Key words: HILT, laser treatment, photobioactivation, tissue welding

The HILT domain by the pulse intensity fluence (pif) formula.

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ABSTRACT

Laser therapy is often used to give relief in acute and chronic pain, increase the speed, quality and tensile strength of tissue repair, and improve the function of damaged neurological tissue. Treatment with laser beams is painless and causes neither a macro-chemical change nor damage in the tissue. In view of the unsatisfactory results obtained with Low Level Laser Therapy (LLLT) in deeper tissue regeneration, we studied the possible use of power laser designing a more efficient system and a new method of treating, faster and more consistently reproducible results. Specifically, LLLT can only produce either the photochemical effect or the photochemical and photo-thermal effects but not all three. Pulsed emission can be used to induce photomechanical effects. HILT principally induces photomechanical and photo-thermal by means of pulsed laser emission characterized by a particular shape of pulse. Unfortunately the formulas commonly used in the laser matter are not able to perfectly describe the HILT pulse shape and its timing and spatial distribution.

The aim of our study was to define a phenomenological formula to describe HILT pulse shape putting together both bi-three dimensional and its timing resolution.

From our experimental data, collected in more of ten years, we extrapolated a mathematical common denominator able to synthesize, in just one formula (PIF), the HILT pulse features.

Applying PIF formula we simulated different possible configurations for HILT, we related it with our clinical and experimental data and we defined the HILT domain in terms of antinflammatory effect, tissue repair, tissue regeneration and toxic dose.

Correlating these data with biological effects of HILT we defined the HILT domains, which are, in our opinion, useful to exactly define the biological capabilities of HILT.

In our opinion, PIF formula is easier to better understand HILT features and its differences with LLLT and Continuous Wave (CW) Power Lasers.

INTRODUCTION

High intensity laser therapy (HILT) or HILT systems was born to induce a non invasive regenerative therapy with a non-painful and non-invasive therapeutic system. Secondary objective of the HILT is the treatment of deep lesions, such as joint lesions.

Since their discovery lasers have been advocated as alternatives to conventional clinical methods for a wide range of medical applications. For many years high powered and highly focused lasers have been used to cut and separate tissue in many surgical techniques. More recently, therapeutic and biostimulating properties of high power laser were discovered. It is believed that laser radiation stimulates several metabolic processes, including cell proliferation and cell differentiation, synthesis of collagen and other proteins, immunomodulation.

LLLT has become a popular treatment in a variety of medical disciplines. This therapy is used with some success but results are obtained only slowly and are inconsistent. The degree of therapeutic effect achieved is variable and heavily depends upon the dosage of radiation, exposure rhythm, and the distance of the treated tissue from the laser source. Applications of several minutes are repeated at intervals of several days and often repeated for months.

In view of the unsatisfactory results obtained with LLLT we studied the possible use of power laser designing a more efficient device and a better method of laser treatment to have faster and more consistently reproducible results. Specifically, LLLT can only produce either the photochemical effect or the photochemical and photo-thermal effects but not all three.

Pulsed emission can be used to induce also photomechanical effects. HILT principally induce photomechanical and photo-thermal effects by means of pulsed laser emission characterized by a particular shape of pulse.

Unfortunately, the formulas commonly used in the laser matter are not able to perfectly describe the

