Copper Dressings as part of the armamentarium in the fight against wounds – much more than an antimicrobial

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Copper plays a critical role in all wound-healing processes. Examples of these include stimulation of angiogenesis, dermal fibroblasts proliferation, and secretion of extracellular matrix proteins and their cross-linking. Copper furthermore has potent wide-spectrum antimicrobial properties. These two key properties of copper endow this mineral as an excellent active ingredient to be used in the effective treatment of both acute and chronic wounds with or without infection. These dressings directly stimulate wound-healing processes, at all wound healing stages, from skin rupture to skin closure and seem to have endless possibilities within the wound management armamentarium. This review will highlight the mode of action of copper and how it could be utilised as a valuable resource in treating hard-to-heal wounds.

Keywords: copper oxide, wound dressings, wound healing, angiogenesis, extracellular matrix, chronic wounds

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Introduction

Copper is a vital mineral essential for various physiological processes across all body tissues, including the skin.[1] It plays a crucial role in wound healing[2,3] by interacting with key wound healing stimulating factors such as platelet-derived growth factor (PDGF) during haemostasis,[4] and vascular endothelial growth factor (VEGF) as well as angiogenin during angiogenesis in the proliferation phase.[5,6] Copper also supports the secretion of collagens and elastin by dermal fibroblasts and the activity of lysyl oxidase (LOX) for extracellular matrix (ECM) formation and stabilisation during the proliferation and remodelling phases.[4,7,8] Additionally, copper modulates matrix metalloproteinases (MMPs)[9] which are key enzymes involved in debridement and skin remodelling. A copper deficiency could delay wound healing.[10] Copper furthermore also acts as a cofactor for superoxide dismutase,[5] protecting against oxidative stress, and for tyrosinase,[11] which is vital for melanin production and skin pigmentation.

Wound infections can delay healing, result in wound deterioration, or even prevent healing. This occurs through various mechanisms: persistent inflammation, metabolic waste accumulation, tissue hypoxia, fragile granulation tissue, reduced fibroblast numbers, decreased collagen production, and impaired re-epithelisation.[12] Infected wounds also suffer from nutrient and oxygen depletion, while activated neutrophils produce harmful enzymes and radicals.[13] Chronic wounds often develop biofilms that shield bacteria from the immune system and antibiotics, leading to antibiotic resistance.[12] Reducing wound microbial contamination enhances healing. Copper, while also essential for microbial function, becomes toxic to microorganisms at high concentrations by altering proteins, permeabilising membranes, and causing lipid peroxidation.[14] Unlike the rapid development of antibiotic-resistant microbes, copper resistance is rare due to its multifaceted damage to microorganisms.[14]

Copper oxide impregnated wound dressings (Figure 1), hereafter referred to as "Copper Dressings", after demonstrating their high safety,

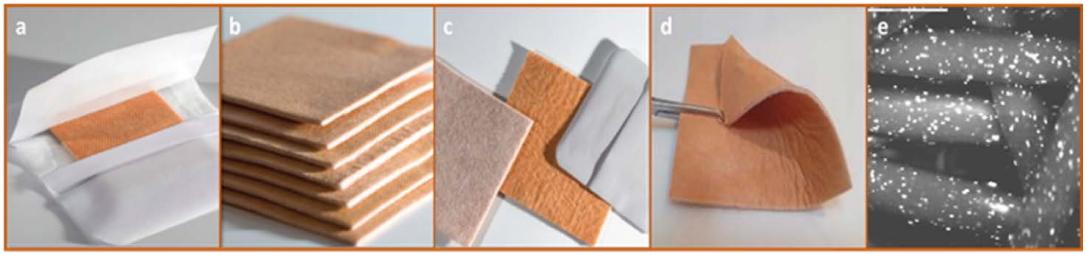

Figure 1: Copper Dressings. The dressings with (a) or without (b) an adhesive contour are composed of an external non-adherent layer (c, orange layer) that is placed in direct contact with the wound bed. This layer allows wound exudate passage to the internal layer (c, beige layer) that can absorb ~10 times its own weight. COD with two external layers (d) are more appropriate for application in deep wounds or tunnels. Both layers are impregnated with copper oxide microparticles (e, white dots). These single-use, sterile, highly absorbent dressings, can be cut to fit the wound size and used for up to seven days or until fully saturated with exudate.

