



## OPINION ARTICLE

# [Translated article] Fractional Laser for Ablative Resurfacing in Onychomycosis

## Láseres ablativos fraccionados en onicomicosis

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Onychomycosis accounts for up to 50% of all nail conditions and disease. Topical and systemic antifungal drugs are the treatment of choice for this disease.<sup>1</sup> When the infection affects > 60% of the nail, systemic antifungals are necessary, although cure rates are only as high as 40% to 80% after several months of ongoing administration, often accompanied by significant side effects<sup>2</sup>. On the other hand, topical therapy has limited success, mainly due to its poor penetration through the nail plate.<sup>2</sup> The high prevalence of the disease, along with the limited effectiveness of conventional therapies, has led to the development of new approaches to treat the disease more effectively.

For a little over a decade, more clinical studies using laser radiation to treat onychomycosis has been reported. Overall, these studies have demonstrated that although laser radiation is less effective than oral therapy, it lacks any type of systemic toxicity, making it a good option during pregnancy, breastfeeding, comorbidity, and old age.<sup>3</sup> The most effective laser treatments, in increasing order of effectiveness, include the use of diode lasers in the near-infrared range at  $\lambda = 870/930 \text{ nm}$ <sup>4</sup>, followed by the fundamental radiation of Nd:YAG lasers (neodymium-doped yttrium aluminum garnet) at  $\lambda = 1064 \text{ nm}$ , in its Q-switched mode, with a mechanism of action based on selective photothermolysis, which has also proven capable of inhibiting fungal growth.<sup>5</sup> More recently, conclusions from a review show that, although

non-fractionated carbon dioxide (CO<sub>2</sub>) lasers are the most effective ones, they come with unpredictable thermal side effects due to how difficult it is to control their penetration into the affected nail, thus making it necessary to use less invasive options.<sup>6</sup> In vitro studies have also been conducted with femtosecond lasers, which have a higher selectivity for focusing their energy and avoiding collateral damage to the structure of the nail, with very promising results. However, this technology presents very complex availability and maintenance issues in the dermatology clinic.<sup>7</sup>

There is a reasonable number of studies supporting the benefits of fractional ablative lasers (FAL) to treat onychomycosis in combination with conventional topical antifungal therapy or photodynamic therapy.<sup>8–11</sup>

FALs have been developed to maximize the safety profile of ablative procedures while preserving their effectiveness. Their mechanism of action regarding onychomycosis, however, is not fully understood. However, some authors hypothesize that tissue ablation induces direct fungicidal effects.<sup>12,13</sup> By vaporizing the target tissue, FALs cause diffuse remodeling that inhibits fungal growth in the surrounding area.<sup>12,13</sup> Additionally, fungi are extremely sensitive to temperatures > 55 °C; the photothermal effect of fractional lasers can increase the temperature of the target tissue, thus playing a direct role in the destruction of fungi in the nail treated with such laser radiation. Recent suggestions propose that it could also modulate the immune response, eventually improving the prognosis of onychomycosis.<sup>14</sup> Finally, the multiple channels created as a result of their fractional ablative effect increase the contact area between the topical antifungal formulation and the nail surface, thus improving the penetration of antifungal agents

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or photosensitizers through the nail plate to reach the nail matrix or bed,<sup>15</sup> resulting in improved treatment efficacy.

A deep understanding of the structure of the nail plate and laser-tissue interactions is crucial to address the challenges posed by laser-based treatments and topical drug administration. There is a growing interest in understanding the mechanisms of action of FALs at both molecular and cellular levels, and how they interact with nail tissue. This is a complex process due to the wide therapeutic range made possible by the numerous parameters that need to be adjusted. This is the main difficulty when designing effective protocols. On the one hand, parameters associated with laser radiation need to be taken into consideration, such as wavelength, total power, power density, total energy, energy density, pulse parameters (frequency and pulse duration), and pixelation level.<sup>16</sup> Additionally, tissue-related parameters must be considered, including the dimension of the affected tissue area, the number of sessions applied, and the frequency of session repetition.