HILT pulse shape and its distribution in time and space.
The aim of our work was to identify rational criteria to design an ideal laser for HILT.
The problem is that, in this matter, there are multiple variables like: wavelength, spot size, energy per pulse, peak power and, pulse duration time. Therefore, to argue in this field it is necessary to explain reason of our choices related to the biological effects.
From our experimental outcomes, collected in more of ten years, we tried to extrapolate a physical common denominator able to synthesize, in just one formula, the HILT pulse shape.
In conclusion, the aim of our study was to define a phenomenological formula able to describe Hilterapia pulse shape putting together both bi-three dimensional and timing resolution.
The Average Power Density, often considered in literature, is defined as the time rate of flow of radiant energy averaged over one full period for square cm (recall that frequency is the inverse of period) [W/cm^2]. Power Density, which is also named radiant flux density, does not supply sufficient information about the temporal and spatial shapes of the pulses.[1]
Peak Pulse Intensity defined as the rate energy flow in every pulse for square cm of the spot area [W/cm^2], gives an idea of the 3D spatial distribution, but it fails to provide information regarding the energetic content of the pulse [J] and its time distribution [s]. [1]
The Pulse Fluence defined as the radiative flux integrated over time per unit area, or else pulse energetic content divided by the spot size [J/cm^2], indicates a mean power during the pulse but does not give the intensity [W/cm^2], or instantaneous power (per unit area). For example, the same fluence may be common to an infinite number of different pulses that have different peak powers and pulse durations τ–on.
We then correlated our experimental results, collected over more ten years of study, with the laser settings applied. After this we extrapolated the common data capable of describing the incident light intensity on the spot size (two-dimensional data), the average light concentration on the spherical light segment that symbolizes the three-dimensional distribution of the light in the subcutaneous tissues (three-dimensional data), and the relationship between the turned off phase (τ-off) and the turned on phase (τ-on) of the light over the entire duration (the period T= τ-on + τ-off) of the laser pulse. [1]

MATERIALS AND METHODS

Experimental trials carried out with HILT in vitro and, in vivo on both animal and human models enabled us to draw a map of the our formula.
Unfortunately the formulas commonly used in the laser matter are not able to perfectly describe the Hilterapia pulse shape and its timing and spatial distribution.
We then created an electronic calculation sheet (Microsoft Excel®) and entered the settings used for each individual session carried out.
Table I illustrates the 29 elements taken into consideration for our analysis.
To assess light distribution into the tissue we used the absorption coefficient data from K.F. Palmer and D. Williams [2]. Additional information on the penetration depth of different laser sources is presented in J. Tuner & L. Hode and Pratesi [3, 4].
Looking for a common denominator able to summarize the HILT features in the space and timing we decided to consider:

1) The skin incident light, or the bi-dimensional element,
2) The three-dimensional light concentration into the subcutaneous tissues, and
3) The relationship between the turned off phase and the pulse time.

The first element, which defines the

Pulse Energy [J]	Spot Size [mm]	Sphere Ray [cm]	Area [cm^2]	Volume Segment Sphere Vks [cm^3]	Water Abs. α [cm-1]	Vks α	Light Penetration Depth [cm]	τ-on [μs]	τ-on [s]
τ-off [s]	τ-on * τ-off	Ep / τ-off	τ-off/Ep	Ep/Vks 1/α	Duty	[1-D]	Peak Power/τ-on	Hz	Peak Power [W]
Pulse Fluence [J/cm^2]	Pulse Fluence [J/cm^2]	Pulse Fluence [J/cm^2]	Pulse Fluence [J/cm^2]	Pulse Fluence [J/cm^2]	Pulse Fluence [J/cm^2]	Pulse Fluence [J/cm^2]	Pulse Fluence [J/cm^2]	Pulse Fluence [J/cm^2]	Pulse Fluence [J/cm^2]

Table I. Table shows parameters considered in our analysis.

