne-Jones G, Morsø L, Hill JC, van der Windt DA. Evidence-based treatment recommendations for neck and low back pain across Europe: a systematic review of guidelines. Eur J Pain, 2021, 25(2):275-295.
55. Zati A, Cardillo I, Fortuna D, Bilotta TW. Conservative treatment of low back pain caused by intervertebral disk displacement: comparison among Nd:YAG laser therapy, TENS and NSAIDs. Las Med Sci, 2003, 18, suppl 2: S25.
56. Finocchiaro S. HILT Therapy. An approach in the treatment of lumbosciatalgy . Atti II Congresso Nazionale Hilterapia, Milano, 2007, pp 42-51.
57. Conte PG, Lelli G, Lopresto A, Mazzaracchio M. Treatment of chronic lumbosciatalgy: back school versus Nd:YAG Atti II convegno Nazionale Hilterapia, Milano, 2007, pp. 67-71.
58. Carrara R. Comparison between II generation of cyclo-oxigenases and HILT in the treatment of backache . Atti II Convegno Nazionale HILTherapia, Milano, 2007, pp. 97-98.
59. Conte PG, Santamato A, Fiore P, Lopresto A, Mazzaracchio M. Treatment of chronic low back pain: back school versus Hilterapia®. Energy for Health, 2009, 3: 10-13.
60. Fiore P. et Al. Short-term effects of high-intensity lasertherapy versus ultrasound therapy in the treatment of low back pain: a randomized controlled trial. Eur Med Phys Rehabil Med, 2011, 47:367-373.
61. Alayat MSM, Atya AM, Ali MME , Shosha TM. Long-term effect of high-intensity laser therapy in the treatment of patients with chronic low back pain: a randomized blinded placebo-controlled trial.

Lasers Med Sci, 2013, DOI 10.1007/s10103-013-1472-5.
62. Vervainioti A. Nd:YAG laser in the management of low back pain. Energy for Health, 2014, 12:16-21.
63. Alayat MSM, Atya AM, Ali MME, Shosha TM. Long-term effects of high-intensity lasertherapy in the treatment of patients with low back pain: a randomized blinded placebo-controlled trial. Lasers Med Sci, 2014 May;29(3):1065-73.
64. Venosa M, Romanini E, Padua R, Cerciello S. Comparison of high-intensity laser therapy and combination of ultrasound treatment and transcutaneous nerve stimulation in patients with cervical spondylosis: a randomized controlled trial. Lasers Med Sci, 2019, 34:947-953 DOI 10.1007/s10103-018-2682-7.
65. Alayat MSM, Mohamed AA, Helal OF, Khaled OA. Efficacy of high-intensity laser therapy in the treatment of chronic neck pain: a randomized double-blind placebo-control trial. Lasers Med Sci, 2016, DOI 10.1007/s10103-016-1910-2 .
66. Alayat MS, Battecha KH, Elsodany AM, Ali MI. Pulsed Nd:YAG laser combined with progressive pressure release in the treatment of cervical myofascial pain syndrome: a randomized control trial. J. Phys. Ther. Sci. 2020, 32: 422–427.
67. Nawal Abd El-Raouf AbuShady et Al. Multimodal Intervention of High-Intensity Laser with Neurodynamic Mobilization in Cervical Radiculopathy. PJMHS 2020, 14(4): 1679-1685.
68. Haladay R, Pingot M, Topol M. The effectiveness of cervical spondylosis therapy with Saunders traction device and High-Intensity laser therapy: a randomized controlled trial. Med Sci Monit, 2017; 23:335-342.
69. Alayat MSM, Alshehrib MA, Shoushad TM, Abdelgalil AA, Al-Attarb WS, Alhasanb H, Khayyatb OK. The effectiveness of high intensity laser therapy in the management of spinal disorders: A systematic review and meta-analysis. Journal of Back and Musculoskeletal Rehabilitation, 2019, 1–16 1 DOI 10.3233/BMR-181341.
70. Ebid AA, Thabet AAEM. Comparison between pulsed high intensity Nd: YAG laser and ultrasound in treatment of osteoporosis in Men. Bioscience Research, 2017, 14(2): 315-322.
71. Alayat MSM, Abdel-Kafy EM, Elsoudany AM, Helal OF, Alshehri MA. Efficacy of high intensity laser therapy in the treatment of male with osteopenia or osteoporosis: a randomized placebo-controlled trial. J. Phys. Ther. Sci. 2017, 29: 1675–1679.