FAL devices currently used include erbium-doped yttrium aluminum garnet (Er:YAG) lasers ( $\lambda = 2940\text{ nm}$ ) and carbon dioxide (CO<sub>2</sub>) lasers ( $\lambda = 10600\text{ nm}$ ). Both lasers emit in the infrared range, with their wavelengths being absorbed by water (the target chromophore represents 10% to 20% of the content of the nail plate) and ablating the nail in a fractionated manner, creating microscopic vertical channels surrounded by a coagulation area.<sup>17</sup> Thanks to their longer wavelength, CO<sub>2</sub> lasers penetrate deeper into the tissue, allowing for more heat deposition and a greater amount of remodeled tissue. Er:YAG lasers emit at a wavelength that is close to the water absorption peak—target chromophore—( $\lambda \sim 3000\text{ nm}$ ), which gives them a safer profile since most energy is absorbed by the epidermis and papillary dermis, resulting in better ablation depth control and less underlying thermal damage. In the field of onychomycosis, more studies are needed to determine which laser is more effective, although most studies to date have used CO<sub>2</sub> lasers, possibly due to their wider availability in clinical settings. In any case, thanks to the higher keratin density and lower water content in nails compared to the skin, higher fluences are required with both types of lasers when specifically treating nails to achieve effective ablation.

The introduction of a keratolytic agent such as urea, applied in occlusion before FAL irradiation, enhances ablation and the fungicidal effect.<sup>18</sup> Urea, as a hygroscopic agent, softens the nail plate and retains water (FAL chromophore) in depth, thus facilitating ablation and remodeling of the affected nail.<sup>18</sup>

The FAL-assisted drug/photosensitizer release has the potential to improve the management of onychomycosis.<sup>16</sup> To maximize drug delivery, two parameters that control the efficacy profile of the photoablative effect can be optimized: density and depth of the ablation zone matrix. The former represents the area of ablated nail, which can be regulated by the number of channels generated per unit of nail surface. The latter represents the extent of the channels through the nail and is mainly controlled by the applied wavelength, power, power density, energy, fluence, pulse duration, and beam profile.<sup>16</sup>

The FAL-assisted drug release process involves in not stranger to risks either. First, the channels facilitate communication with the vascular system of the nail bed, thus

leading to systemic absorption, which means that the potential systemic toxicity of topically applied drugs needs to be considered. On the other hand, FAL breaks the nail barrier, thus potentially introducing pathogenic microorganisms found on its surface or in non-sterilized topical preparations. This type of administration should only be considered in well-controlled environments, using active ingredients suitable for delivery, at an appropriate concentration, and in a sterile vehicle.<sup>19</sup> As long as these pharmaceutical characteristics are maintained, the number of sessions applied is often adjusted based on the severity of onychomycosis, always controlling the use of suitable laser parameters.

It is possible to adapt topical therapies to specific skin diseases, controlling and customizing laser-tissue interactions with these lasers. The induced channels are long and wide enough to distribute not only drugs but also macromolecules, nano- and microparticles, and cells. The channels can be actively filled along their entire length with physical pressure techniques, thus allowing sustained drug release into the nail bed.<sup>20</sup> The FAL-assisted drug delivery modality is a significant technological advancement, with the potential to become a technology with a wide range of applications leading to topical therapy optimization for numerous dermatological patients.

Based on everything we have discussed to this point we can conclude that there is a foundational knowledge to support the beneficial effects of FALs to treat onychomycosis. This knowledge should be conveyed to health professionals so they can consider this innovative technology in their routine clinical practice, especially in patients who do not wish to undergo or are contraindicated for oral antifungal therapy, which is much more invasive. We should mention that the studies published so far are insufficient to establish a general dosing regimen for this laser radiation due to the large number of parameters that need to be considered. Therefore, due to the significant potential of this technology, there is a need to increase the amount and systematic nature of clinical research in this field, first to clarify the mechanism of action through which FALs show potential antifungal properties, and eventually to define the optimal laser parameters for the curative process of onychomycosis, along with topical and photodynamic therapy.

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