	Pulse Energy [J]	Spot Size [mm]	Sphere Ray [cm]	Area [cm²]	Volume Segment Sphere Vks [cm³]	Water Abs. α [cm⁻¹]	Vks α	Light Penetration Depth [cm]	τ-on [µs]	τ-on [s]
LLLT	0.01	5	0.25	0.20	0.16	0.5	0.31469	0.70	1000	1.00E-03
Antinflammatory	0.1	5	0.25	0.20	0.16	0.14	1.12388	1.07	200	0.0002
Chicken study	0.35	5	0.25	0.20	0.16	0.14	1.12388	1.07	120	0.00012
Toxic dose, chicken	0.35	4	0.2	0.13	0.08	0.14	0.57543	0.86	120	0.00012
HCT8 & VERO	0.15	6	0.3	0.28	0.14	0.14	1.00980	1.04	200	0.0002
Humans	0.35	5	0.25	0.20	0.16	0.14	1.12388	1.07	120	0.00012
1st Sheep study	2	10	0.5	0.79	1.26	0.14	8.99107	2.15	130	0.00013
Chondrocytes	0.15	8	0.4	0.50	0.25	0.14	1.79520	1.26	200	0.0002
2nd Sheep study	2	10	0.5	0.79	1.26	0.14	8.99107	2.15	130	0.00013
	τ-off [s]	**τ-on * τ-off**	**Ep / τ-off**	**τ-off/Ep**	**Ep/Vks 1/α**	**Duty**	**[1-D]**	**Peak Power/τ-on**	**Hz**	**Peak Power [W]**
LLLT	9.00E-03	0.000009	1.111111	0.900000	0.031778	10.00%	90.00%	50,930	100.00	10
Antinflammatory	0.0524316	1.0486E-05	1.907248	0.524316	0.088977	0.38%	99.62%	12,732,395	19.00	500
Chicken study	0.0332133	3.9856E-06	10.537937	0.094895	0.311420	0.36%	99.64%	123,787,178	30.00	2,917
Toxic dose, chicken	0.0332133	3.9856E-06	10.537937	0.094895	0.608242	0.36%	99.64%	193,417,466	30.00	2,917
HCT8 & VERO	0.0664667		2.241725	0.446085	0.147554	0.30%	99.70%	13,181,175	15	745
Humans	0.0332133	3.9856E-06	10.537937	0.094895	0.311420	0.36%	99.64%	123,787,178	30.00	2,917
1st Sheep study	0.49987	6.4983E-05	4.001040	0.249935	0.222443	0.03%	99.97%	150,679,236	2.00	15,385
Chondrocytes	0.4998		0.298119	3.354362	0.082999	0.04%	99.96%	7,414,411	2	745
2nd Sheep study	0.49987	6.4983E-05	4.001040	0.249935	0.222443	0.03%	99.97%	150,679,236	2.00	15,385
	Average Power [W]	**Average I [W/cm²]**	**Pulse Fluence [J/cm²]**	**Peak Intensity [W/cm²]**	**Total fluence [J/cm²]**	**Tx Area [cm²]**	**Energy delivered [J]**	**Exposure time [min.]**	**Exposure Time [s]**	**PIF [J/cm³]²**
LLLT	1.00	5.09	0.05	51	10	50	500	8.3	500.0	0.0015
Antinflammatory	2	9.68	0.51	2,546	10	50	500	4.4	263.2	0.05
Chicken study	10.5	53.48	1.78	14,854	10	50	500	0.8	47.6	0.55
Toxic dose, chicken	10.5	83.56	2.79	23,210	10	50	500	0.8	47.6	1.69
HCT8 & VERO	2.23500	7.91	0.527	2,636	10	200	109	0.8	48.8	0.78
Humans	10.5	53.48	1.78	14,854	10	50	500	0.8	47.6	0.55
1st Sheep study	4	5.09	2.55	19,588	10	200	2000	8.3	500.0	0.57
Chondrocytes	0.29800	0.59	0.297	1,483	10	200	109	6.1	365.8	0.25
2nd Sheep study	4	5.09	2.55	19,588	10	200	2000	8.3	500.0	0.57

Table II shows parameters and laser settings used in our experimental studies carried out so far.

intensity of light within the target region, is a two dimensional energy per pulse:

$$I_p \cdot \tau on$$

Where Ip is the Peak Intensity (Wp/cm²) (Peak Power [Wp] divided by the surface area of the spot [cm²]), and, τ-on is the Pulse duration.

To further define the pulse into a three dimensional relationship (Ep), the energy per pulse, by the irradiated tissue volume (Vks). Giving the formula:

$$\frac{E_p}{V_{ks}} \cdot \alpha$$

Where Vks is the Volume of the Sphere segment (hemi-discoid). This volume of tissue is an area which is being radiated by the laser. The Volume Vks is calculated by:

$$V_{ks} = 10.07\ R_{sp}^{3}$$

where Rsp is the spot size ray and h = 2/3 of sphere ray.