72. Thabet AAM, Mohamed MSE, Ali MMI, Helal OF. High Intensity Laser Versus low Intensity Laser Therapy in Management of Postmenopausal Osteoporosis. Bull. Fac. Ph. Th. Cairo Univ., 2011, Vol. 16, No.1
73. Ganzi GP, Gurin E. Hilt treatment in epicondylitis. I Convegno Nazionale Terapia Hilt, Firenze 2006, pp. 53-62.
74. Dundar U, Turkmen U, Toktas H, Ulasli AM, Solak O. Lasers Effectiveness of high-intensity laser therapy and splinting in lateral epicondylitis; a prospective, randomized, controlled study. Med Sci, 2015,30:1097–1107 DOI 10.1007/s10103-015-1716-7
75. Yesil H, Dundar U, Toktas H, Eyvaz N, Yeşil M. The effect of high intensity laser therapy in the management of painful calcaneal spur: a double blind, placebo-controlled study. Lasers in Medical Science, 2020, 35: 841–852. https://doi.org/10.1007/s10103-019-02870-w.
76. Akkurt F, Akkurt HE, Yılmaz H, Olgun Y and Sen Z. Efficacy of High-Intensity Laser Therapy and Silicone Insole in Plantar Fasciitis. Int J Phys Med Rehabil 2018, 6:5 DOI: 10.4172/2329-9096.1000484.
77. Rivetti V. Management of Tietze syndrome pain with Hilterapia® – a case report. Energy for Health, 2020, 20: 10-11.
78. Bodini G, Croce AM. La sindrome del tunnel carpale: trattamento con HIlterapia. Spera Medical Journal 2007, 5:16-20.
79. Gabrhel J, Popracová Z, Tauchmannová H, Nemšák M. Hilterapia® - high intensity laser therapy in the treatment of severe tendon and ligament injuries. Energy for Health, 2014, 13:20-25.
80. Valent A. Management of chronic Achilles tendinopathy with High Intensity Laser Therapy (HILT®) and eccentric exercises. Energy for Health 2014, 13: 10-13.
81. Mezzalira M, Germano S. Report on the use of HIRO TT: validation of practice experience. Energy for Health. 2020, 20: 12-15.
82. Song HJ, Seo HJ, Lee Y, Kim SK. Effectiveness of high-intensity laser therapy in the treatment of musculoskeletal disorders. A systematic review and meta-analysis of randomized controlled trials. Medicine 2018, 97:51(e13126).
83. Thabet AAEM, Mahran HG,Ebid AA, Alshehri MA. Effect of pulsed high intensity laser therapy on delayed caesarean section healing in diabetic women. J. Phys. Ther. Sci. 2018, 30: 570–575.
84. Alayat MS, El-Sodany AM, Ebid AA, Shousha TM, Abdelgalil AA, Alhasan H, Alshehri MA. Efficacy of high intensity laser therapy in the management of foot ulcers: a systematic review. J. Phys. Ther. Sci. 2018, 30: 1341–1345.
85. Ebida AA,Thabet AA, Helal OF. Effect of pulsed high intensity Nd:YAG laser in treatment of chronic diabetic foot ulcer. Energy for Health 2011, 7: 25-30.
86. Ebid A, El Kafi EMA, Alayat M. Effect of Pulsed Nd:YAG Laser in the Treatment of Neuropathic Foot Ulcers in Children with Spina Bifida: A Ran-

domized Controlled Study. Photomedicine and Laser Surgery 2013, 31(12) DOI:10.1089/pho.2013.3533
87. Bodini D, Croce AM. Treatment of proprioceptive balance disorders: comparison between kinesistherapy and Hilterapia®. Energy for Health, 2009, 3: 6-9.
88. Ebid AA, El-Sodany AM. Long-term effect of pulsed high-intensity laser therapy in the treatment of post-mastectomy pain syndrome: a double blind, placebo-control, randomized study. Lasers Med Sci 2015, 30:1747–1755. DOI 10.1007/s10103-015-1780-z.
89. Ebid AA, Ibrahim AR, Omar MT, El Baky AMA. Long-term effects of pulsed high-intensity laser therapy in the treatment of post-burn pruritus: a double-blind, placebo-controlled, randomized study. Lasers Med Sci 2017, 32:693–701. DOI 10.1007/s10103-017-2172-3.
90. Nicolaou V. Hilterapia® and lymphoedema. Energy for Health, 2010, 5:32-33.
91. Demartis F, De Cristofaro R, Fasulo M., Boccalandro E, Cobianco A, Santagostino E. Analgesic effects of high intensity laser therapy (hilt) for chronic hemophilic artrhopathy: a pilot study on safety, tolerability and clinical outcomes. Energy for Health 2013, 11: 4-8.
92. Elnaggar R K. Pulsed Nd:YAG laser: effects on pain, postural stability, and weight-bearing pattern in children with hemophilic ankle arthropathy. Lasers in Medical Science 2020, 35:1075–1083.
93. Alayat MSM, Elsodany AM, El Fiky AA. Efficacy of high and low level laser therapy in the treatment of Bell's palsy: A randomized double blind placebo-controlled trial. Lasers Med Sci 2014, 29:335–342 DOI 10.1007/s10103-013-1352-z
94. Germano S, Broglia D, Salvò F, Firpo E, Mezzali M. Pulsed Nd:YAG laser and thermal exchange: a new therapeutic strategy in pain manegement. Experience on 100 patients. Energy for Health 2018, 17: 12-20.