biocompatibility and antimicrobial efficacy, were cleared for treating acute and chronic wounds, including diabetic ulcers, pressure injuries, and venous ulcers, by the FDA, EU, and other global regulatory bodies.[15]

Molecular mechanism of enhanced wound healing by Copper Dressings

The hypothesis that external *in situ* application of copper ions in hard-to-heal chronic wounds can stimulate wound healing was demonstrated in a murine diabetic wound model.[2,16] The application of Copper Dressings on full-thickness non-infected wounds under aseptic conditions resulted in statistically significant faster wound closure than the application of similar control dressings or silver dressings. Histological, immunohistochemistry and PCR analyses demonstrated enhanced generation of new blood vessels, sebaceous glands, and hair follicles, and increased expression of proangiogenic factors such as VEGF, fibroblast growth factor receptor 3 (FGFR3), transforming growth factor (TGF)-β and, importantly, the key wound healing stimulating factor – hypoxia-inducible factor-1alpha (Hif-1α). In a healthy individual Hif-1α is upregulated following wounding due to the local hypoxia in the damaged skin.[17] This upregulation leads to a cascade of events that results in angiogenesis, increased metabolism, dermal cells division and migration, growth factors release, immune cells recruitment, ECM synthesis, and epithelisation (Figure 2).[17,18] In a diabetic individual, and probably in other chronic conditions, Hif-1α is stagnated.[17,18]

As Figure 2 illustrates, the suggested molecular mechanisms, by which the copper ions released from the copper dressing enhance the wound healing processes, is through the upregulation of the stagnated Hif-1α.[16] Recently it has been found that SLC31A1, a copper transporter is reduced in diabetic foot ulcers, explaining also in part wound chronicity.[19]

Laboratory studies conducted with other copper-containing dressings support the role of copper to directly stimulate the wound healing processes. For example, chitosan-based copper nanocomposites have been shown to accelerate healing in excision wound models by promoting fibroblast proliferation, collagen synthesis, and re-epithelialisation.[20] Similarly, copper peroxide-loaded gelatin sponges provide enhanced wound healing through improved oxygenation and angiogenesis.[21] Copper nano-architectures in topical creams have also been found in animal studies to accelerate the healing of burn wounds by reducing inflammation and promoting tissue regeneration.[22]

Clinical studies showing enhanced healing of chronic non-infected wounds by Copper Dressings

Several studies have been published since the Copper Dressings have been in clinical use.[23-28] All of them clearly support the capacity of the Copper Dressings to stimulate wound healing of hard-to-heal chronic wounds. Most of these studies described the healing of not infected wounds by the Copper Dressings and in wounds that did not respond favourably to other wound management interventions. Weitman et al. reported a case report of a lupus patient that arrived at the hospital with an initially minor superficial wound with an area of approximately 4 cm^2.[24] Eventually she was hospitalised for eight months during which time the wound increased in size to ~300 cm^2. During this period the wound was treated with every possible standard of wound care in place, such as negative pressure wound therapy, pressure chambers, two skin grafts after escharotomy, and a multiple of antimicrobial dressings. At this stage, the wound was not infected, but it was still