$\frac{E_p}{V_{ks}}$ must be considered in relation to the wavelength (λ). For this reason we consider Vks as an equivalent of the Volume normalized to the water absorption coefficient α, that varies in relation to λ. For example, according to Palmer data [2], for λ of 1,064 nm α is 0.14 cm^{-1} while for λ 980 nm α is 0.5 cm^{-1}.

Third element of the formula:

$$\frac{\tau off}{T}$$

Describes the relationship between the off phase and T. T = τ-on + τ-off.

It is important to express this relationship between turned off phase and total pulse period of time (T). The turned off phase maintains the tissue temperature. It is important that the tissue does not over-heat and cause potential thermal damage.

Therefore, we can write the formula as:

$$PIF\left(\frac{J}{cm^3}\right)^2 = I_p \tau on \frac{E}{10.07 r^3} \alpha \cdot \frac{\tau_{off}}{\tau_{off} + \tau_{on}}$$

RESULTS

Graph 1 below shows the correlation between the characteristics of the HILT pulse, expressed in PIF $[J/cm^3]^2$, and the biological effects observed in experimental trials. Each data point represents the PIF of a pulsed laser beam applied in a particular setting, e.g., to chickens, sheep, or humans in vivo. The vertical lines extending from each point are error bars. The dashed horizontal lines indicate a range of acceptable PIFs for tissue regeneration: from just under 0.2 $[J/cm^3]^2$ to just under 1.0 $[J/cm^3]^2$. Below 0.1 $[J/cm^3]^2$, there may be just an anti-inflammatory effect and not a regenerative effect; whereas for PIFs exceeding 1.0 $[J/cm^3]^2$ there may be a histo-toxic effect.

Applying the PIF formula we can also to carried out a fast and easy comparison among different shape of pulses and different wavelengths. PIF values in Table III and Table IV show the results of our simulations.

We carried out also a comparison between PW and CW emission at the same wavelength (λ: 1,064 nm).

Table V shows that the value is 6 order of factors lowers in CW than in the HILT.

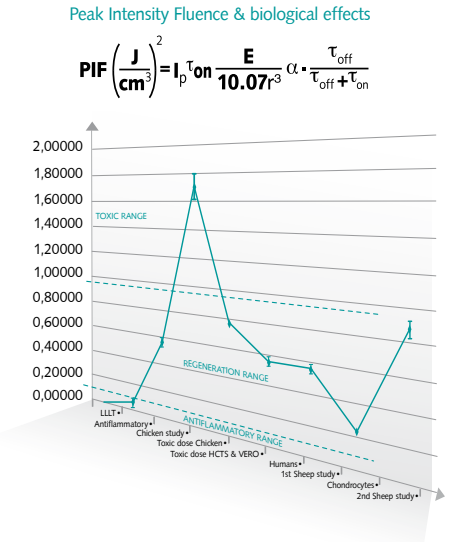

Fig.1. This graph shows the relationship between the pulse HILT features, expressed as PIF $[J/cm^3]^2$, and HILT biological effects observed in our experimental trials.

Table III, PIF value for: λ 910 nm, Average Power 5 W, Peak Power 1400 W, τ-on 200 ns	
E/pulse [J]	0.0002857
Diam. Spot Size [mm]	20
Spot size area [cm^2]	3.141592654
Ray [cm]	1
Vks [cm^3]	0.16
α [cm^{-1}]	0.075
Duty [%]	0.35%
τ-on [s]	0.000000200
τ–off [s]	0.00005694
PRF [Hz]	17500
Peak Power [W]	1,429
Average Power [W]	5
Average I [W/cm^2]	1.591549431
Pulse Fluence [J/cm^2]	0.00009095
Peak Intensity [W/cm^2]	454.73
PIF $[J/cm^3]^2$	1.93E-10

