

## Editorial

# A renaissance in low-level laser (light) therapy – LLLT

## Renaissance der Low-Level-Laser(Licht)therapie – LLLT

This special issue on low-level laser (light) therapy (LLLT) has been assembled by soliciting individual contributions from a broad spectrum of specialists in the field throughout the world.

LLLT also known as photobiomodulation, is the drug-free, non-invasive and safe (FDA approved) clinical application of light – usually produced by low to mid power lasers or light emitting diodes (LED) with a power output in the range of 1–500 mW – to a patient to promote tissue regeneration and healing, reduce inflammation and relieve pain. The light is typically of narrow spectral range (1–40 nm bandwidth), in the visible (red) or near infrared (NIR) spectrum (600–1000 nm), and achieves an average power density (irradiance) between 1 mW/cm<sup>2</sup> and 5 W/cm<sup>2</sup> [1].

The reason why the technique is termed “low-level” or “cold laser” therapy is that the optimum level of energy density (J/cm<sup>2</sup>) delivered to the tissues is low when compared to other forms of laser therapy such as those used for ablation, cutting, and thermally coagulating tissue. In general, the power densities used for LLLT are lower than those needed to produce heating of tissue (i.e., <100 mW/cm<sup>2</sup>, depending on wavelength and tissue type), and the total energy delivered to the treated area is usually below 10 J/cm<sup>2</sup>. A common reference is the “Guidelines for Skin Exposure to Laser Light” in the International Standards Manual (IEC-825) which considers an exposure below 200 mW/cm<sup>2</sup> as a safe exposure [2].

LLLT, i.e., the use of low levels of visible or NIR light for reduction of inflammation and pain [3], healing of wounds, muscle and nerve injuries [4], and prevention of tissue damage by reducing cellular apoptosis (for example, due to ischemia and reperfusion injury) [5], has been known for almost 50 years since shortly after the invention of lasers in 1960 [6]. However, despite many reports of positive findings from experiments conducted *in vitro*, in animal models and in randomized controlled clinical trials, the mechanisms of LLLT in biological tissues remains not fully elucidated. It is likely this is due to two main reasons: firstly, the complexity in interpretation of

scientific and clinical data generated in different labs and clinical settings, and secondly, inconsistency in the use of light sources (medical devices) and treatment protocols including, illumination parameters (such as wavelength, fluence, power density, pulse structure, etc.) and the treatment schedule. Unfortunately, these variations led to an increase in the number of negative studies and created some controversy despite the overwhelming number of positive clinical results [7]. It is noteworthy that many pre-clinical and clinical studies have been and still are conducted without proper scientific methodology. Therefore, it is critical that all the characteristics of the light emitted by lasers or LEDs must be specified if data are to be useful. A requirement for a good phototherapy study, using LLLT in the visible or NIR region, whether from a laser, an LED, or a filtered incandescent lamp is to specify everything about the light source, i.e., wavelength(s), total power, power density, total energy, fluence, coherence, pulse structure (both frequency and pulse duration), polarization, area of exposure, illumination time, and treatment repetition [8]. There are published experimental and clinical studies that were conducted with good scientific methodology, but they did not fully describe the light parameters, therefore these studies cannot be repeated or extended by another researcher. Such publications are useless.

In recent years, major advances have been made in understanding the mechanisms that operate at the molecular, cellular and tissue levels during LLLT. Mitochondria are thought to be the main site for the initial effects of light. New discoveries in the last decade have significantly altered our view on mitochondria. They are no longer viewed as only energy-making cellular compartments but rather individual cells-within-the-cell that are involved in numerous signalling and second messenger pathways [9]. In particular, it has been suggested that many important cellular components such as specific enzymes and ion channels [for instance nitric oxide synthase (NOS), ATP-dependent K<sup>+</sup> channels, and poly-(ADP-ribose) polymerase, have a distinct, mitochondrial variant]. For example, the intriguing possibility that mitochondria are significant

sources of nitric oxide (NO) via a unique mitochondrial NOS variant [10] has attracted intense interest among research groups because of the potential for NO to affect functioning of the electron transport chain [11]. One theory maintains that the fundamental molecular process in LLLT is the photodissociation of inhibitory NO from cytochrome c oxidase (unit IV in the respiratory chain) thus increasing ATP production, oxygen consumption, raising mitochondrial membrane potential and modulating production of reactive oxygen species [12]. However, other groups have proposed that cellular membranes, ion channels, porphyrins and flavoproteins may act as primary photoacceptors [13]. There is likely to be more than one reaction involved in the primary mechanisms of LLLT. There are no grounds to believe that only one of these processes occurs when tissue is irradiated. An important question for future research is which of these reactions is responsible for a certain wavelength effect.