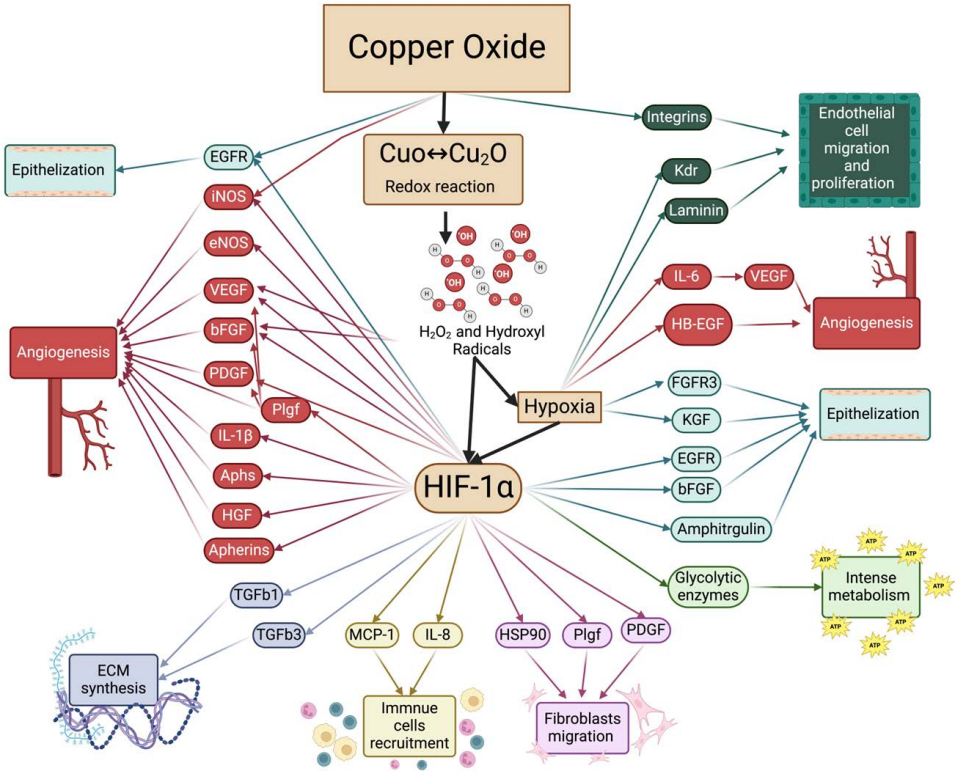

Figure 2: Molecular mechanisms of enhanced wound healing by Copper Dressings (based on the model published in ref [16])

deteriorating. Wound healing was achieved only when the wound was treated with Copper Dressings. Another example is the study conducted in a rehabilitation centre in which silver dressing was used as a standard-of-care, also in non-infected wounds in order to protect the wounds from pathogens. Gorel et al. achieved enhanced wound closure of post-amputation non-infected wounds that responded poorly to silver dressings when they switched to the application of Copper Dressings.[23] Interestingly, some of the stagnated wounds' size was reduced dramatically when they switched to the Copper Dressings. Melamed et al. reported the stimulation of non-infected stagnated diabetic wounds by the Copper Dressings.[27] Patients with non-infected wounds, who, during the screening period, responded poorly to the standard-of-care, were included in the study and treated with Copper Dressings. There was a 53.2% reduction in the mean wound area (p = 0.003) within one month of treatment. The reduction in wound size was even more dramatic in patients with non-weight-bearing wounds (66.9%; $p < 0.001$).

Taken together, it is clear that the Copper Dressings stimulate wound healing, even of hard-to-heal chronic wounds, not solely due to their potent antimicrobial properties, but via direct stimulation of wound repair. Due to the limited number of patients in the published studies, further research is needed to compare the efficacy of Copper Dressings, silver-impregnated dressings, and standard-of-care dressings in managing infected and non-infected wounds. Future studies, including randomised controlled trials with larger patient populations, should be conducted to provide further evidence. The Copper Dressings have already been used in more than 70 000 wounds worldwide without any adverse events being recorded, but with an extremely positive response to their application. In conclusion, due to its multifaceted activities throughout all phases of wound healing, Copper Dressings may be an indispensable asset in the current armamentarium for the fight against wounds, especially of chronic wounds, including non-infected wounds, throughout the continuum of wound care until wound closure.

Conflict of interest

Dr Gadi Borkow is the chief scientist of MedCu Technologies. Dr Eyal Melamed is a medical consultant of MedCu Technologies. The article reviews MedCu Technologies copper impregnated wound dressings. MedCu Technologies is the manufacturer of the dressings, and as such, both Dr Borkow and Dr Melamed have a conflict of interest. Ithamar Cheyne has no conflict of interests.

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Ethical approval

The authors declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010.

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