Table IV, PIF value for: λ 1064 nm, Average Power 5 W, Peak Power 1400 W, τ-on 120 us	
E/pulse [J]	0.1666667
Diam. Spot Size [mm]	5
Spot size area [cm^2]	0.196349541
Ray [cm]	0.25
Vks [cm^3]	0.16
α [cm^{-1}]	0.14
Duty [%]	0.36%
τ-on [s]	0.000120000
τ–off [s]	0.03321333
PRF [Hz]	30
Peak Power [W]	1,389
Average Power [W]	5
Average I [W/cm^2]	25.46479089
Pulse Fluence [J/cm^2]	0.84882636
Peak Intensity [W/cm^2]	7,073.55
PIF $[J/cm^3]^2$	1.25E-01

Table V, PIF value for: λ 1,064 nm, CW, Average Power 5 W	
E/pulse [J]	5.0000000
Diam. Spot Size [mm]	5
Spot size area [cm^2]	0.196349541
Ray [cm]	0.25
Vks [cm^3]	0.16
α [cm^{-1}]	0.14
Duty [%]	100.00%
τ-on [s]	0.999999999
τ–off [s]	0.00000000
PRF [Hz]	1
Peak Power [W]	5
Average Power [W]	5
Average I [W/cm^2]	25.46
Pulse Fluence [J/cm^2]	25.46
Peak Intensity [W/cm^2]	25.46
PIF $[J/cm^3]^2$	1.13E-07

DISCUSSION

From our experimental outcomes we observed that in order to have a regenerative effect on the tissues and a promote cell differentiation, pulses provided with HILT should have a Peak Intensity Fluence (PIF) ranging from 0.1 $[J/cm^3]^2$ to 1 $[J/cm^3]^2$. PIFs over 1.0 $[J/cm^3]^2$ may be dangerous. PIFs below 0.1 may have only an anti-inflammatory effect. In contrast, LLLT systems used for pain management have a PIF between 0.0 (i.e., the beams are continuous-wave beams) and 0.0015 $[J/cm^3]^2$, or approximately 100 to 1000 times lower than the PIF for Hilterapia.

In view of the unsatisfactory results

obtained with LLLT we studied the possible use of power laser designing a more efficient device and a better method of laser treatment to have faster and more consistently reproducible results. Specifically, LLLT mostly produces photochemical effects or photochemical and photo-thermal effects, but it is not able to produce the photomechanical ones.

Pulsed emission must be used to induce photomechanical effect, possibly associated with others. In HILT, thanks to the particular shape of pulse, photo-thermal and photomechanical effects are predominant.

An interesting application of the PIF formula is to disclose differences between two apparently similar lasers used in therapy: HILT vs. a near infrared (λ: 910 nm) pulsed laser, 5 W of average power and 1,400 W in peak power (see Table III). Comparing this laser with a laser used for Hilterapia at the same average power (5 W) and at the same peak power (1,400 W) we can easily disclose the very big difference between them. In fact, for the 910 nm laser the PIF value is 9 order of magnitude lower (1.93 * 10-10) than the HILT one (1.25 * 10-1).

Moreover, we applied the same method, to compare Hilterapia pulse and Nd:YAG Continuous Wave (CW) laser at the same parameters (average power: 5 W, spot size 5 mm in diameter). Table V shows the PIF value of the CW laser (PIF : 1.13 * 10-7) that is 6 order of magnitude lower than the laser used for Hilterapia.

These simple examples show clearly as could be useful the use of the PIF formula to disclose the big differences among so many parameters used in the laser field. Talking about the peak power and average power it is not exhaustive of the laser features.

In our case, to be able to induce an effective photomechanical stimulation of tissue structures, in particular the extracellular environment, it is necessary to have a pulse shape with certain features. It is necessary to deliver a proper amount of energy per pulse in a right time involving as much tissue as possible.

To do this and to be able to stimulate tissue regeneration in a deeper soft tissue it is necessary to manage very well the laser light features and its interaction with tissues.

ABSORPTION COEFFICIENT

The absorption coefficient (α) is important to understand the choice of the wavelength and the spot size and the relationship between themselves.

