Efficacy and safety of red and infrared light in the adjunctive treatment on diabetic foot ulcers: A systematic review and meta-analysis

A total of 28 studies, involving 1471 patients, were included. The meta-analysis showed that groups treated with red and infrared light had a significantly higher ulcer healing rate [risk ratio (RR) = 1.93, 95 % confidence interval (CI) (1.63, 2.28), $P < 0.00001$], shorter ulcer healing time [mean difference (MD) = 18.52, 95 % CI (8.58, 28.47), $P < 0.00001$], increased peak blood flow velocity in the dorsalis pedis artery [mean difference (MD) = 6.54, 95 % CI (4.01,9.08)], $P < 0.00001$), and reduced wound pain score [mean difference (MD) = −4.33, 95 % CI (−4.94, −3.71)], $P < 0.00001$) compared to the control group. However, there was no statistically significant difference in the incidence of adverse events [odds ratio (OR) = 0.32, 95 % CI (0.09, 1.17), $P = 0.08$] between the two methods.

The International Working Group on the Diabetic Foot (IWGDF) defines Diabetic Foot (DF) as lower extremity infections, ulceration, and/or deep tissue destruction caused

by neuropathy and various degrees of lower limb vascular disease in patients with diabetes [1]. DF is one of the most severe complications of diabetes, with a high recurrence rate of diabetic foot ulcers (DFUs) (1-year recurrence rate of approximately 30.6%–31.6 % [2,3] and 2-year recurrence rate of 58.5 % [4]). Some patients undergo toe or limb amputation due to worsening conditions, and the amputation rate is 15–40 times higher than that in non-diabetic patients. Furthermore, the annual mortality rate of patients with DFUs is as high as 11 %, and for those who undergo amputation, it increases to 22 % [5]. The global medical cost of diabetes is $727 billion, of which China accounted for $110 billion [6]. Therefore, it imposes a tremendous burden on the society and families.

Phototherapy or light therapy is the most common wound treatment [7], particularly for DFUs. As a non-invasive therapy, the use of light with specific wavelengths can accelerate wound healing [8] and promote tissue repair by stimulating cell activity [9]. Phototherapy uses visible (red and blue light) and invisible light (infrared and ultraviolet light) derived from various light sources (super-luminous diodes, polarised light, semiconductors, or diode lasers). Different wavelengths of light have varied therapeutic effects on wounds, whereas light with similar wavelengths exhibits similar actions [10].

Blue light is often used in combination with red light in phototherapies [[11], [12], [13]]. At high doses, blue light inhibits the proliferation and migration of skin keratinocytes [14] and induces production of skin free radicals [15]. This effect can lead to oxidative stress in the skin, damaging its barrier function and further influencing wound healing [15]. Ultraviolet light can damage the skin and suppress the immune system. In contrast, through photothermal and photochemical changes, red and infrared light activate mitochondrial activity in cells, increase cellular energy production, enhance blood circulation, reduce inflammation, and promote the formation of collagen and new cells in the wound area [16], which can promote wound healing. Red and infrared light are common spectral ranges of lasers and light-emitting diode (LED) light sources and are commonly used in wound healing studies. Lasers typically use red light (~600–700 nm wavelength) and near-infrared light (~700–1100 nm wavelength), which penetrate deep into the skin and promote cell repair and regeneration. LEDs have a wide range of wavelengths with low power and sufficient treatment duration; however, they typically have a lower power density than lasers [17].

Despite a mention of light and laser therapy for DFUs in the 2023 IWGDF guideline [18], current evidence is considered controversial; the results of some studies did not show statistically significant differences [[19], [20], [21]], probably

due to heterogeneity among the interventions used. Moreover, these studies had small sample sizes with a lack of rigorous design. Therefore, the use of phototherapy for the treatment of DFUs is not yet a guideline recommendation.

Current research on phototherapy for treating DFUs shows significant heterogeneity, with various light sources used and a lack of standardised classification criteria. Different forms of adjunctive phototherapy exist for DFUs, making it challenging to fully understand the role of phototherapy in current laser-based studies. Red and infrared light are commonly used in clinical research for phototherapy. Despite extensive research on red light, diabetic foot ulcer (DFU) wounds often progress to severe disease. Near-infrared light, which is known for its ability to penetrate deeper into wounds, underscores the need for future studies focusing on the potential of phototherapy in healing DFUs using near-infrared light alone or in combination with red light. However, there is a lack of comprehensive and systematic evidence to support their effectiveness. A meta-analysis provides a method for evaluating and consolidating research findings using a consistent standard (wavelength), which can help reduce discrepancies and improve reliability. This study aimed to conduct a systematic review and meta-analysis to assess the effects of red or infrared light on DFUs.