One of the key factors that affect the efficacy of LLLT is the realization that there exists a biphasic dose response that directly correlates with the characteristics of the wavelength and the amount of energy absorbed by chromophore or photoacceptor, the light energy density (the radiant exposure or light fluence if measured below the surface) [14]. The important role of biphasic response has been demonstrated by a number of studies in cell culture, animal models, and in clinical studies [15].

Scientific evidence continues to demonstrate that pulsed light does have biological and clinical effects that are different from those of continuous wave (CW) light. Several studies revealed that the LLLT in pulsed wave mode of operation can better penetrate through the melanin and other skin barriers, supporting the hypotheses that pulsing is beneficial in reaching deep target tissue and organs [16].

The data undeniably demonstrate the benefit and the advantageous effect of pulsing in LLLT and are also providing a new insight into the molecular mechanisms associated with the LLLT clinical efficacy [17, 18]. While CW and standard pulsed lasers are limited to <1–2 cm therapeutic efficient penetration, superpulsed infrared laser technology is able to show therapeutic efficacy at up to 10 cm into tissue and benefit target tissues such as: bones, tendons, ligaments and cartilage. Many applications of LLLT may require deep penetration of the light energy, such as: lower back, neck, and hip joint pain and inflammation. Therefore, if the power densities needs to be greater than a few mW/cm<sup>2</sup> and is to be delivered safely to target tissues >5 cm below the skin surface, the effective treatment can only be achieved by using superpulsed lasers [19]. The data indicate that pulsing and particularly

superpulsing is playing an important role in LLLT especially for clinical applications where deep tissue penetration is required.

After a chequered history, the current renaissance in LLLT has been fueled in part by the realization of its immuno-regulatory properties [20], its neuroprotective properties [21] and its preferential action on stem cells and progenitor cells [22]. The spectrum of inflammatory mediators, upregulated in chronic pathological conditions, suggests many routes for future therapeutic intervention. It may be that multiple wavelengths administration, targeted at different inflammatory mechanisms, will prove far more effective than utilization of any single agent. In many cases, the data suggest exploiting targets that so far have not been considered important in the immunological field.

This interesting topic is addressed in a review by Hahm et al. [23] who discuss the role of the “pain, inflammation and immune response (PII) axis” in LLLT. These authors cover the role of inflammatory cytokines, neuropeptides, prostanoids, kinins, and histamine in pain and inflammation and how they may respond to LLLT.

A review by Vatansever and Hamblin [24] discusses the use of far-infrared radiation (FIR,  $\lambda=3\text{--}12\ \mu\text{m}$ ) that has been shown to have biological effects that are similar to the more commonly employed red and NIR wavelengths. In addition to being delivered by light sources, these wavelengths can be produced by FIR-emitting ceramic nanoparticles that can be included into wearable garments that require no external power source.

A third review by Ferraresi et al. [25] concentrates on the effect of LLLT on muscle tissue. Due to the large number of mitochondria present in myocytes, muscles respond very well to LLLT. Treatment can be used both to increase healing, and decrease pain and inflammation after muscle injury and to decrease muscle fatigue and increase performance in athletes.

The first experimental paper is also on LLLT for muscle disorders. Vatansever et al. [26] report that LLLT delivered to aged rats after cryoinjury of the tibialis anterior muscle was able to increase expression of MyoD and VEGF genes, increase capillary density and improve maturation of satellite cells into myoblasts and myotubes.

Marquina et al. [27] carried out a randomized placebo-controlled clinical trial to evaluate a dual wavelength, multiple diode laser cluster probe with five super-pulsed 905 nm NIR laser diodes, each emitting at 40 mW average power and four CW 660 nm visible red laser diodes, each emitting at 25 mW in combination with standard chiropractic techniques on 126 patients with osteoarthritis and knee pain. Improvement was found in visual analog scale for pain relief

and osteoarthritis measures, with a statistical and clinical significance of  $p < 0.01$  from baseline to the 30-day follow-up.

Almuslet and Osman [28] treated 24 patients with chronic plaque psoriasis with PDT using three CW diode lasers with red wavelengths (671–675 nm) with output powers of 16, 50 and 100 mW (8 patients per group) to activate the photosensitizer (Levulan® Kerastick® topical solution). Sixty-two percent of the patients treated with 100 mW achieved complete clearance compared with 25% for those treated with 50 mW and 0% for those treated with 16 mW.

It is a great honor for us to act as guest editors for this special issue. We hope that the fast growing field of LLLT

will continue to offer painless, non-invasive and highly effective drug-free solutions that will be recognized by every major industrialized nation in the world for mitigation of a plethora of medical conditions and will be widely available to the highly trained practitioner to control disease, particularly when conventional therapies have failed or have unacceptable side effects. Many thanks to all the authors for their excellent contributions.

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