According to Dörschel [5] the optical penetration depth (x) of the light is inversely proportional to the index of water absorption (α) coefficient, i.e., $x = 1/\alpha$ when water is the main chromophore. Therefore, the higher the water absorption coefficient, the poorer the penetration of the radiation through the tissue.

In order to achieve the greatest possible penetration, the laser light radiation is preferably minimally absorbed by the tissue chromophores, i.e., the wavelength of the laser light should not correspond to peak absorption wavelengths of the tissue chromophores.

Zhao et al. [6] described the 3.3 mm interracial human skin light transmittance for beams of visible and near-infrared wavelengths. Similar results hold for human skin with lighter colors, e.g., skin from European, African and Asian subjects, although the variation in transmittance is especially significant with darker skin, that is, subjects with hypermelanic skins (African skins). Generally, transmittance increases with beam diameter and, independently, with wavelength. Maximum transmittance occurs for beams at λ = 1064 nm and beam diameters of 12 mm. This wavelength is only partially absorbed by the skin, melanin and subcutaneous fat and is able to go into deepest tissues (i.e., joint cartilage).

PHOTOMECHANICAL EFFECT

One important aspect underlying Hilterapia is to have a photomechanical effect at a therapeutic level on the tissues and/or cells being treated by the laser light. With a photomechanical effect, at least part of the energy of a laser light can be converted into one or more forms of mechanical forces on the tissues and/or cells being treated by the laser light.

Such mechanical forces can have a physical effect on the cells and/or tissues being treated and cause the cells and/or tissues to change shape and/or size, resulting in such effects as stimulating cell metabolism, proliferation, differentiation, and then tissue regeneration.

According to a first aspect, by applying an appropriately defocused laser beam, having specific characteristics, at a given area of the tissue epidermis of a patient, the laser beam can have a photomechanical effect, possibly associated with others, on the tissues and/or cells being treated, in particular, those tissues and/or cells that are located deeply within the body of a patient under treatment, e.g., the cartilage tissue.

A laser beam directed orthogonal to the surface of the tissue is partly reflected back due to the variation of refraction index when passing from the surrounding ambient (air) and the tissue. The remaining fraction of the laser beam energy is transmitted to and through the tissue and is absorbed and diffused several times by different chemical substances contained in the tissue.

When the pulsed laser beam impacts the second medium, an elastic pressure wave is immediately created in the second medium itself and propagates from the surface deep down into the medium. The amplitude of the wave is directly proportional to the intensity of the light beam and inversely proportional to the pulse duration time. The wave amplitude also depends on the light properties (λ) and the physical-chemical structure of the second medium.

Following is a formula describing the relationship between the sound wave shape created in the tissue hit by a high-intensity pulsed laser beam:

$$p_2(z,t) = \rho_2 v_2^2 \left(\frac{\alpha \sqrt{\hat{k}_1 \hat{k}_2}}{K_1 \sqrt{\hat{k}_2} + K_2 \sqrt{\hat{k}_1}} \frac{1}{v_2 + r v_1} \left(\beta_1 \sqrt{\hat{k}_1} + \beta_2 \sqrt{\hat{k}_2} \right) \right) I\left(t - \frac{z}{v_2} \right)$$

where the thermal diffusion coefficient is $\hat{k}_i = \frac{K_i}{(\rho_i c_i)}$; the dimensional coefficient is $r = \frac{(\rho_2 v^2)}{(\rho_1 v_1^2)}$; I is laser pulse intensity; c_i is specific heat; β_i is linear expansion coefficient; K_i is thermal conductivity; ρ_i is density; v_i is sound speed; α is optical absorption coefficient of the tissue; z is depth; and t is time.

The relationships between incident laser light and the photomechanical or photoacoustic effects generated in the tissue include: (1) a direct relationship between the intensity of the incident light and the intensity of the transitory mechanical deformation created in the tissue; and (2) a direct relationship between the frequency of the wave and the pulse duration (τ_{on}) of the laser. That is, the shape of the acoustic wave is related to the shape of the laser pulse. The intensity of the mechanical effect may also depend on the optical, thermal, and mechanical features of the medium.

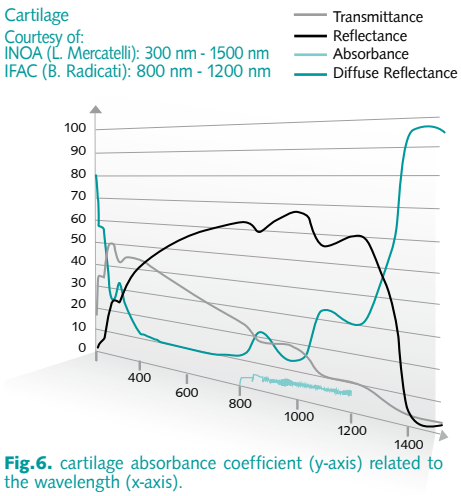

Fig.6. cartilage absorbance coefficient (y-axis) related to the wavelength (x-axis).

When the peak power of the pulse, the pulse duty cycle (the fractional amount of the time of the laser is "on" during any given period: τ/T) and the pulse frequency are properly selected, the photomechanical effects in the irradiated tissues can substantially result in transitory modifications of extracellular matrix (ECM) properties and organization which affect cell behaviour.

It is very important to point out that an intimate connection exists between ECM and cells, in the case of cartilage between ECM and chondrocytes. Any spatial deformation of the ECM is therefore automatically transferred to the cells as a mechanical stimulus.

Graph (6) below shows the cartilage absorbance coefficient (y-axis) related to the wavelength (x-axis). We can notice that in the near infrared, compared to the visible spectra, we have peak absorption coefficient.

When a pulsed high intensity laser beam with an appropriate wavelength that falls within one of the absorption peaks of cartilage (e.g., a wavelength of 1064 nm) is used to treat a cartilage tissue, it is mostly absorbed by ECM. This specific absorption by ECM via the pulsed emitting of this particular laser light is responsible for immediate tissue dilatation followed by contraction during the cooling phase. This transitory spatial deformation of the ECM is automatically transferred to the cells as a mechanical stimulus.

It is known that the musculoskeletal system, which includes bones, cartilage, skeletal muscles and ligaments, responds to such mechanical stimulation with changes in metabolism, cytoskeletal organization, rate of proliferation, and state of differentiation during development. Chondrocytes also respond to mechanical forces by changing their metabolism, their state of differentiation, and their proliferation. They respond differently to mechanical force, depending on the magnitude, frequency, and mode of mechanical stimulation [7-27].

PHOTOTHERMAL EFFECT

The laser light is at least partially converted into a thermal wave, which is responsible for the photoexpansion effect observed with outright temperature increases of up to 41°C. During τ-off time, there is a rapid cooling and the medium (e.g., the tissues) moves towards a photocontraction effect.

An additional important parameter having an influence on thermal accumulation and therefore on the temperature increase is the overall volume of tissue under treatment. Keeping the irradiated surface (i.e., the laser spot) and the irradiated energy constant, an increase of the peak power per pulse increases the irradiated volume. The reason for this is that a higher peak power provokes a deeper penetration of the laser in the tissue, and therefore an increase in the overall volume absorbing the laser energy.

The larger the irradiated volume the smaller the temperature increase. Therefore, and contrary to what might appear at first glance, an increase of the peak power of each laser pulse improves the conditions of treatment from the point of view of tissue temperature control.

It has been therefore recognized that in order to obtain an effective treatment of the deep tissues without damaging more superficial and surrounding tissues, we must use a pulsed laser

source with low pulse frequency, high peak power and short pulses (i.e., low duty cycle values: short τ-on times and long τ-off times).
The area of the laser spot is also very important in order to maximize the greatest possible penetration, while minimizing the amount of scatter. Zhao [6] demonstrated that by increasing the diameter of the spot size there is a reduction in the scattering angle (the larger the diameter of the spot, the lower the scattering angle). This results in a deeper penetration, more uniform diffusion of the radiation in the tissue, and therefore an increased therapeutic effect.
In addition, because $\Delta T = \Delta Q/(ck \times m)$ at the same energy per pulse, the greater the volume treated, the lower the thermal increase to the tissues.
One way to increase the volume treated, especially when the penetration depth is preferably kept at a constant value, is to increase the spot size. By properly selecting the above discussed parameters, the tissue temperature in the treated volume is kept below a certain temperature, e.g., 42°C or even lower, and preferably below 40°C.

CONCLUSION

The main object of the Hilterapia is the non invasive regenerative therapy with a non-painful and non-invasive therapeutic system. Secondary objectives of the HILT is treatment of deep lesions, such as lesions of the articular cartilage. This can be obtained thanks to Hilt's photomechanical effects which are predominant on the others.
While all therapeutic laser systems can deliver the energy needed to have a photochemical effect on the tissues and/or cells being treated, pulsed high intensity lasers can exert a photomechanical effects of therapeutic value. High peak power values (e.g., those at least 1 kW) and high peak intensity values (e.g., those at least 1 kW/cm^2) allow a pulsed laser light to have a predominant photomechanical effect on the tissues and/or cells being treated, which, per se or in combination with other effects, can achieve extraordinary and unexpected therapeutic results.
In the regenerative field it is critical the relationship between shape of pulse and duty cycle, for example, in a 'in vivo' experiment [28] on knee joint in rats, it has been shown that even an high average power density of 5.8 W/cm^2 may not be sufficient to induce cartilage regeneration.
In conclusion to be able to design an ideal Hilterapia we have to follow some general rules: the deeper the penetration of the laser radiation, the longer the time between subsequent laser pulses, to allow for thermal dissipation; the higher the energy content per laser pulse, the lower the pulse frequency, i.e., the frequency at which the laser pulses are repeated; the higher the power level per pulse, the lower the fluence; the higher the peak power of each pulse, the shorter shall be the pulse duration (low duty cycle); the higher the peak power, at constant spot area, the larger will be the volume interested by the radiation and therefore the lower will be the increase in temperature due to heat accumulation; the higher the energy per pulse, the shorter will be the total exposure time to the laser radiation; and the shorter the total exposure time to the laser radiation, the lower will be the heat accumulation.
Big pulses, characterized by high peak power and a high amount of energy per pulse, are useful for transferring in depth high amount of energy in accordance with Lambert Beer's law. Thermal increase of tissue temperature is directly correlated to the amount of energy supplied. In order to obtain the correct control of the temperature trend while achieving the photomechanical effect during treatment, should be necessary that the PIF is in the range 0.1 – 1 [J/cm^3]^2.

$$\mathbf{PIF}\left(\frac{\mathbf{J}}{\mathbf{cm}^3}\right)^2 = \mathbf{I_p}\,\tau\mathbf{on}\,\frac{\mathbf{E}}{\mathbf{10.07}r^3}\,\alpha\cdot\frac{\tau_{off}}{\tau_{off}+\tau_{on}}$$

High energy delivered in this way is safe and allows for a sudden dramatic dilation of the volume throughout the tissue when the light is on, followed by a cooling beat when the light is off, thereby creating a photomechanical effect.

ACKNOWLEDGEMENTS

We synthetized more of ten years of studies and so, there are many people to say many thanks for them helping in this hard challenge.Roberto Buda, IOR; Antonio Crovace, UNIBA; Emiliano Di Cicco, El.En; Franco Fusi, UNIFI; Daniela Giannessi, IFC-CNR; Sandro Giannini, IOR; Julie Glowacki, Harvard Medical School; Brunella Grigolo, IOR; Leonardo Manetti, El.En; Fabrizio Margheri, El.En; Fabio Martinelli, El.En; Luca Mercatelli, INOA; Monica Monici, ASACampus; Cesare Paolini, DEKA; Steven Reinecke, El.En; Giacomo Rossi, UNICAM; Alessandro Zati, IOR

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